Pediatrics Exam Companion
Past Papers & Important Questions

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Neonatology

1. Trends of neonatal, infant and under-five mortality in Nepal and strategies to improve child health

Subject: Neonatology

Definitions

- **Neonatal Mortality Rate (NMR):** Deaths within first 28 days of life per 1,000 live births.
- **Infant Mortality Rate (IMR):** Deaths within first year of life per 1,000 live births.
- **Under-Five Mortality Rate (U5MR):** Deaths within first 5 years of life per 1,000 live births.

Mortality Trends in Nepal (NDHS Data)

- **Historical Decline:** Massive reduction in U5MR and IMR over the last 25 years (NDHS 1996 vs. NDHS 2022).
- **Current Rates (NDHS 2022):**
    - **U5MR:** 33 per 1,000 live births (Down from 118 in 1996).
    - **IMR:** 28 per 1,000 live births (Down from 78 in 1996).
    - **NMR:** 21 per 1,000 live births (Down from 50 in 1996).
- **Exam Trap/Trend Analysis:** While U5MR and IMR have declined steadily, **NMR decline has stagnated** over the last decade (was 21 in 2016, remains 21 in 2022).
- **Proportional Shift:** Neonatal deaths now account for ~75% of infant deaths and ~63% of under-five deaths in Nepal.
- **SDG 2030 Targets (Nepal):** NMR ≤ 12/1,000; U5MR ≤ 25/1,000.

Major Causes of Mortality

- **Neonatal:** Prematurity/Low Birth Weight (LBW), Birth asphyxia (HIE), Neonatal sepsis/infections.
- **Post-neonatal (1–59 months):** Pneumonia, Diarrhea, Undernutrition (underlying cause in ~45% of deaths), Vaccine-preventable diseases.

Strategies to Improve Child Health (Nepal Context)

1. Maternal & Perinatal Interventions

- **Aama Surakshya Programme:** Provides free institutional delivery and transport incentives to mothers.
- **SBA Training:** Scaling up Skilled Birth Attendants at primary health centers.
- **Antenatal Care (ANC):** Minimum 8 ANC visits (WHO 2016 guideline adopted), iron-folic acid supplementation, maternal TT/Tdap immunization.

2. Neonatal Specific Strategies (ENAP - Every Newborn Action Plan)

- **Essential Newborn Care (ENC):** Immediate drying, skin-to-skin contact, delayed cord clamping, early initiation of breastfeeding.

- **Chlorhexidine Cord Care:** Application of 7.1% Chlorhexidine digluconate (*Navi Mallam*) to the umbilical stump immediately after birth to prevent omphalitis/sepsis.
- **Kangaroo Mother Care (KMC):** Promoted for preterm and LBW infants to prevent hypothermia and promote growth.
- **Helping Babies Breathe (HBB):** Golden minute resuscitation training for frontline workers.
- **Comprehensive Newborn Care Package (CNCP):** Establishment of Level II (SNCU) and Level III (NICU) care facilities across provincial and district hospitals.
- **Free Newborn Care (FNC):** Government provision for free treatment of sick newborns in public hospitals.

3. Infant & Child Strategies

- **CB-IMNCI (Community-Based Integrated Management of Neonatal and Childhood Illnesses):** Protocol-based management of pneumonia, diarrhea, malaria, measles, and malnutrition by health workers and Female Community Health Volunteers (FCHVs).
- **National Immunization Program (NIP):** Routine immunization including PCV, Rotavirus, MR, and JE vaccines.
- **Nutrition Programs:**
    - Biannual Vitamin A supplementation and deworming (Albendazole) campaigns.
    - Multi-Sectoral Nutrition Plan (MSNP) to combat stunting and wasting.
    - Promotion of Infant and Young Child Feeding (IYCF) practices (exclusive breastfeeding for 6 months, complementary feeding).
- **WASH Initiatives:** Water, Sanitation, and Hygiene programs to reduce diarrheal diseases.

4. Health System Strengthening

- **FCHV Network:** Over 50,000 Female Community Health Volunteers mobilizing communities for health education, oral rehydration salts (ORS), zinc distribution, and early referral.
- **Suahaara Project:** USAID-funded integrated nutrition program targeting the "1,000 days" window (conception to 2 years).

Exam Summary

- **Current NDHS 2022 stats:** U5MR = 33, IMR = 28, NMR = 21.
- **Key Trend:** NMR is stagnant and constitutes the majority of U5MR; shifting focus to neonatal survival is the current national priority.
- **SDG 2030 Targets:** NMR ≤ 12, U5MR ≤ 25.
- **Flagship Nepal Interventions:** *Navi Mallam* (Chlorhexidine), *Aama Surakshya* (Institutional delivery), FCHV-led CB-IMNCI, and Vitamin A campaigns.

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2. Government programs to improve neonatal health in Nepal

Subject: Neonatology

Overview & Targets

- **Goal:** Reduce Neonatal Mortality Rate (NMR) to < 12 per 1,000 live births by 2030 (Current NMR: ~21/1000 per NDHS 2022).
- **Core Strategy:** Shift from solely community-based interventions to strengthening facility-based newborn care.
- **Guiding Policy:** Nepal Every Newborn Action Plan (NENAP) 2016 & Safe Motherhood and Reproductive Health Rights Act 2018.

Financial & Access Programs

- **Aama Surakshya Karyakram (Aama Program):**
    - Provides free institutional delivery services at government facilities.
    - Provides transport incentives to mothers.
    - Provides cash incentives for completing 4 standard Antenatal Care (ANC) visits.
    - *Impact:* Drastically increased institutional delivery rates, reducing birth asphyxia and sepsis.
- **Free Newborn Care Scheme:** Free treatment for sick newborns in government hospitals (up to 28 days of life).

Preventive & Promotive Programs

- **Chlorhexidine (CHX) Navel Care Program:**
    - Application of 7.1% Chlorhexidine digluconate gel to the umbilical cord stump immediately after birth.
    - *Fact:* Nepal was a global pioneer in scaling this up.
    - *Impact:* Significantly reduces omphalitis and neonatal mortality from sepsis.
- **Nyano Jhola (Warm Bag) Program:**
    - Distribution of a package containing a baby wrap, cap, socks, and a maternal gown to mothers delivering in health facilities.
    - *Aim:* Prevention of neonatal hypothermia and promotion of immediate skin-to-skin contact.
- **Kangaroo Mother Care (KMC):**
    - Established in secondary and tertiary facilities for Low Birth Weight (LBW) and preterm infants.
    - Focuses on continuous skin-to-skin contact and exclusive breastfeeding.

Community-Based Interventions

- **CB-IMNCI (Community-Based Integrated Management of Neonatal and Childhood Illness):**
    - Spearheaded by Female Community Health Volunteers (FCHVs).
    - Includes postnatal home visits (Days 1, 3, 7).
    - Focus: Counseling on exclusive breastfeeding, cord care, keeping the baby warm, and identifying danger signs.

- **PSBI (Possible Severe Bacterial Infection) Management:**
    - FCHVs and primary health workers identify PSBI.
    - *Update (WHO/MoHP):* Simplified antibiotic regimens used at the peripheral level (Oral Amoxicillin + IM Gentamicin) when referral is not feasible.

Facility-Based Newborn Care (Tiered System)

- **NBCC (Newborn Care Corner):**
    - Located inside the delivery room at all birthing centers.
    - Equipped for essential newborn care and basic neonatal resuscitation (Helping Babies Breathe protocol).
- **NBSU (Newborn Stabilization Unit):**
    - Located at primary level hospitals.
    - Manages moderate complications: provision of IV fluids, phototherapy, KMC, and oxygen therapy.
- **SNCU (Special Newborn Care Unit) / NICU:**
    - Located at secondary and tertiary hospitals.
    - Equipped for severe sepsis, CPAP for respiratory distress, and advanced life support.

Surveillance & Quality Improvement

- **MPDSR (Maternal and Perinatal Death Surveillance and Response):** Institutionalized system to audit perinatal deaths and implement corrective actions.
- **Birth Defect Surveillance:** Initiated in major tertiary hospitals to track congenital anomalies.

Exam Summary: Must-Write Buzzwords

- **Aama Program** (Institutional delivery incentive)
- **Nyano Jhola** (Hypothermia prevention)
- **Chlorhexidine 7.1% Gel** (Cord care, sepsis prevention)
- **CB-IMNCI & FCHVs** (Community-level PSBI management)
- **Tiered Care:** NBCC → NBSU → SNCU
- **Target:** NMR < 12/1000 by 2030 (NENAP/SDG)

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3. Strategies to reduce neonatal mortality in Nepal to achieve MDG/SDG goals

Subject: Neonatology

Context & Targets

- **SDG 3.2 Target:** Reduce Neonatal Mortality Rate (NMR) to ≤12 per 1,000 live births by 2030.
- **Nepal Current Status:** NMR is ~21 per 1,000 live births (NDHS 2022).
- **Major Causes:** Prematurity (23%), Neonatal Sepsis/Infections (~20%).

- **Core Strategy:** Continuum of Care (Pre-pregnancy → Antenatal → Intrapartum → Postnatal).

Antenatal Strategies (Maternal Care)

- **ANC Visits:** Minimum 8 contacts (WHO 2016 guideline) to monitor high-risk pregnancies.
- **Nutrition & Supplementation:** Iron-folic acid, calcium, and maternal nutrition to prevent Low Birth Weight (LBW).
- **Infection Control:** Tetanus-diphtheria (Td) immunization, screening/treatment for Syphilis, HIV, and asymptomatic bacteriuria.
- **Preterm Labor Management:** Antenatal corticosteroids (dexamethasone/betamethasone) for threatened preterm labor (24–34 weeks) to prevent RDS.

Intrapartum Strategies (Safe Delivery)

- **Institutional Delivery:** Promotion via Nepal's *Aama Surakshya Karyakram* (Safe Motherhood Program) providing free delivery and transport incentives.
- **Skilled Birth Attendants (SBA):** Mandatory presence of SBA at every delivery.
- **Fetal Monitoring:** Routine use of partograph to detect prolonged/obstructed labor early.
- **Neonatal Resuscitation:** Implementation of *Helping Babies Breathe (HBB)*; ensuring ventilation with bag and mask within the "Golden Minute" for asphyxiated newborns.
- **Cord Practices:** Delayed cord clamping (1–3 minutes) to prevent anemia and IVH in preterms.

Postnatal & Essential Newborn Care (ENC)

- **Thermoregulation:** Immediate drying, skin-to-skin contact, and *Nyano Jhola* (warm clothes/wrap program in Nepal) to prevent hypothermia.
- **Kangaroo Mother Care (KMC):** Standard of care for stable LBW/preterm infants to promote growth and prevent hypothermia.
- **Nutrition:** Early initiation of exclusive breastfeeding within 1 hour of birth; zero pre-lacteal feeds.
- **Cord Care:** Application of 7.1% Chlorhexidine digluconate (*Navi Mallam*) to the umbilical stump immediately after cutting (highly successful Nepal-specific intervention).
- **Prophylaxis:** Routine Vitamin K (1 mg IM) and eye care.

Community & Primary Care Strategies

- **FCHV Empowerment:** Utilizing Female Community Health Volunteers (FCHVs) for postnatal home visits (days 1, 3, 7).
- **CB-IMNCI Implementation:** Community-Based Integrated Management of Neonatal and Childhood Illnesses for early detection of danger signs.
- **PSBI Management:** Outpatient management of Possible Severe Bacterial Infection (PSBI) with simplified antibiotic regimens (oral amoxicillin + IM gentamicin) when referral is not feasible.

Facility-Level & Advanced Care

- **CEONC Strengthening:** Expanding Comprehensive Emergency Obstetric and Neonatal Care facilities.

- **SNCU/NICU Expansion:** Upgrading district hospitals with Special Newborn Care Units (SNCUs).
- **Respiratory Support:** Widespread availability of bubble CPAP and surfactant therapy for preterm RDS at secondary/tertiary centers.
- **Transport:** Establishing dedicated neonatal transport systems with transport incubators to prevent hypothermia during referral.

Exam Summary

- **Target:** SDG 3.2 aims for NMR ≤12/1,000 live births by 2030.
- **Big 3 Killers:** Prematurity, Asphyxia, Sepsis.
- **Nepal-Specific High-Yield Interventions:** *Navi Mallam* (Chlorhexidine cord care), *Nyano Jhola* (hypothermia prevention), *Aama Program* (institutional delivery), and FCHV-led CB-IMNCI.
- **Golden Interventions:** Antenatal corticosteroids, Helping Babies Breathe (Golden Minute), KMC for LBW, and early exclusive breastfeeding.

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4. Community based newborn care program

Subject: Neonatology

Rationale & Concept

- **Need:** Neonatal mortality contributes to >60% of Infant Mortality Rate (IMR); 75% of neonatal deaths occur in the first week of life.
- **Concept:** Provision of essential newborn care at the doorstep by trained frontline health workers (e.g., ASHA in India) to bridge the facility-community gap.
- **Flagship Program (India):** Home Based Newborn Care (HBNC) launched in 2011 under National Health Mission (NHM).
- **Goal:** Reduce Neonatal Mortality Rate (NMR) and promote early child development.

Key Implementer

- **ASHA (Accredited Social Health Activist):** Primary service provider.
- **Incentive:** Paid ₹250 per newborn for completing the scheduled visits.
- **Equipment:** Provided with an HBNC kit (weighing scale, digital thermometer, mucus extractor, blanket, clock).

Schedule of Visits (High-Yield)

- **Institutional Delivery (6 visits):** Days 3, 7, 14, 21, 28, and 42.
- **Home Delivery (7 visits):** Days 1, 3, 7, 14, 21, 28, and 42.
- **LBW/Premature Babies:** Require more frequent, intensive monitoring (extra visits often mandated by state protocols).
- **Update (HBYC):** Home Based Care for Young Child now extends visits beyond 42 days to 3, 6, 9, 12, and 15 months to ensure immunization and nutrition.

Core Interventions (During Visits)

- **Thermal Protection:** Counseling on delayed bathing, appropriate clothing, and Kangaroo Mother Care (KMC) for Low Birth Weight (LBW) infants.
- **Nutrition:** Support for early initiation (within 1 hour) and exclusive breastfeeding; counseling on correct latch/positioning.
- **Infection Prevention:** Handwashing education, clean cord care.
    - *Current Guideline:* Dry cord care is standard; 7.1% Chlorhexidine application is recommended *only* in high neonatal mortality settings/home deliveries.
- **Monitoring:** Weighing the baby, checking temperature, counting respiratory rate.

Identification of Danger Signs (Referral Criteria)

- Refusal to feed or poor sucking.
- Fast breathing (>60 breaths/minute) or severe chest indrawing.
- Fever (>37.5°C) or hypothermia (<35.5°C).
- Lethargy, unconsciousness, or seizures.
- Severe jaundice (yellowing of palms and soles) or early jaundice (<24 hours).
- Umbilical stump bleeding or purulent discharge.
- *Action:* Immediate stabilization (warmth, feed if possible) and referral to Special Newborn Care Unit (SNCU) or nearest facility.

Management of LBW Babies (<2500g)

- Identify LBW on Day 1 or first visit.
- Counsel mothers on strict KMC (duration, positioning).
- Advise frequent breastfeeding (every 2 hours).
- Ensure rigorous prevention of hypothermia and hypoglycemia.
- Refer immediately if weight drops >10% or baby exhibits any danger sign.

Programmatic Integration & Updates

- **INAP (India Newborn Action Plan):** Launched in 2014, aligns with Global Every Newborn Action Plan (ENAP).
- **INAP 2030 Target:** Single-digit Neonatal Mortality Rate (NMR < 10 per 1,000 live births) and Stillbirth Rate (SBR < 10 per 1,000).
- **SNCU Follow-up:** HBNC workers trace and monitor babies discharged from SNCUs to prevent post-discharge mortality.

Exam Summary

- **HBNC Schedule:** 6 visits for facility delivery (starts Day 3); 7 visits for home delivery (starts Day 1); ends on Day 42.
- **Key Worker:** ASHA, equipped with HBNC kit (thermometer, weighing scale).

- **Core Triad:** Warmth (KMC), Exclusive Breastfeeding, Infection Prevention (Hand hygiene/cord care).
- **Referral Triggers:** RR >60/min, Temp <35.5°C or >37.5°C, refusal to feed, lethargy, severe jaundice.
- **Update:** INAP targets single-digit NMR (<10/1000) by 2030; HBNC now extended via HBYC up to 15 months.

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5. Optimal feeding strategy for low birth weight babies

Subject: Neonatology

Definitions

- **LBW (Low Birth Weight):** <2500 g
- **VLBW (Very Low Birth Weight):** <1500 g
- **ELBW (Extremely Low Birth Weight):** <1000 g

Goals of Feeding

- Achieve postnatal growth rate matching intrauterine growth (15–20 g/kg/day).
- Target Head Circumference (HC) growth: 0.5–1 cm/week.
- Target Length growth: 1 cm/week.
- Prevent Extrauterine Growth Restriction (EUGR) and Necrotizing Enterocolitis (NEC).

Choice of Milk

- **First-line:** Mother's Own Milk (MOM) – protects against NEC, sepsis, and retinopathy of prematurity (ROP).
- **Second-line:** Pasteurized Donor Human Milk (PDHM) from a certified milk bank.
- **Third-line:** Preterm infant formula (only if MOM and PDHM are unavailable).
- **Contraindicated:** Animal milk, diluted milk formulas.

Methods of Feeding (Maturation-based)

- **< 32 weeks:** Orogastric (OG) or Nasogastric (NG) tube (due to absent suck-swallow-breathe coordination).
- **32–34 weeks:** Paladai, cup, or spoon feeding (transition phase).
- **> 34 weeks:** Direct Breastfeeding (DBF) on demand.

Initiation & Progression Strategy

- **Trophic Feeds / Minimal Enteral Nutrition (MEN):**
    - Start within 24 hours of life if hemodynamically stable.
    - Volume: 10–24 ml/kg/day.
    - Purpose: Primes the gut, prevents mucosal atrophy, stimulates motility; does *not* count toward nutritional goals.

- **Progression:**
    - Advance by 15–30 ml/kg/day based on tolerance (WHO/IAP guidelines).
    - Maximum target volume: 150–180 ml/kg/day.
- **Target Nutrients:** 110–130 kcal/kg/day (energy) and 3.5–4.0 g/kg/day (protein).

Parenteral Nutrition (PN) Integration

- **Indication:** ELBW, VLBW, or sick LBW infants who cannot reach full enteral feeds rapidly.
- **Early Amino Acids:** Start at 1.5–2.0 g/kg/day on Day 1 to prevent protein catabolism (*High-yield*).
- **Lipids:** Start at 1 g/kg/day on Day 1, advance to 3 g/kg/day.
- **Weaning:** Taper PN as enteral feeds increase; discontinue PN when enteral volume reaches 100–120 ml/kg/day.

Fortification & Supplementation

- **Human Milk Fortifier (HMF):**
    - Indicated for VLBW/ELBW babies.
    - Add when enteral feeds reach 100 ml/kg/day.
    - Provides extra protein, calcium, and phosphorus.
- **Vitamin D:** 400–800 IU/day starting within the first few days.
- **Iron:** 2–4 mg/kg/day starting at 2–4 weeks of age (or when full enteral feeds are established) to prevent anemia of prematurity; continue for 6–12 months.
- **Multivitamins:** Started once full feeds are established.

Monitoring & Feed Intolerance

- **Current Update (AAP/Recent Guidelines):** Routine checking of Gastric Residual Volumes (GRV) is *discouraged* in asymptomatic preemies as it delays time to full feeds.
- **Red Flags for Intolerance/NEC (Stop feeds & evaluate):**
    - Bilious or bloody aspirate/emesis.
    - Abdominal distension (increase in girth >2 cm).
    - Visible bowel loops or erythema of the abdominal wall.
    - Gross or occult blood in stools.
    - Systemic instability (new-onset apnea, bradycardia, lethargy).

Facilitating Factors

- **Kangaroo Mother Care (KMC):** Promotes lactation, stabilizes infant temperature, and encourages early direct breastfeeding.
- **Non-Nutritive Sucking (NNS):** Using a pacifier/empty breast during tube feeds accelerates the transition to oral feeding.

Complications of Suboptimal Feeding

- **Delayed/Inadequate:** Hypoglycemia, EUGR, neurodevelopmental impairment, osteopenia of prematurity.
- **Aggressive/Formula-heavy:** Necrotizing Enterocolitis (NEC), feed intolerance, aspiration.

Exam Summary: Must-Write Points

- **Hierarchy of milk:** MOM > Donor Milk > Preterm Formula.
- **Method:** Tube (<32 wks) → Paladai (32-34 wks) → Direct Breastfeeding (>34 wks).
- **MEN (Trophic feeds):** Start <24 hrs at 10-24 ml/kg/day to prime gut; advance by 15-30 ml/kg/day.
- **HMF:** Add to breast milk when feeds reach 100 ml/kg/day for VLBW infants.
- **Update:** Routine checking of gastric residuals is no longer recommended; rely on clinical signs of intolerance (distension, bilious aspirate).
- **Supplements:** Iron (2-4 mg/kg/day starting at 2-4 wks) and Vitamin D (400-800 IU/day).

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6. Care of low birth weight and very low birth weight infants

Subject: Neonatology

Definitions

- **Low Birth Weight (LBW):** Birth weight < 2500 g (regardless of gestational age).
- **Very Low Birth Weight (VLBW):** Birth weight < 1500 g.
- **Extremely Low Birth Weight (ELBW):** Birth weight < 1000 g.
- **Composition:** Comprises premature infants (<37 weeks) and Small for Gestational Age (SGA/IUGR) infants.

Etiology & Risk Factors

- **Maternal:** Severe malnutrition, pre-eclampsia/eclampsia, anemia, multiple gestation, infections (TORCH, UTI, chorioamnionitis).
- **Placental:** Placental insufficiency, abruptio placentae, placenta previa.
- **Fetal:** Chromosomal anomalies, congenital malformations, fetal infections.

Delivery Room Care (Golden Hour)

- **NRP Guidelines (8th Ed):** Maintain delivery room temperature at 23–25°C (74–77°F).
- **Thermoregulation:** For VLBW (<32 weeks), place in food-grade polyethylene wrap/bag immediately *without* drying; use a radiant warmer and transport incubator.
- **Cord Clamping:** Delayed cord clamping (30–60 seconds) if vigorous; improves hemodynamics and reduces intraventricular hemorrhage (IVH) and necrotizing enterocolitis (NEC).
- **Respiratory:** Early CPAP (PEEP 5–8 cm H_2O) preferred over routine intubation for spontaneously breathing VLBW infants. Target SpO_2: 90–95%.

Thermoregulation

- **Target:** Maintain axillary temperature 36.5–37.5°C.
- **Incubators:** Humidified incubators for VLBW (prevents insensible water loss).
- **Kangaroo Mother Care (KMC):**
    - *WHO 2022 Update:* Immediate KMC (iKMC) recommended for LBW/VLBW infants immediately after birth, even before full clinical stabilization.
    - Provides thermal control, promotes breastfeeding, and reduces mortality/sepsis.

Respiratory Care

- **Surfactant:** Early rescue therapy via INSURE (INtubate-SURfactant-Extubate) or LISA/MIST (Less Invasive Surfactant Administration) to minimize barotrauma.
- **Apnea Prophylaxis:** Caffeine citrate (loading 20 mg/kg, maintenance 5–10 mg/kg/day) routinely for all infants <28–32 weeks or <1250 g.
- **Oxygen Therapy:** Avoid hyperoxia. Strict SpO2 targets (90–95%) to prevent Retinopathy of Prematurity (ROP) and Bronchopulmonary Dysplasia (BPD).

Fluids & Nutrition

- **IV Fluids:** Start Day 1 fluids at 70–80 ml/kg/day (VLBW) with 10% Dextrose. Restrict fluids if PDA or BPD develops.
- **Total Parenteral Nutrition (TPN):** Start Day 1 for VLBW/ELBW to prevent catabolism (early amino acids 1.5–3 g/kg/day; early lipids 1 g/kg/day).
- **Enteral Nutrition:**
    - **Minimal Enteral Nutrition (MEN):** Trophic feeds (10–15 ml/kg/day) started Day 1–2 to prime the gut and prevent NEC.
    - **Choice of Milk:** Mother's Own Milk (MOM) is the gold standard. Pasteurized Donor Human Milk (PDHM) is the second choice. Avoid formula if possible (NEC risk).
    - **Fortification:** Add Human Milk Fortifier (HMF) when feeds reach 100 ml/kg/day to meet high calcium, phosphorus, and protein needs.

Infection Prevention

- Strict hand hygiene (most effective measure).
- Aseptic central line (UVC/UAC/PICC) insertion and daily review of line necessity.
- Avoid prolonged, routine empirical broad-spectrum antibiotics (increases risk of fungal sepsis and NEC).

Neurological & Supportive Care

- **Minimal Handling:** Cluster care to reduce stress, pain, and IVH risk.
- **Positioning:** Midline head positioning for the first 72 hours (reduces IVH).
- **Anemia of Prematurity:** Minimize phlebotomy. Transfuse PRBCs only based on strict restrictive guidelines.

Screening & Diagnostics

- **Neurosonogram (Cranial USG):** Perform at Day 3–7 (for IVH) and at 1 month/term equivalent (for Periventricular Leukomalacia - PVL).
- **ROP Screening:** First screen at 4 weeks postnatal age or 31 weeks Post-Menstrual Age (PMA), whichever is later.
- **Hearing Screen:** OAE or AABR before discharge.
- **Metabolic:** Thyroid (TSH) and newborn screening at Day 3–5.

Complications

- **Early (<7 days):** RDS, Hypothermia, Hypoglycemia, IVH, Early-onset sepsis, PDA.
- **Intermediate (1–4 weeks):** NEC, Late-onset sepsis, Apnea of prematurity.
- **Late (>4 weeks):** BPD, ROP, Osteopenia of prematurity, Neurodevelopmental delay, Cerebral palsy.

Discharge Criteria

- Sustained weight gain (15–20 g/kg/day).
- Maintaining temperature in an open cot.
- Taking full feeds directly (breast/paladai/katori).
- No recent apneic episodes (off caffeine for 5–7 days).

Prevention

- Adequate maternal nutrition and spacing.
- **Antenatal Corticosteroids:** Dexamethasone/Betamethasone for mothers at risk of preterm delivery (24–34 weeks) to prevent RDS, IVH, and neonatal mortality.
- **MgSO4:** Antenatal administration for fetal neuroprotection (prevents cerebral palsy) if delivery expected <32 weeks.

Exam Summary

- **Golden Hour:** Plastic wrap for VLBW, delayed cord clamping, early CPAP over intubation.
- **WHO 2022 Update:** Immediate Kangaroo Mother Care (iKMC) is now standard for LBW/VLBW infants.
- **Nutrition:** Start TPN and Minimal Enteral Nutrition (MEN) on Day 1; Mother's Own Milk is the ultimate NEC preventer.
- **Prophylaxis:** Caffeine citrate for apnea; strict SpO2 targeting (90-95%) to prevent ROP/BPD.
- **Mandatory Screens:** Cranial USG (Day 3-7), ROP screen (4 weeks postnatal/31 weeks PMA), Hearing screen before discharge.

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7. Follow up of preterm and NICU graduates

Subject: Neonatology

Definition & Criteria

- **Target Population (High-Risk Neonates):** Require structured multidisciplinary follow-up to detect growth, developmental, and sensory delays.
- **Inclusion Criteria (IAP Guidelines):**
    - Birth weight < 1500 g (VLBW) or Gestational age < 32 weeks.
    - Perinatal asphyxia (HIE Stage II/III).
    - Mechanical ventilation > 24 hours.
    - Shock, severe sepsis, or meningitis.
    - Severe hyperbilirubinemia requiring exchange transfusion.
    - Symptomatic hypoglycemia or neonatal seizures.
    - Major congenital malformations or inborn errors of metabolism.

Follow-Up Schedule

- **First Visit:** 48–72 hours post-discharge (assess feeding, weight, jaundice).
- **High-Risk Clinic Routine:** 1, 3, 6, 9, 12, 18, and 24 months.
- **Long-Term:** Annually until 6–8 years (to assess school performance and learning disabilities).
- **Corrected Age (CA):** Used for growth and development assessment until 2 years of age.
    - *Formula:* CA = Chronological age in weeks – (40 – Gestational age at birth in weeks).

Growth & Nutrition

- **Monitoring:** Weight, Length, and Head Circumference (HC) at every visit.
- **Growth Charts:**
    - Use **Fenton preterm growth charts** until 50 weeks Post-Menstrual Age (PMA).
    - Transition to **WHO growth charts** (using Corrected Age) after 50 weeks PMA.
- **Supplementation:**
    - **Vitamin D:** 400–800 IU/day up to 1 year.
    - **Iron:** 2–4 mg/kg/day elemental iron starting at 2–4 weeks of age until 1 year (prevents anemia of prematurity).
    - **Calcium/Phosphorus:** If history of Osteopenia of Prematurity (monitor Serum ALP, Ca, PO4 at 4–6 weeks postnatal age).

Neurodevelopmental Assessment

- **First Year:** Focus on tone, posture, and primitive reflexes.
    - Use **Amiel-Tison method** for tone assessment.
    - *Red Flags:* Persistent fisting > 3 months, head lag > 4 months, asymmetry of movement, absence of social smile by 3 months (CA).
- **Standardized Tools:**
    - **DASII** (Developmental Assessment Scales for Indian Infants) at 6, 12, and 24 months.

    - **BSID-III/IV** (Bayley Scales of Infant and Toddler Development) for definitive cognitive, motor, and language scoring.

- **Intervention:** Immediate referral to Early Intervention Program (EIP) for physiotherapy/occupational therapy if abnormalities detected.

Sensory Screening

- **Vision (ROP Screening):**
    - *Criteria:* BW < 2000 g or GA < 34 weeks (or larger unstable infants).
    - *Timing:* First screen at 31 weeks PMA or 3–4 weeks postnatal age (whichever is later).
    - *Follow-up:* Until retinal vascularization is complete (usually 40–44 weeks PMA).
- **Hearing Screening:**
    - *Tools:* OAE (Otoacoustic Emissions) and AABR (Automated Auditory Brainstem Response).
    - *High-Risk Protocol:* Must have AABR prior to discharge.
    - *Follow-up:* Diagnostic BERA (Brainstem Evoked Response Audiometry) by 3 months if screening failed; initiate hearing aids/cochlear implant evaluation by 6 months.

Immunization

- **Rule:** Administer vaccines according to **Chronological Age**, not corrected age.
- **Hepatitis B Trap:** If BW < 2000 g and mother is HBsAg negative, delay the first Hep B dose until 1 month of age or at discharge (due to reduced immunogenicity). If mother is HBsAg positive, give Hep B vaccine + HBIG within 12 hours regardless of weight.
- **Special Vaccines:**
    - Palivizumab (RSV prophylaxis) for infants with Bronchopulmonary Dysplasia (BPD) or severe prematurity, if guidelines/affordability permit.
    - Pneumococcal and Influenza vaccines strictly recommended.

Complications Monitoring

- **Anemia of Prematurity:** Check Hb/Reticulocyte count at 4–6 weeks.
- **BPD/Chronic Lung Disease:** Monitor oxygen requirement, growth failure, and cor pulmonale (ECHO if suspected).
- **Inguinal Hernia:** High incidence in preterms; examine at every visit.
- **Cryptorchidism:** Monitor for spontaneous descent up to 6 months corrected age.

Exam Summary

- **Corrected Age Rule:** Use for growth/milestones until 24 months; *never* use for immunization.
- **Nutrition:** Fenton charts until 50 weeks PMA → WHO charts; Iron drops start at 2–4 weeks.
- **ROP Timing:** Screen at 3–4 wks postnatal or 31 wks PMA (whichever is later).
- **Hearing:** AABR is mandatory for NICU graduates; BERA by 3 months if abnormal.

- **Neurodevelopment:** Amiel-Tison for tone; BSID/DASII for formal developmental quotient. Early intervention is the cornerstone of management.

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8. Follow up of very preterm and VLBW infants for neurodevelopment monitoring

Subject: Neonatology

Definition & Target Group

- **Target:** Very Low Birth Weight (VLBW, <1500g) and Very Preterm (<32 weeks gestation) infants.
- **Core Principle:** Always use **Corrected Age (CA)** for developmental assessment until 24 months.
- *CA Formula:* Chronological age in weeks - (40 - Gestational age in weeks).
- **Goal:** Early detection of Cerebral Palsy (CP), neurodevelopmental impairment (NDI), and sensory deficits.

High-Risk Predictors (Etiology of NDI)

- Intraventricular Hemorrhage (IVH) grade III/IV.
- Periventricular Leukomalacia (PVL) – highest risk for spastic diplegia.
- Bronchopulmonary Dysplasia (BPD) / prolonged mechanical ventilation.
- Neonatal sepsis or meningitis.
- Severe small for gestational age (SGA) / intrauterine growth restriction (IUGR).
- Symptomatic hypoglycemia or hyperbilirubinemia requiring exchange transfusion.

Follow-up Schedule

- **First visit:** 7–10 days post-discharge.
- **Routine High-Risk Clinic:** 1, 3, 6, 9, 12, 18, and 24 months (Corrected Age).
- **Annual visits:** 3 to 6 years of age (to monitor school readiness, specific learning disabilities, and ADHD).

Neurodevelopmental Assessment Tools

- **< 5 months CA:** Prechtl's General Movements Assessment (GMA) – *Absence of fidgety movements at 3-5 months is highly predictive of CP.*
- **2 to 24 months CA:** Hammersmith Infant Neurological Examination (HINE) – *Scores <57 at 3 months predict severe CP.*
- **Standardized Cognitive/Motor Scales:**
    - Bayley Scales of Infant and Toddler Development (BSID-IV) – *Gold standard*.
    - Developmental Assessment Scales for Indian Infants (DASII) – *Standardized for Indian population*.
- **Tone Assessment:** Amiel-Tison method for passive/active tone and angles (e.g., popliteal, scarf sign).

Sensory Monitoring

- **Vision (ROP Screening):**
    - First screen: 31 weeks Post-Menstrual Age (PMA) or 3–4 weeks postnatal age (whichever is later).
    - Follow-up until retinal vascularization is complete.
    - Check for strabismus, refractive errors (myopia of prematurity), and cortical visual impairment (CVI) at 6 and 12 months.
- **Hearing:**
    - Universal screen before discharge: Otoacoustic Emissions (OAE) or Automated Auditory Brainstem Response (AABR).
    - High-risk VLBW require **AABR** (detects auditory neuropathy missed by OAE).
    - If fail: Diagnostic BERA (Brainstem Evoked Response Audiometry) by 3 months.

Growth & Nutrition Monitoring

- **Charts:** Use **Fenton preterm charts** until 50 weeks PMA, then switch to **WHO growth standards** (using CA).
- **Parameters:** Strict serial monitoring of Weight, Length, and Occipitofrontal Circumference (OFC).
- *Microcephaly or poor OFC growth strongly correlates with poor neurodevelopmental outcomes*.

Clinical Red Flags (Indications for Escalation)

- Early rolling over (<2 months) – *Sign of extensor hypertonia*.
- Early handedness (<12 months) – *Sign of contralateral hemiplegia*.
- Fisting of hands beyond 2–3 months CA.
- Persistence of Moro reflex beyond 6 months CA.
- Lack of visual fixation and tracking by 3 months CA.
- W-sitting or scissoring of legs.

Management: Early Intervention Therapy (EIT)

- Initiate immediately upon detecting abnormal tone/delay; do not wait for a formal CP diagnosis.
- **Multidisciplinary team:** Pediatrician, physiotherapist, occupational therapist, speech-language pathologist, ophthalmologist, audiologist.
- **Neuroplasticity window:** Maximum benefit achieved if intervention starts <6 months of age.
- Family-centered care: Train parents in home-based sensory stimulation and handling techniques.

Exam Summary

- **Must-write formula:** Assess using Corrected Age (CA) up to 24 months.

- **Top predictive tools:** GMA (General Movements Assessment) and HINE for early CP detection (<6 months).
- **Sensory non-negotiables:** AABR for hearing (due to auditory neuropathy risk); ROP screening at 3-4 weeks postnatal.
- **Growth:** Fenton charts until 50 weeks PMA → WHO charts (Corrected Age).
- **Key clinical trap:** Early handedness or early rolling over are NOT advanced milestones; they are red flags for spasticity/hemiplegia.

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9. Small for gestational age infant: evaluation and management

Subject: Neonatology

Definition & Classification

- **Small for Gestational Age (SGA):** Birth weight (BW) < 10th percentile for gestational age (GA)
- **Severe SGA:** BW < 3rd percentile
- **SGA vs. IUGR:** SGA is a cross-sectional birth weight metric; IUGR (Intrauterine Growth Restriction) implies a clinical/ultrasound deviation from expected fetal growth trajectory
- **Symmetrical SGA (20-30%):**
    - Weight, length, and head circumference (HC) all < 10th percentile
    - Insult timing: Early pregnancy (hyperplastic phase)
    - Cellular level: Decreased cell *number*
- **Asymmetrical SGA (70-80%):**
    - Weight < 10th percentile; length and HC relatively spared (Brain-sparing effect)
    - Insult timing: Late pregnancy (hypertrophic phase)
    - Cellular level: Decreased cell *size*

Etiology

- **Maternal:** Pregnancy-induced hypertension (PIH), chronic kidney disease, severe malnutrition, substance abuse (smoking, alcohol, cocaine), autoimmune disorders (APLA)
- **Placental:** Placental insufficiency, abruptio placentae, chronic infarctions, twin-to-twin transfusion syndrome (TTTS), circumvallate placenta
- **Fetal:** Chromosomal anomalies (Trisomy 13, 18, 21), congenital infections (TORCH, primarily CMV and Rubella), multiple gestations, inborn errors of metabolism

Clinical Features

- **General Appearance:** Wasted, "old man" look, alert and wide-eyed (due to chronic hypoxia)
- **Skin/Fat:** Loose skin folds (especially over buttocks/thighs), decreased subcutaneous fat, poor brown fat stores
- **Abdomen:** Scaphoid (due to small liver/depleted glycogen)
- **Cord:** Thin, dry, frequently meconium-stained

- **Skeletal:** Wide cranial sutures and large anterior fontanelle (impaired membranous bone growth)

Complications (The "Hypo"s and "Poly"s)

- **Perinatal Asphyxia:** Poor placental reserve during labor contractions
- **Meconium Aspiration Syndrome (MAS):** Intrauterine hypoxia triggers fetal gasping and meconium passage
- **Hypothermia:** Due to high surface-area-to-body-mass ratio and depleted brown fat
- **Hypoglycemia:** Decreased hepatic glycogen stores and impaired gluconeogenesis
- **Polycythemia:** Chronic fetal hypoxia stimulates excessive erythropoietin (EPO) production
- **Hypocalcemia:** Associated with asphyxia and delayed parathyroid response
- **Immunologic:** Neutropenia (often seen with maternal PIH) and impaired cellular immunity

Evaluation & Diagnosis

- **Growth Plotting:** Use **INTERGROWTH-21st** or **Fenton** charts for accurate percentile allocation
- **Ponderal Index (PI):** $[Weight (g) \times 100] / [Length (cm)]^3$
    - PI < 2.0: Indicates asymmetrical SGA
    - PI > 2.0: Indicates symmetrical SGA or constitutionally small infant
- **Routine Screening (All SGA):**
    - Blood glucose: Screen at 2h, 6h, 12h, 24h of life (or per AAP/IAP high-risk protocols)
    - Hematocrit (venous): Screen at 12–24 hours (peak of physiologic polycythemia)
    - Temperature monitoring: Q4H initially
- **Targeted Workup (Symmetrical/Dysmorphic SGA):**
    - TORCH titers and neonatal urine CMV PCR
    - Karyotype or chromosomal microarray
    - Cranial ultrasound (to check for periventricular calcifications or ventriculomegaly)

Management

- **Delivery Room:** Anticipate need for resuscitation. Avoid delayed cord clamping if asphyxiated. Prevent heat loss immediately (dry, wrap, hat).
- **Thermoregulation:** Early Kangaroo Mother Care (KMC); use radiant warmer/incubator if unstable. Target axillary temperature 36.5–37.5°C.
- **Hypoglycemia Management (AAP Guidelines):**
    - *Asymptomatic:* Early, frequent enteral feeds (within 1 hr of birth). Target pre-feed glucose > 45 mg/dL.
    - *Symptomatic or Glucose < 40 mg/dL:* IV 10% Dextrose bolus (2 mL/kg) → Maintenance Glucose Infusion Rate (GIR) of 6–8 mg/kg/min.
- **Polycythemia Management:**

    - Ensure adequate hydration.
    - *Symptomatic + Venous Hct > 65%* OR *Asymptomatic + Venous Hct > 70%:* Perform Partial Exchange Transfusion (using Normal Saline) to drop Hct to 50-55%.
- **Nutrition:** High caloric requirement for catch-up growth (110–130 kcal/kg/day). Supplement with human milk fortifier (HMF) if preterm SGA.

Prognosis & Outcomes

- **Catch-up Growth:** 80–90% achieve normal growth percentiles by 2 years of age.
- **Endocrine Intervention:** Growth Hormone (GH) therapy is FDA-approved for SGA infants who fail to show catch-up growth by 2–4 years of age.
- **Neurodevelopment:** Symmetrical SGA (viral/genetic) has a poorer cognitive prognosis. Asymmetrical SGA outcomes depend largely on the severity of perinatal asphyxia and hypoglycemia.
- **Adult Disease Risk (Barker Hypothesis / Fetal Origins of Adult Disease):** Intrauterine nutritional reprogramming significantly increases lifetime risk of Metabolic Syndrome, Type 2 Diabetes Mellitus, Hypertension, and Coronary Artery Disease.

📝 **Exam Summary: Must-Write Points**

- **Definition:** BW < 10th percentile; Symmetrical (early insult, ↓ cell number) vs. Asymmetrical (late insult, ↓ cell size, brain-sparing).
- **Ponderal Index:** Key differentiator (<2.0 = Asymmetrical).
- **Classic Complications:** Hypothermia, Hypoglycemia, Hypocalcemia, Polycythemia, Perinatal Asphyxia, MAS.
- **Management Priorities:** Early feeding (prevent hypoglycemia), strict thermoregulation (KMC), and venous hematocrit screening.
- **Barker Hypothesis:** High-yield buzzword linking SGA to adult metabolic syndrome and cardiovascular disease.

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10. Neonatal hypoglycemia: risk factors, diagnosis and management

Subject: Neonatology

Definition & Operational Thresholds

- **Operational Threshold:** No single absolute value; intervention is based on age, symptoms, and risk factors.
- **Actionable level (AAP/IAP):** Plasma glucose <47 mg/dL (2.6 mmol/L).
- **Treatment Targets:** >45 mg/dL in the first 24 hours; >50 mg/dL after 24 hours.

Risk Factors (Etiology)

- **Decreased Substrate/Stores:**
    - Prematurity & Late-preterm infants

  - Intrauterine Growth Restriction (IUGR) / Small for Gestational Age (SGA)
  - Delayed onset of feeding / Starvation
- **Hyperinsulinism (Increased Utilization):**
  - Infant of Diabetic Mother (IDM)
  - Large for Gestational Age (LGA)
  - Syndromic: Beckwith-Wiedemann syndrome, Costello syndrome
  - Pathologic: Nesidioblastosis, focal adenoma
- **Increased Metabolic Demand:**
  - Perinatal asphyxia / Hypoxic Ischemic Encephalopathy (HIE)
  - Neonatal sepsis
  - Hypothermia
  - Polycythemia / Erythroblastosis fetalis
- **Endocrine & Metabolic Disorders:**
  - Panhypopituitarism, Adrenal insufficiency
  - Inborn Errors of Metabolism (Galactosemia, Glycogen Storage Diseases, Fatty acid oxidation defects)

Clinical Features

- **Asymptomatic:** Most common presentation (detected on routine screening).
- **Neurogenic (Autonomic):** Tremors, jitteriness, excessive sweating (diaphoresis), tachycardia, pallor.
- **Neuroglycopenic (Brain energy failure):** Lethargy, poor feeding, weak or high-pitched cry, hypotonia, apnea, cyanosis, seizures, coma.

Diagnosis & Screening

- **Who to screen:** Routine screening of healthy term infants is *not* recommended. Screen only high-risk (IDM, LGA, SGA, Preterm, stressed) or symptomatic infants.
- **Timing of screening:**
  - IDM/LGA: 1–2 hours of life (peak risk for hyperinsulinemia).
  - SGA/Preterm: 2–3 hours of life (pre-feed).
- **Methodology:** Point-of-care (POC) glucometer. *Rule:* Always confirm low POC values with a laboratory plasma glucose, but **do not delay treatment** while waiting for results.
- **The "Critical Sample":** Required if hypoglycemia is persistent (>48 hrs) or requires high Glucose Infusion Rate (GIR >8–10 mg/kg/min).
  - *Timing:* Draw *during* a hypoglycemic episode (<40 mg/dL) before giving IV dextrose.
  - *Tests:* Plasma glucose, insulin, C-peptide, growth hormone, cortisol, beta-hydroxybutyrate (ketones), lactate, free fatty acids (FFA), and ammonia.

Management

1. Asymptomatic Hypoglycemia

- **Glucose 25–40 mg/dL (First 4 hours):**
  - *Current AAP/IAP First-line:* **40% Dextrose Gel** (200 mg/kg = 0.5 mL/kg) massaged into buccal mucosa + immediate feeding (breast milk/formula).
  - Recheck glucose in 1 hour.
- **Glucose <25 mg/dL (First 4 hours) OR <35 mg/dL (4–24 hours):**
  - Feed + Administer IV Dextrose.

2. Symptomatic OR Refractory Hypoglycemia

- **Immediate IV Bolus:** 2 mL/kg of **10% Dextrose** (200 mg/kg) over 1 minute.
  - *Trap:* Never use >10% Dextrose for a bolus; it triggers rebound hyperinsulinemia.
- **Maintenance IV Dextrose:** Start at a GIR of 6–8 mg/kg/min.
  - *GIR Formula:* GIR (mg/kg/min) = [IV Rate (mL/hr) × Dextrose %] / [Weight (kg) × 6]
- **Titration:** If glucose remains <45 mg/dL, repeat 2 mL/kg 10% Dextrose bolus and increase GIR by 1–2 mg/kg/min (up to 12–15 mg/kg/min).
  - *Access rule:* Peripheral veins tolerate up to 12.5% Dextrose. Central venous access (UVC or PICC) is mandatory for >12.5% Dextrose.

3. Pharmacotherapy (for persistent hyperinsulinemic hypoglycemia)

- **Glucagon:** 0.5–1 mg/dose IM/IV (mobilizes hepatic glycogen; highly effective in IDM/LGA).
- **Hydrocortisone:** 5 mg/kg/day IV in 2 divided doses (reduces peripheral glucose utilization).
- **Diazoxide:** First-line for prolonged hyperinsulinism (keeps K-ATP channels open).
- **Octreotide:** Used if refractory to diazoxide.

Complications & Prognosis

- **Acute:** Apnea, intractable seizures, cardiopulmonary arrest.
- **Long-term Neurodevelopmental:** Cognitive impairment, cerebral palsy, epilepsy, cortical blindness.
- **Classic MRI Finding: Occipital lobe injury** (parieto-occipital cortex and subcortical white matter are most vulnerable to neonatal hypoglycemia).

💡 **Exam Summary: Must-Write Points**

- **Action Threshold:** <47 mg/dL (2.6 mmol/L) demands intervention.
- **GIR Formula:** [Rate × % Dextrose] / [Weight × 6]; starting target is 6–8 mg/kg/min.
- **Bolus Rule:** Always 2 mL/kg of **10%** Dextrose. Never use 25% or 50% dextrose in neonates (causes rebound hyperinsulinemia and hyperosmolarity).

- **Dextrose Gel:** 40% buccal dextrose gel is the modern first-line for asymptomatic hypoglycemia.
- **Radiology Buzzword:** Selective **occipital lobe** damage on MRI.

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11. Neonatal seizures: clinical patterns and prognostic features

Subject: Neonatology

Definition

- Paroxysmal alteration in neurologic function (motor, behavioral, and/or autonomic) occurring within the first 28 days of life.

Pathophysiology

- **Immature brain excitability:** High density of excitatory synapses (NMDA/AMPA) and delayed maturation of inhibitory synapses.
- **GABA Paradox:** In neonates, GABA acts as an *excitatory* neurotransmitter due to high intracellular chloride concentrations (high NKCC1, low KCC2 transporter expression).

Etiology (By Timing)

- **< 24 hours:** Hypoxic-Ischemic Encephalopathy (HIE) (most common overall, ~50%), severe trauma, Pyridoxine dependency.
- **24–72 hours:** Intracranial hemorrhage (IVH/SAH), metabolic (hypoglycemia, hypocalcemia), drug withdrawal.
- **> 72 hours:** CNS infections (meningitis, encephalitis), metabolic disorders, genetic epilepsies, cerebral dysgenesis.

Clinical Patterns (Core)

- **Subtle Seizures:**
    - Most common type overall (especially in preterms).
    - *Ocular:* Tonic horizontal deviation, sustained eye opening/staring, blinking.
    - *Oral-buccal-lingual:* Sucking, smacking, chewing, drooling.
    - *Limb:* Bicycling, pedaling, rowing movements.
    - *Autonomic:* Apnea (usually accompanied by other subtle signs), tachycardia, BP changes.
- **Clonic Seizures:**
    - Most common in term infants.
    - Rhythmic jerking (1–3 Hz), focal or multifocal.
    - *Key feature:* Cannot be suppressed by gentle restraint (differentiates from jitteriness).
- **Tonic Seizures:**
    - Sustained posturing (focal or generalized).
    - Generalized tonic extension mimics decerebrate posturing.

- Often unassociated with EEG discharges; high association with severe IVH in preterms.

- **Myoclonic Seizures:**
  - Rapid, isolated, non-rhythmic jerks (focal, multifocal, or generalized).
  - Often indicates severe diffuse brain damage or early myoclonic encephalopathy.

Seizures vs. Jitteriness (Exam Trap)

- **Jitteriness:** Stimulus-sensitive, lacks abnormal eye movements, predominant tremor, *stops with passive flexion/restraint*.
- **Seizures:** Not stimulus-sensitive, abnormal eye movements present, clonic jerking, *not suppressed by restraint*.

Diagnosis

- **Bedside Labs:** Blood glucose, ionized calcium, magnesium, electrolytes, ABG.
- **Neurophysiology:** Continuous Video-EEG is the **Gold Standard**.
  - *aEEG (Amplitude-integrated EEG):* Used for rapid bedside screening and continuous monitoring in NICU.
- **Neuroimaging:**
  - *Cranial USG:* First-line for preterms (detects IVH, hydrocephalus).
  - *MRI Brain:* Modality of choice for term infants (detects HIE, stroke, structural anomalies); perform once stable.
- **Advanced:** CSF analysis (rule out meningitis), metabolic screening (ammonia, lactate, tandem mass spectrometry), genetic epilepsy panels.

Management

- **Acute Stabilization:** Airway, Breathing, Circulation. Correct hypoglycemia (<45 mg/dL) or hypocalcemia immediately.
- **First-line AED:**
  - **Phenobarbital:** 20 mg/kg IV loading dose (WHO/IAP standard). May repeat 10 mg/kg up to max 40 mg/kg.
- **Second-line AED:**
  - **Levetiracetam:** 40–60 mg/kg IV loading. (*Update:* Increasingly preferred over phenytoin due to better safety profile and lack of neuronal apoptosis risk, though phenobarbital remains official first-line).
  - **Phenytoin/Fosphenytoin:** 20 mg/kg IV loading.
- **Third-line/Refractory:**
  - Midazolam infusion or Lidocaine infusion.
- **Therapeutic Trial for Refractory Seizures:**
  - Always give **Pyridoxine (100 mg IV)** under EEG monitoring to rule out pyridoxine-dependent epilepsy. Follow with Pyridoxal-5-phosphate and Folinic acid if no response.

Prognostic Features (Core)

Good Prognostic Factors:

- Normal background EEG (most reliable predictor).
- Late onset (>72 hours), excluding CNS infection.
- Transient metabolic etiologies (e.g., late-onset hypocalcemia).
- Benign Familial Neonatal Seizures (BFNS - "fifth-day fits").
- Normal neurological examination between seizures.

Poor Prognostic Factors:

- Severely abnormal background EEG (burst suppression, flat trace, low voltage).
- Prematurity.
- Early onset (<24 hours) secondary to severe HIE.
- Seizure types: Myoclonic or generalized tonic patterns.
- Etiology: Severe structural anomalies, major IVH, CNS infections.
- Refractory seizures requiring >2 AEDs.

Complications & Outcomes

- Cerebral palsy (highest risk with HIE and severe IVH).
- Post-neonatal epilepsy (~15-30% risk).
- Intellectual disability and neurodevelopmental delay.
- Feeding difficulties and microcephaly.

Exam Summary

- **Most common cause:** HIE (occurs <24 hours).
- **Most common clinical type:** Subtle seizures.
- **Jitteriness vs. Seizure:** Restraint stops jitteriness, but not a seizure.
- **Gold standard diagnosis:** Continuous Video-EEG.
- **First-line drug:** Phenobarbital 20 mg/kg IV.
- **Best prognostic indicator:** Background EEG activity (normal background = good prognosis; burst suppression = poor prognosis).
- **Must-do for refractory cases:** IV Pyridoxine trial.

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12. Perinatal asphyxia: pathophysiology and neurological features of hypoxic ischemic encephalopathy

Subject: Neonatology

Definition

- **Perinatal Asphyxia:** Impaired placental/pulmonary gas exchange leading to hypoxemia, hypercapnia, and metabolic acidosis (Cord pH < 7.0, Base Deficit ≥ 16 mmol/L).
- **Hypoxic-Ischemic Encephalopathy (HIE):** The clinical syndrome of disturbed neurologic function in the earliest days of life manifesting as altered consciousness, tone/reflex changes, and seizures following asphyxia.

Pathophysiology Occurs in distinct temporal phases; understanding these is critical for the timing of neuroprotection.

- **Primary Energy Failure (Immediate):**
  - Hypoxia/ischemia → Impaired oxidative phosphorylation → ↓ ATP production.
  - Failure of Na+/K+ ATPase pump → Intracellular accumulation of Na+, Ca2+, and water → **Cytotoxic edema**.
- **Latent Phase (1–6 hours):**
  - Reperfusion and resuscitation restore cerebral blood flow.
  - Transient partial recovery of cellular metabolism.
  - *Clinical significance:* Represents the critical **"therapeutic window"** for initiating therapeutic hypothermia.
- **Secondary Energy Failure (6–72 hours):**
  - **Excitotoxicity:** Massive release of excitatory neurotransmitters (Glutamate) → Overactivation of NMDA receptors → Massive intracellular Ca2+ influx.
  - **Oxidative stress:** Generation of reactive oxygen species (ROS) and nitric oxide (NO) → Lipid peroxidation.
  - **Inflammation:** Microglial activation and cytokine release.
  - **Cell Death:** Culminates in delayed neuronal death via apoptosis (programmed) and necrosis.

Neurological Features (Modified Sarnat Staging) Clinical features are categorized by severity to guide prognosis and treatment (Therapeutic Hypothermia is indicated for Stage II and III).

- **Stage I (Mild HIE):**
  - *Level of consciousness:* Hyperalert / Irritable.
  - *Tone & Posture:* Normal tone, mild distal flexion.
  - *Reflexes:* Hyperactive stretch reflexes, exaggerated Moro.
  - *Autonomic:* Sympathetic overactivity (Tachycardia, dilated pupils, sparse secretions).
  - *Seizures:* **Absent**.
  - *Duration:* Resolves within 24 hours.
- **Stage II (Moderate HIE):**
  - *Level of consciousness:* Lethargic / Obtunded.
  - *Tone & Posture:* Hypotonia, strong distal flexion.

  - *Reflexes:* Weak/incomplete Moro, sluggish suck.
  - *Autonomic:* Parasympathetic overactivity (Bradycardia, constricted pupils, profuse secretions).
  - *Seizures:* **Common** (focal or multifocal).
  - *Duration:* 2 to 14 days.
- **Stage III (Severe HIE):**
  - *Level of consciousness:* Stuporous / Comatose.
  - *Tone & Posture:* Flaccid, decerebrate posture.
  - *Reflexes:* Absent Moro, absent suck/gag.
  - *Autonomic:* Depressed vital functions, absent pupillary light reflex, apnea.
  - *Seizures:* Refractory seizures or isoelectric (silent) EEG.
  - *Duration:* Days to weeks (high mortality/morbidity).

Systemic Features (Multiorgan Dysfunction)

- *Renal:* Acute Kidney Injury (oliguric/non-oliguric) — most common systemic complication.
- *Cardiac:* Transient myocardial ischemia, tricuspid regurgitation, hypotension.
- *Pulmonary:* PPHN (Persistent Pulmonary Hypertension of the Newborn), MAS.
- *GI/Hepatic:* Necrotizing Enterocolitis (NEC), elevated transaminases.
- *Hematologic:* DIC, thrombocytopenia.

Diagnosis

- **Cord Blood Gas:** pH < 7.0, Base Deficit ≥ 16 mmol/L.
- **Apgar Score:** ≤ 5 at 10 minutes.
- **Neurophysiology:** aEEG (amplitude-integrated EEG) is the gold standard for continuous bedside monitoring to detect subclinical seizures and assess background activity.
- **Neuroimaging (MRI Brain):**
  - Gold standard; best performed between days 3–5 and again after day 10.
  - *Acute profound asphyxia:* Lesions in deep gray matter (Basal ganglia, Thalamus).
  - *Prolonged partial asphyxia:* Lesions in watershed/parasagittal white matter.

Management

- **Resuscitation:** Per current Neonatal Resuscitation Program (NRP) guidelines.
- **Supportive Care (The "Normos"):** Maintain normoxia (avoid hyperoxia to prevent ROS damage), normocapnia (CO_2 35-45 mmHg), normoglycemia, and normal blood pressure.
- **Therapeutic Hypothermia (TH):**
  - *Criteria:* Gestational age ≥ 36 weeks (AAP/IAP guidelines), evidence of acute perinatal asphyxia, and clinical evidence of Moderate-to-Severe HIE (Sarnat II/III).

  - *Protocol:* Target core temperature 33.5°C for 72 hours, followed by slow rewarming (0.5°C per hour).
  - *Timing:* Must initiate within **6 hours** of life.
- **Seizure Management:**
  - *First-line:* Phenobarbitone (20 mg/kg IV loading dose).
  - *Second-line:* Levetiracetam or Fosphenytoin.

Prognosis

- *Mild HIE:* ~100% normal neurological outcome.
- *Moderate HIE:* 20–30% risk of long-term sequelae.
- *Severe HIE:* >75% risk of death or severe neurodevelopmental disability.
- *Long-term Sequelae:* Spastic quadriplegia, dyskinetic cerebral palsy, epilepsy, microcephaly, intellectual disability, cortical visual impairment.

Exam Summary

- **Must-write Patho:** Primary energy failure (edema) → Latent phase (therapeutic window) → Secondary energy failure (glutamate excitotoxicity, calcium influx, apoptosis).
- **Must-write Clinical:** Modified Sarnat Staging is mandatory for grading HIE and determining hypothermia eligibility (Stage II/III).
- **Must-write Imaging:** MRI is the modality of choice; basal ganglia/thalamus involvement implies severe acute insult.
- **Must-write Management:** Therapeutic hypothermia (33.5°C for 72 hrs) initiated < 6 hours of life in infants ≥ 36 weeks is the standard of care for neuroprotection.

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13. Neuroprotective strategies in hypoxic ischemic encephalopathy

Subject: Neonatology

Basics & Pathophysiology

- **Definition:** Evolving brain injury secondary to perinatal asphyxia (hypoxia + ischemia).
- **Biphasic Injury Model:**
  - *Primary Energy Failure:* Immediate ATP depletion, cytotoxic edema, cell death.
  - *Latent Phase:* 1–6 hours post-insult; transient recovery of oxidative metabolism (the critical **"Therapeutic Window"**).
  - *Secondary Energy Failure:* 6–72 hours; mitochondrial failure, excitotoxicity (glutamate), oxidative stress, apoptosis, and neuroinflammation.

Criteria for Neuroprotection (Therapeutic Hypothermia) *Standard NICHD / NNF India Criteria (Must meet A + B + C)*

- **A. Gestational Age:** ≥36 weeks (some protocols allow ≥35 weeks) AND Birth weight ≥1800g.
- **B. Evidence of Asphyxia (Any one):**

  - Cord/first hour ABG pH $\le$ 7.0 or Base Deficit ≥16 mmol/L.
  - If pH 7.01–7.15 or BD 10–15: Need Apgar $\le$ 5 at 10 mins OR continued PPV/ventilation at 10 mins.

- **C. Evidence of Encephalopathy:**
  - Moderate to Severe HIE (Sarnat Stage II or III) on clinical exam.
  - Presence of clinical seizures.
  - Abnormal amplitude-integrated EEG (aEEG).

Therapeutic Hypothermia (TH) – The Gold Standard *Only proven neuroprotective intervention for term/near-term HIE.*

- **Initiation:** Strictly within **< 6 hours** of birth.
- **Target Temperature:** 33.5°C (Whole body cooling) or 34.5°C (Selective head cooling). Whole body is preferred.
- **Duration:** 72 hours of continuous cooling.
- **Rewarming:** Slow and controlled at **0.5°C per hour** over 6–8 hours (prevents rebound seizures/hypotension).
- **Mechanism:** Decreases cerebral metabolism (5% per 1°C drop), suppresses excitatory amino acids, inhibits apoptosis, reduces free radicals.
- **Contraindications:** Major lethal congenital anomalies, severe coagulopathy with active bleeding, imperforate anus (if using rectal probe).
- **Adverse Effects:** Sinus bradycardia (expected, usually ~80-100 bpm), thrombocytopenia, coagulopathy, subcutaneous fat necrosis, exacerbation of PPHN.

Supportive Neuroprotection (Strict Homeostasis) *Optimal intensive care is independently neuroprotective.*

- **Temperature:** STRICTLY avoid hyperthermia (>37.5°C) in non-cooled infants (accelerates apoptosis).
- **Oxygenation:** Avoid hyperoxia (generates free radicals) and hypoxia. Target SpO2 90–95%.
- **Ventilation:** Strictly avoid hypocapnia ($PaCO_2$ < 35 mmHg causes severe cerebral vasoconstriction and worsens ischemia). Target $PaCO_2$ 40–50 mmHg.
- **Hemodynamics:** Maintain MAP > 35–40 mmHg to ensure cerebral perfusion (autoregulation is often lost in HIE). Use Inotropes (Dobutamine/Epinephrine) if needed.
- **Metabolic:** Maintain normoglycemia (75–100 mg/dL). Hypoglycemia worsens injury; hyperglycemia increases lactic acidosis. Maintain normal Calcium and Magnesium.
- **Seizure Control:** Phenobarbital (20 mg/kg loading) remains first-line. Levetiracetam is second-line. Treat both clinical and subclinical (aEEG) seizures aggressively.

Emerging / Adjunctive Pharmacological Strategies *Currently experimental; used in trials often alongside TH.*

- **Erythropoietin (Epo):** Anti-apoptotic, anti-inflammatory, promotes neurogenesis. *Update (HEAL Trial 2022): High-dose Epo + TH did not improve outcomes over TH alone in severe HIE.*

- **Melatonin:** Highly lipophilic, crosses BBB easily, potent free-radical scavenger.
- **Xenon Gas:** Noble gas, potent non-competitive NMDA receptor antagonist; reduces glutamate excitotoxicity.
- **Topiramate:** AMPA/Kainate receptor antagonist; prevents seizure-induced secondary injury.
- **Magnesium Sulfate:** NMDA receptor blocker. (Standard for *maternal* administration for preterm neuroprotection; limited postnatal role in term HIE).
- **Stem Cell Therapy:** Mesenchymal stem cells or umbilical cord blood cells (anti-inflammatory, promotes neural repair).

Monitoring & Prognosis

- **Neuromonitoring:** Continuous aEEG (gold standard for early background assessment and subclinical seizures).
- **Neuroimaging:** MRI Brain (T1/T2 and DWI) done at **Day 4 to 7** of life is the most accurate prognostic tool. Classic moderate/severe HIE involves basal ganglia and thalami.
- **Prognosis:** High risk for dyskinetic/spastic cerebral palsy, epilepsy, intellectual disability, and cortical visual impairment.

Exam Summary: High-Yield Must-Write Points

- **Therapeutic Window:** Neuroprotection must begin in the *latent phase* (< 6 hours of life).
- **Gold Standard:** Therapeutic Hypothermia (Target 33.5°C for 72 hours, rewarm at 0.5°C/hr).
- **Cooling Criteria:** $\ge$36 wks + Asphyxia evidence (pH $\le$ 7.0 / BD ≥16) + Mod/Severe Encephalopathy.
- **Supportive Care Traps:** Never allow hyperthermia, hyperoxia, hypocapnia, or hypoglycemia.
- **Adjuncts (Buzzwords):** Epo (anti-apoptotic), Xenon (NMDA blocker), Melatonin (antioxidant) — all currently experimental.

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14. Neonatal resuscitation program updates and post resuscitation care

Subject: Neonatology

Basics & Principles

- **Goal:** Establish adequate ventilation and oxygenation; restore cardiac output.
- **Golden Minute:** Initial steps, evaluation, and initiation of positive pressure ventilation (PPV) must occur within 60 seconds of birth.
- **Current Standard:** AAP/AHA NRP 8th Edition (2021).

NRP 8th Edition Updates (Must-Know)

- **Pre-birth Briefing:** Now explicitly includes an "Umbilical Cord Management Plan" (delayed cord clamping vs. immediate) alongside the 4 standard questions (Gestational age? Fluid clear? How many babies? Additional risk factors?).
- **Meconium-Stained Amniotic Fluid (MSAF):**

  - *Previously:* Intubate and suction non-vigorous infants.
  - *Now:* Routine intubation/tracheal suctioning is **not** recommended. Clear mouth/nose with bulb syringe; immediately initiate PPV if apneic or HR < 100 bpm.
- **Epinephrine Dosing (IV/IO):**
  - *Previously:* 0.01 to 0.03 mg/kg.
  - *Now:* Simplified to a suggested initial dose of **0.02 mg/kg** (0.2 mL/kg of 0.1 mg/mL concentration).
- **Epinephrine Flush Volume:**
  - *Previously:* 0.5 to 1 mL normal saline (NS).
  - *Now:* **3 mL NS flush** for all weights (pushes drug out of dead space into central circulation).
- **Endotracheal Epinephrine:** Dose remains 0.1 mg/kg (1 mL/kg). Use only while establishing vascular access.
- **Discontinuation of Resuscitation:**
  - *Previously:* Consider stopping after 10 minutes of asystole.
  - *Now:* Consider stopping after **20 minutes** of absent heart rate (allows time for optimal CPR interventions).
- **Cardiac Monitor:** Recommended earlier (attach as soon as an alternate airway is placed or chest compressions begin).

Resuscitation Algorithm (Core Steps)

- **Initial Steps:** Warm, dry, stimulate, position airway, suction (only if obstructing).
- **Assess:** Apnea, gasping, or HR < 100 bpm → Start PPV (room air for ≥35 weeks; 21-30% O2 for <35 weeks).
- **MR. SOPA:** Ventilation corrective steps if HR not rising and chest not moving (Mask adjustment, Reposition, Suction, Open mouth, Pressure increase, Alternate airway).
- **Compressions:** If HR < 60 bpm despite 30 seconds of *effective* PPV (chest movement confirmed).
  - Ratio: 3 compressions to 1 breath (90 compressions, 30 breaths per minute).
  - Requires 100% FiO2 and an advanced airway (ET tube or LMA).
- **Medications:** If HR < 60 bpm despite 60 seconds of effective compressions + PPV → Epinephrine (IV/IO preferred).

Post-Resuscitation Care (Systems Approach)

- **Thermoregulation:**
  - Target normothermia: 36.5°C to 37.5°C.
  - *Exception:* **Therapeutic Hypothermia** (target 33.5°C for 72 hours) if ≥36 weeks gestation, evolving Hypoxic-Ischemic Encephalopathy (HIE), and meets strict criteria (initiate within 6 hours of birth).

- **Respiratory:**
    - Avoid hyperoxia (causes oxidative stress); titrate FiO2 to maintain SpO2 90–95%.
    - Avoid hypocapnia (causes cerebral vasoconstriction/ischemia); target PaCO2 35–45 mmHg.
- **Cardiovascular:**
    - Monitor for hypotension, poor perfusion, and pulmonary hypertension (PPHN).
    - Volume expansion (10 mL/kg NS over 5-10 mins) only if evidence of acute blood loss or hypovolemic shock.
    - Inotropes (Dopamine/Epinephrine) if hypotensive despite volume.
- **Metabolic/Endocrine:**
    - High risk of hypoglycemia (depleted glycogen stores).
    - Initiate early IV dextrose (D10W at 60-80 mL/kg/day); target blood glucose >50 mg/dL.
    - Monitor calcium and electrolytes (risk of hypocalcemia, SIADH, or acute kidney injury).
- **Neurologic:**
    - Serial exams using Sarnat staging for HIE.
    - Monitor for seizures (clinical and subclinical via aEEG).
    - *1st line anti-seizure:* Phenobarbital (20 mg/kg loading dose).
- **Infection/Hematologic:**
    - Resuscitation is an unsterile procedure; obtain blood cultures and start broad-spectrum antibiotics (Ampicillin + Gentamicin).
    - Monitor Hb, platelets, and coagulation profile (risk of DIC).

Complications

- **Airway/Pulmonary:** Pneumothorax (from PPV), vocal cord injury, tracheal perforation.
- **CPR-related:** Rib fractures, liver laceration.
- **Systemic:** Multi-organ dysfunction syndrome (MODS) secondary to asphyxia.

Prognosis

- Determined by Apgar score at 10 and 20 minutes, time to spontaneous respirations, and severity of HIE.
- Normal neurodevelopmental outcome is highly unlikely if HR remains absent at 20 minutes despite optimal CPR.

Exam Summary

- **NRP 8th Ed Trap:** Never routinely intubate for meconium, even if non-vigorous; focus is on immediate PPV.
- **Epinephrine Update:** IV dose is 0.02 mg/kg followed strictly by a **3 mL** NS flush (irrespective of baby's weight).

- **Cessation:** Counsel parents for withdrawal of support at **20 minutes** of asystole (not 10).
- **Post-CPR Respiration:** Strictly avoid hyperoxia (SpO2 >95%) and hypocapnia (PaCO2 <35) to prevent brain injury.
- **Neuroprotection:** Assess all resuscitated infants ≥36 weeks for therapeutic hypothermia eligibility within the first 6 hours of life.

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15. Respiratory distress syndrome of prematurity: prevention and treatment

Subject: Neonatology

Basics

- **Definition:** Acute respiratory illness of prematurity caused by quantitative/qualitative deficiency of pulmonary surfactant.
- **Etiology:** Prematurity (incidence inversely proportional to gestational age), maternal diabetes (hyperinsulinemia inhibits surfactant), perinatal asphyxia, male sex, second born twin.
- **Surfactant:** Produced by Type II pneumocytes; peaks at 35 weeks; composed of DPPC (dipalmitoylphosphatidylcholine) and proteins (SP-A, B, C, D).

Pathophysiology

- Surfactant deficiency → increased alveolar surface tension.
- Progressive diffuse microatelectasis → decreased functional residual capacity (FRC) and lung compliance.
- V/Q mismatch → hypoxemia, hypercapnia, and acidosis.
- Acidosis → pulmonary vasoconstriction → right-to-left shunting (via PDA/PFO) → worsening hypoxemia.
- Epithelial injury → proteinaceous exudate (hyaline membranes).

Clinical Features

- **Onset:** Within minutes to hours of birth; peaks at 48–72 hours.
- **Signs:** Tachypnea (>60/min), expiratory grunting (attempt to maintain FRC), nasal flaring, intercostal/subcostal retractions.
- **Severe:** Central cyanosis, apnea, diminished breath sounds.

Diagnosis

- **CXR (Gold Standard):** Bilateral reticulogranular pattern (ground-glass), prominent air bronchograms, low lung volumes (bell-shaped thorax). Severe: "White-out" lungs.
- **ABG:** Hypoxemia, hypercapnia, mixed respiratory-metabolic acidosis.
- **Lab:** Sepsis screen/blood culture (to rule out congenital pneumonia/sepsis, which mimics RDS).
- **Echocardiography:** To rule out structural heart disease and assess PDA.

Prevention (High-Yield)

- **Antenatal Corticosteroids (ACS):** Standard of care.
    - *Indication:* Threatened preterm labor between 24 and 34 weeks (AAP/ACOG: consider up to 36+6 weeks for late preterm).
    - *Regimen:* Betamethasone (12 mg IM, 2 doses, 24 hrs apart) OR Dexamethasone (6 mg IM, 4 doses, 12 hrs apart).
    - *Effect:* Accelerates pneumocyte maturation; reduces RDS, IVH, NEC, and neonatal mortality.
- **Tocolytics:** Used strictly to delay delivery by 48 hours to allow ACS effect.
- **Delivery Room (DR) Management:**
    - Delayed cord clamping (30–60 seconds) to improve transitional hemodynamics.
    - Avoid routine intubation; prophylactic early CPAP (5–8 cm H2O) via T-piece resuscitator starting in the DR.
    - Strict thermoregulation (polyurethane bags for <32 weeks).

Treatment: Respiratory Support

- **Primary Mode:** Continuous Positive Airway Pressure (CPAP) or Non-Invasive Positive Pressure Ventilation (NIPPV).
- **Target SpO2:** 90–95% (Avoid hyperoxia to prevent ROP/BPD).
- **Mechanical Ventilation (MV):** Indicated for CPAP failure.
    - *Failure criteria:* FiO2 >0.30–0.40 to maintain SpO2 >90%, pH <7.20, pCO2 >60–65 mmHg, or recurrent apnea.
    - *Modes:* Synchronized intermittent mandatory ventilation (SIMV) or High-frequency oscillatory ventilation (HFOV) as rescue.

Treatment: Surfactant Therapy

- **Preparation:** Natural (porcine/bovine) preferred over synthetic (faster weaning, lower mortality). Examples: Poractant alfa (200 mg/kg), Beractant (100 mg/kg).
- **Timing:** Early rescue (<2 hours of life) is superior to late rescue.
- **Indication:** Clinical RDS requiring CPAP with FiO2 >0.30 (European Consensus 2022 Update).
- **Administration Methods:**
    - *Now Preferred:* **LISA / MIST** (Less Invasive Surfactant Administration / Minimally Invasive Surfactant Therapy) via thin catheter while maintaining spontaneous breathing on CPAP.
    - *Alternative:* **INSURE** (INtubate, SURfactant, Extubate) if LISA unavailable/unsuccessful.

Treatment: Supportive Care

- **Fluids:** Restrict initially (60–80 mL/kg/day) to prevent PDA opening and pulmonary edema.
- **Antibiotics:** Ampicillin + Aminoglycoside (Gentamicin) until early-onset sepsis is ruled out.
- **Caffeine Citrate:** Load 20 mg/kg, maintenance 5-10 mg/kg/day. Routine use in <1250g or <30 weeks to prevent apnea, facilitate extubation, and reduce BPD.

Complications

- **Acute:** Air leak syndromes (pneumothorax, PIE), pulmonary hemorrhage, PDA, intraventricular hemorrhage (IVH).
- **Chronic:** Bronchopulmonary dysplasia (BPD), Retinopathy of prematurity (ROP), neurodevelopmental impairment.

Prognosis

- Excellent survival (>90%) for >28 weeks with timely ACS, CPAP, and surfactant.
- Diuresis at 48–72 hours marks the onset of clinical recovery and improving lung compliance.

Exam Summary: Must-Write Points

- **Pathognomonic CXR:** Reticulogranular (ground-glass) pattern with air bronchograms and low volumes.
- **Prevention Core:** Antenatal Betamethasone/Dexamethasone for threatened preterm delivery (24–34 weeks).
- **Initial Management:** Delivery room CPAP via T-piece; avoid routine endotracheal intubation.
- **Surfactant Rule:** Give early (<2 hrs) if FiO2 >0.30 on CPAP.
- **Latest Update:** LISA/MIST is the preferred method of surfactant delivery to avoid mechanical ventilation trauma.
- **Adjuvants:** Caffeine citrate for all very preterm infants to reduce apnea and BPD.

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16. Surfactant therapy in neonates

Subject: Neonatology

Basics & Composition

- **Source:** Secreted by Type II alveolar pneumocytes (starts at 20 weeks, peaks at 35 weeks).
- **Lipids (90%):** Dipalmitoylphosphatidylcholine (DPPC) is the primary surface-active component.
- **Proteins (10%):**
    - SP-A & SP-D: Hydrophilic (innate immunity, opsonization).
    - SP-B & SP-C: Hydrophobic (essential for rapid spreading and adsorption of lipids). *Note: SP-B deficiency is fatal.*

Mechanism of Action

- **Laplace's Law ($P = 2T/r$):** Surfactant decreases surface tension (T) as alveolar radius (r) decreases.
- **Physiologic effect:** Prevents end-expiratory alveolar collapse ⇒↑ Functional Residual Capacity (FRC) ⇒↑ lung compliance ⇒↓work of breathing.

Types of Surfactant

- **Natural (Animal-derived):** Contains SP-B and SP-C. Clinically superior (faster weaning, lower mortality).
    - *Porcine:* Poractant alfa (Curosurf) – higher phospholipid concentration, smaller volume needed.
    - *Bovine:* Beractant (Survanta), Calfactant (Infasurf).
- **Synthetic:** Protein-free (older, largely abandoned) or Protein-containing (Lucinactant/Surfaxin - contains synthetic SP-B analog).

Indications

- **Primary:** Respiratory Distress Syndrome (RDS) in preterm neonates.
- **Secondary (Off-label/Rescue):**
    - Meconium Aspiration Syndrome (MAS) – overcomes surfactant inactivation.
    - Pulmonary hemorrhage – replaces blood-inactivated surfactant.
    - Neonatal ARDS / Severe pneumonia.

Treatment Strategies & Updates

- **Prophylactic (at birth):** *Previously* routine for <26 weeks. *Now (European RDS Guidelines 2022):* Discouraged. Stabilization with early CPAP is preferred.
- **Early Rescue (Current Standard):** Administered within 1–2 hours of life if failing non-invasive ventilation.
    - *Threshold:* FiO$_2$ > 0.30 on CPAP pressure ≥6 cm H$_2$O to maintain SpO$_2$ 90-94%.
- **Late Rescue:** Given after 2 hours for established RDS (less effective).

Administration Methods

- **LISA / MIST (Less/Minimally Invasive Surfactant Therapy):**
    - *Current preferred method*.
    - Given via a thin catheter (e.g., Hobart, feeding tube) passed through vocal cords using direct laryngoscopy.
    - Infant remains spontaneously breathing on CPAP. Prevents positive pressure barotrauma.
- **INSURE (INtubate, SURfactant, Extubate):**
    - Intubate, give surfactant via ETT, brief PPV, and rapidly extubate to CPAP.
- **Traditional:** Given via Endotracheal Tube (ETT) in mechanically ventilated infants.

Dosage & Technique

- **Dose (Poractant alfa):** Initial dose 200 mg/kg (proven superior to 100 mg/kg for reducing need for redosing).
- **Subsequent doses:** 100 mg/kg (max 3 total doses, given 6–12 hours apart if still requiring intubation and high FiO$_2$).

- **Preparation:** Warm to room temperature naturally (do not artificially heat); do not shake (prevents frothing).

Complications

- **During administration:** Transient hypoxia, bradycardia, ETT blockage, unilateral administration (usually right mainstem ⇒asymmetric chest rise).
- **Post-administration:**
    - **Pulmonary Hemorrhage:** Rapid ↑ in lung compliance ⇒↓pulmonary vascular resistance ⇒massive Left-to-Right shunt via PDA.
    - **Air Leaks (Pneumothorax):** If ventilator Peak Inspiratory Pressure (PIP) is not rapidly down-titrated as compliance improves (Volutrauma).

Monitoring & Post-Care

- **Immediate:** Continuous SpO$_2$ and HR monitoring.
- **Ventilator weaning:** Must aggressively wean FiO$_2$ and PIP immediately after administration to prevent hyperoxia and barotrauma.
- **Efficacy markers:** Rapid drop in FiO$_2$ requirement, improved chest expansion, clearing of reticulogranular pattern on CXR.

Exam Summary: High-Yield Must-Writes

- **Key components:** DPPC (lipid) reduces tension; SP-B/C (proteins) aid spreading.
- **Current Guidelines (2022):** Early CPAP + Early Rescue (if FiO$_2$ > 0.30) has replaced routine prophylactic administration.
- **Preferred Delivery:** LISA/MIST (preserves spontaneous breathing, ↓BPD risk).
- **Dose:** Poractant alfa 200 mg/kg initial dose is superior.
- **Major Pitfall:** Failure to rapidly wean ventilator pressures post-administration leads to fatal pneumothorax or pulmonary hemorrhage.

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17. CPAP therapy in neonatal respiratory disorders

Subject: Neonatology

Definition & Mechanism

- **Definition:** Maintenance of continuous positive pressure throughout the respiratory cycle in a spontaneously breathing neonate.
- **Mechanism of Action:**
    - Splints upper airways (prevents obstructive apnea)
    - Prevents alveolar end-expiratory collapse
    - Increases Functional Residual Capacity (FRC)
    - Improves Ventilation/Perfusion (V/Q) matching

- Reduces Work of Breathing (WOB)
- Conserves endogenous surfactant
- Stimulates pulmonary stretch receptors (Hering-Breuer reflex), reducing central apnea

Indications

- **Preterm Infants:**
  - Respiratory Distress Syndrome (RDS) – *Current standard: Early prophylactic/rescue CPAP right from the delivery room*
  - Apnea of prematurity
  - Post-extubation facilitation (prevents extubation failure)
- **Term/Late Preterm Infants:**
  - Transient Tachypnea of the Newborn (TTNB)
  - Meconium Aspiration Syndrome (MAS) – mild to moderate
  - Pneumonia / Sepsis
- **Airway Abnormalities:** Tracheomalacia, bronchomalacia

Contraindications

- **Absolute:**
  - Congenital Diaphragmatic Hernia (CDH) – *Requires intubation; CPAP causes bowel distension in thorax*
  - Choanal atresia / Cleft palate
  - Untreated tension pneumothorax
  - Severe cardiovascular instability / shock
  - Absent spontaneous breathing / frequent severe apneas
- **Relative:** Tracheoesophageal fistula (TEF), severe abdominal wall defects (Gastroschisis/Omphalocele)

Delivery Systems & Interfaces

- **Pressure Generators:**
  - **Bubble CPAP (bCPAP):** Expiratory limb submerged in water. Bubbling creates stochastic resonance (oscillations) which improves gas exchange. *Most common and cost-effective.*
  - **Ventilator-derived CPAP:** Constant flow.
  - **Variable Flow CPAP (Infant Flow Driver):** Uses fluidic flip mechanism; reduces expiratory resistance.
- **Patient Interfaces:**
  - **Short binasal prongs:** *Gold standard interface.* Lowest resistance, highly effective.
  - **Nasal masks:** Often alternated with prongs to prevent pressure injuries.

- **Nasopharyngeal prongs:** Higher resistance, less commonly used.

Initiation & Management

- **Initial Settings:**
  - Pressure: Start at 5–6 cm H2O (Max: 8 cm H2O).
  - Flow: 5–8 L/min (to wash out CO2 and meet inspiratory demand).
  - FiO2: Titrate to maintain target SpO2 (90–95% for preterms; 90–97% for terms).
- **Supportive Care:**
  - Insert an open orogastric (OG) tube to vent the stomach (prevents "CPAP belly").
  - Provide heated and humidified gas (37°C, 100% relative humidity).
  - Use hydrocolloid barrier dressings to protect the nasal septum.
  - Ensure proper sizing of prongs (should fit snugly without blanching the nares).

CPAP Failure Criteria & Escalation

- *Indicates need for intubation or minimally invasive surfactant therapy (LISA/MIST/INSURE)*
- **Oxygenation failure:** FiO2 requirement > 0.30 (in preterms < 28 weeks) or > 0.40 (older preterms/terms) to maintain SpO2 > 90%.
- **Ventilation failure:** PaCO2 > 60–65 mmHg with respiratory acidosis (pH < 7.20).
- **Clinical failure:** Increased work of breathing (severe retractions, Silverman-Anderson score > 6), frequent apneas (>2 episodes requiring bag-and-mask ventilation).

Weaning

- **Criteria to start weaning:** Clinically stable, minimal retractions, FiO2 < 0.21–0.30.
- **Method:**
  - Gradually reduce pressure by 1 cm H2O every 12–24 hours.
  - Once at 4–5 cm H2O in room air (FiO2 0.21), trial off CPAP.
  - Can step down to High Flow Nasal Cannula (HFNC) if borderline stability.
  - *Do not wean FiO2 and Pressure simultaneously.*

Complications

- **Nasal trauma:** Septal necrosis, columellar injury, snub nose (*Most common complication*).
- **Pulmonary:** Air leaks (Pneumothorax, pneumomediastinum), overdistension leading to CO2 retention.
- **Gastrointestinal:** "CPAP belly" (gastric distension), feeding intolerance.
- **Neurological:** Altered cerebral blood flow if excessive PEEP decreases venous return.

Exam Summary

- **Core Principle:** CPAP maintains FRC and splints the airway in a *spontaneously breathing* neonate.

- **Delivery Room Standard:** Early Bubble CPAP is first-line for preterm RDS; reduces need for mechanical ventilation.
- **Surfactant Threshold (Update):** FiO2 > 30% on CPAP 6 cm H2O is the current trigger for surfactant administration via LISA/MIST.
- **Absolute Contraindications:** CDH, Choanal Atresia, Untreated Pneumothorax.
- **Highest Yield Interface:** Short binasal prongs.
- **Must-Do Clinical Step:** Always place an open OG tube to decompress the stomach.

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18. Meconium aspiration syndrome: pathophysiology and management

Subject: Neonatology

Basics

- **Definition:** Respiratory distress in a neonate born through meconium-stained amniotic fluid (MSAF) with compatible radiological findings.
- **Risk Factors:** Post-term gestation (>41 weeks), fetal hypoxia/distress, small for gestational age (SGA), maternal preeclampsia/hypertension.

Pathophysiology

- **Aspiration Mechanism:** Intrauterine hypoxia → fetal vagal stimulation → passage of meconium + deep fetal gasping → in-utero or intrapartum aspiration.
- **Airway Obstruction:**
    - *Complete:* Leads to distal atelectasis.
    - *Partial (Ball-Valve Effect):* Air enters during inspiration but is trapped during expiration → hyperinflation → high risk of air leaks (pneumothorax).
- **Chemical Pneumonitis:** Meconium contains bile salts and pancreatic enzymes → intense inflammatory response (IL-8, TNF-α) within 24–48 hours.
- **Surfactant Inactivation:** Free fatty acids and bile acids in meconium strip surfactant from alveoli and inhibit its function → microatelectasis.
- **Persistent Pulmonary Hypertension (PPHN):** Chronic intrauterine hypoxia + acute postnatal acidosis/hypoxia → pulmonary vasoconstriction → right-to-left shunting across Patent Ductus Arteriosus (PDA) and Foramen Ovale (PFO).

Clinical Features

- **General:** Meconium staining of umbilical cord, skin, and nail beds (indicates prolonged exposure).
- **Respiratory:** Early-onset tachypnea, prominent grunting, severe retractions, cyanosis.
- **Physical Exam:** Barrel-shaped chest (due to hyperinflation), crackles, and rhonchi on auscultation.

Diagnosis

- **Chest X-Ray (CXR):** Classic triad of patchy/coarse infiltrates, hyperinflation (flattened diaphragms), and alternating areas of atelectasis. High incidence of air leaks (pneumothorax/pneumomediastinum).
- **Arterial Blood Gas (ABG):** Hypoxemia, hypercapnia, and mixed respiratory-metabolic acidosis.
- **Echocardiography:** Gold standard to rule out congenital heart disease and confirm/quantify PPHN (elevated RV pressures, right-to-left shunt).

Management

- **Delivery Room Resuscitation (NRP 8th Ed, 2021 Update):**
  - *Update Flag:* Routine endotracheal intubation for tracheal suctioning in **non-vigorous** infants is **NO LONGER** recommended.
  - Initial steps: Warm, dry, stimulate, clear secretions from mouth and nose with a bulb syringe.
  - If apneic, gasping, or HR < 100 bpm: Initiate Positive Pressure Ventilation (PPV) immediately.
- **Supportive NICU Care:**
  - Minimal handling to avoid agitation (agitation worsens PPHN).
  - Adequate sedation and analgesia (e.g., Fentanyl, Morphine).
  - Maintain normothermia, normoglycemia, and correct acidosis.
- **Respiratory Support:**
  - *Targets:* Pre-ductal SpO2 90–95%, PaO2 55–80 mmHg, PaCO2 40–50 mmHg.
  - *Non-Invasive:* CPAP for mild-to-moderate work of breathing.
  - *Conventional Ventilation:* Use moderate PEEP (avoid high PEEP to prevent worsening air trapping/pneumothorax), short inspiratory times, and faster rates.
  - *High-Frequency Oscillatory Ventilation (HFOV):* Indicated for failure of conventional ventilation, severe air leaks, or severe PPHN.
- **Surfactant Therapy:**
  - Exogenous surfactant bolus (improves oxygenation, reduces need for ECMO).
  - *Surfactant lavage* (using dilute surfactant to wash out meconium) is used in some centers but requires specialized expertise.
- **PPHN Management:**
  - **Inhaled Nitric Oxide (iNO):** First-line pulmonary vasodilator; starting dose 20 ppm.
  - **Hemodynamic Support:** Maintain systemic blood pressure > pulmonary pressure to reverse shunting (use Dopamine, Epinephrine, or Hydrocortisone).
- **Rescue Therapy:**
  - **ECMO (Extracorporeal Membrane Oxygenation):** Indicated if Oxygenation Index (OI) > 40, refractory hypoxemia, or severe right heart failure.

Complications

- **Acute:** Pneumothorax (15–30%), Pulmonary hemorrhage, Hypoxic-Ischemic Encephalopathy (HIE) secondary to perinatal asphyxia.
- **Long-term:** Reactive airway disease (asthma-like symptoms in infancy), neurodevelopmental delays (related to HIE).

Prevention

- Avoid post-term deliveries (routine induction of labor at 41 weeks).
- Strict intrapartum fetal heart rate monitoring to detect and intervene for fetal hypoxia.
- *Note:* Routine amnioinfusion is **not** recommended for preventing MAS in MSAF, though it may be used to relieve umbilical cord compression.

Exam Summary

- **NRP 8th Ed Trap:** Do NOT routinely intubate/suction non-vigorous babies; start PPV immediately if HR < 100 or apneic.
- **Pathology Triad:** Ball-valve obstruction (air trapping), chemical pneumonitis, surfactant inactivation.
- **CXR Buzzwords:** Patchy infiltrates + hyperinflation + flattened diaphragms.
- **PPHN Link:** Hypoxia/acidosis causes pulmonary vasoconstriction; manage with iNO and systemic vasopressors to reverse right-to-left shunt.
- **ECMO Trigger:** Oxygenation Index (OI) > 40.

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19. Persistent pulmonary hypertension of newborn

Subject: Neonatology

Definition

- Failure of normal circulatory transition after birth
- Characterized by sustained elevated pulmonary vascular resistance (PVR) leading to right-to-left shunting across the ductus arteriosus (PDA) or foramen ovale (PFO)
- Results in severe hypoxemia without structural heart disease

Etiology

- **Maladaptation (Structurally normal lungs):** Meconium Aspiration Syndrome (MAS) [most common], RDS, pneumonia, sepsis, perinatal asphyxia
- **Maldevelopment (Hypoplastic lungs):** Congenital diaphragmatic hernia (CDH), oligohydramnios (Potter sequence), pleural effusions
- **Idiopathic (Primary PPHN):** Remodeling/hypertrophy of pulmonary vessels; associated with maternal SSRI use (3rd trimester) or NSAID use (premature ductal closure)

Pathophysiology

- High PVR → Pulmonary artery (PA) pressure exceeds systemic vascular resistance (SVR)

- Deoxygenated blood shunts Right-to-Left via PFO and/or PDA
- Profound systemic hypoxemia → Hypoxia and acidosis further increase PVR (vicious cycle)
- Right ventricular (RV) overload → RV failure and tricuspid regurgitation (TR)

Clinical Features

- **Profile:** Typically term or post-term infant (rare in preterm)
- **Presentation:** Severe cyanosis and respiratory distress within first 12–24 hours
- **Hallmark:** Hypoxemia out of proportion to chest X-ray findings (especially in idiopathic PPHN)
- **Cardiovascular:** Prominent/loud P2, systolic murmur of TR, right ventricular heave

Diagnosis

- **Pre- & Post-ductal SpO2:** >10% difference between right hand (pre-ductal) and lower limb (post-ductal)
- **ABG:** PaO2 gradient >20 mmHg between right radial (pre-ductal) and umbilical artery (post-ductal) lines
- **Hyperoxia Test:** PaO2 fails to rise >100 mmHg on 100% FiO2 (differentiates from parenchymal lung disease, but does not rule out cyanotic CHD)
- **Echocardiography (Gold Standard):**
    - Confirms structurally normal heart (rules out cyanotic CHD)
    - Demonstrates R-to-L or bidirectional shunting at PDA/PFO
    - Estimates PA pressures via TR jet velocity
    - Assesses RV function and septal flattening
- **Chest X-ray:** Variable; clear/black lungs (idiopathic) or patchy opacities (MAS/pneumonia)
- **Oxygenation Index (OI):** $(FiO_2 \times Mean Airway Pressure \times 100) / PaO_2$. Determines need for iNO (OI >15–25) or ECMO (OI >40)

Management

- **General & Supportive:**
    - Minimal handling and strict normothermia (cold stress increases PVR)
    - Adequate sedation and analgesia (fentanyl); avoid routine paralysis
    - Maintain normal hematocrit (>35-40%) to optimize oxygen delivery
- **Hemodynamic Support:**
    - Goal: Maintain systemic BP > PA pressure to reverse shunt
    - **First-line inotropes:** Dopamine or Epinephrine
    - **Vasopressin:** Emerging drug of choice to specifically raise SVR without raising PVR
- **Ventilation Strategy (Gentle Ventilation):**
    - *Previously:* Hyperventilation to induce alkalosis. *Now:* Contraindicated (causes cerebral ischemia and sensorineural hearing loss)

    - Target PaCO2: 40–50 mmHg; Target pH: 7.30–7.40
    - Target Pre-ductal SpO2: 90–95% (avoid hyperoxia, which causes oxidative stress)
    - High-Frequency Oscillatory Ventilation (HFOV): Indicated for severe parenchymal disease (MAS, RDS) to recruit lungs optimally
- **Pulmonary Vasodilators:**
    - **Inhaled Nitric Oxide (iNO):** Gold standard. Selective pulmonary vasodilator. Starting dose: 20 ppm.
    - **Sildenafil:** PDE-5 inhibitor. Enteral/IV. Used if iNO is unavailable, contraindicated, or for weaning off iNO.
    - **Milrinone:** PDE-3 inhibitor. Useful if associated with RV/LV dysfunction.
    - **Bosentan / Prostacyclins (Iloprost):** Refractory cases.

Rescue Therapy

- **ECMO (Extracorporeal Membrane Oxygenation):**
    - Indicated if OI > 40 despite maximal medical therapy and iNO
    - Reversible lung disease, gestational age > 34 weeks, weight > 2 kg, no major intracranial hemorrhage (ICH)

Complications & Prognosis

- **Short-term:** Pneumothorax, RV failure, systemic hypotension, pulmonary hemorrhage
- **Long-term:** Sensorineural hearing loss (SNHL) [requires strict audiology follow-up], neurodevelopmental delay, chronic lung disease / asthma

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Exam Summary: Must-Write Points

- **Pathognomonic sign:** Pre- and post-ductal SpO2 gradient >10% or PaO2 gradient >20 mmHg.
- **Gold standard investigation:** Echocardiography (proves R-to-L shunt, rules out cyanotic CHD).
- **Ventilation update:** Avoid hyperventilation; target normal PaCO2 (40-50) and pH (7.30-7.40) to prevent cerebral ischemia.
- **Definitive medical therapy:** Inhaled Nitric Oxide (iNO) at 20 ppm.
- **ECMO indication:** Oxygenation Index (OI) > 40.

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20. Neonatal sepsis: newer approaches to diagnosis and treatment

Subject: Neonatology

Definition & Basics

- **Early-Onset Sepsis (EOS):** Occurs ≤72 hours of life; vertical transmission (maternal genitourinary tract).

- **Late-Onset Sepsis (LOS):** Occurs >72 hours of life; horizontal transmission (nosocomial or community).

Etiology

- **EOS:** *E. coli* (most common in preterm), Group B Streptococcus (GBS - most common in term), *Listeria monocytogenes*, *Klebsiella*.
- **LOS:** Coagulase-negative *Staphylococcus* (CONS - most common in CLABSI), *Klebsiella*, *Acinetobacter*, *Candida*.

Clinical Features

- Non-specific: Lethargy, poor feeding, temperature instability (hypothermia more common in preterm).
- Systemic: Apnea, tachypnea, tachycardia/bradycardia, prolonged capillary refill time (CRT), mottling.

Newer Approaches to Risk Stratification

- **AAP Update (EOS Risk Calculator):** Kaiser Permanente Neonatal EOS Calculator is now widely recommended for infants ≥34 weeks.
- **Mechanism:** Uses multivariate modeling (gestational age, highest maternal temp, ROM duration, maternal GBS status, intrapartum antibiotics) combined with the neonate's clinical exam.
- **Goal:** Drastically reduces unnecessary empiric antibiotic usage and NICU admissions.

Diagnosis: Newer Approaches

- *Note: Blood culture remains the gold standard, but newer modalities offer rapid, targeted results.*
- **Molecular Diagnostics (Multiplex PCR):** e.g., BioFire FilmArray. Detects pathogen DNA and antimicrobial resistance genes (e.g., *mecA*, *vanA*) directly from blood within 1–2 hours.
- **MALDI-TOF MS:** Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry. Rapidly identifies bacterial/fungal species from positive culture broths within minutes.
- **Next-Generation Sequencing (NGS):** Cell-free DNA (cfDNA) sequencing; highly sensitive for culture-negative sepsis and fastidious organisms.
- **Advanced Biomarkers:**
    - **Procalcitonin (PCT):** Rises faster (within 2–4 hours) and is more specific for bacterial infection than CRP; useful for guiding antibiotic duration.
    - **Interleukin-6 (IL-6):** Extremely early marker (peaks at 2 hours); highly sensitive when combined with CRP.
    - **Neutrophil CD64 (nCD64):** Upregulated surface receptor during bacterial infection; very high negative predictive value.
    - **Presepsin:** Soluble CD14 subtype; rises early and correlates well with sepsis severity.

- **Predictive Monitoring: HeRO monitor** (Heart Rate Observation). Analyzes heart rate variability; detects transient decelerations/reduced variability 24 hours *before* clinical signs of LOS appear.

Management: Newer Approaches & Adjuncts

- *Conventional First-line:* Ampicillin + Gentamicin (EOS); Cefotaxime/Piperacillin-Tazobactam + Amikacin/Vancomycin (LOS, unit-specific).
- **Antimicrobial Stewardship (AMS):**
    - **Current Standard:** Discontinue empiric antibiotics at 36–48 hours if blood culture is sterile and the infant is clinically well.
    - **Avoid:** Prolonged empiric antibiotics (increases risk of NEC, fungal sepsis, and mortality).
- **Pentoxifylline:** Phosphodiesterase inhibitor; decreases TNF-alpha. Significant mortality reduction when used as an adjunct in preterm infants with severe sepsis.
- **Probiotics & Synbiotics:** *Bifidobacterium* and *Lactobacillus* strains. IAP/AAP acknowledge their role in preventing LOS and NEC in Very Low Birth Weight (VLBW) infants.
- **Lactoferrin:** Bovine lactoferrin supplementation reduces the incidence of LOS in preterm infants (antimicrobial and immunomodulatory properties).
- **Obsolete/Discouraged Therapies:**
    - **IVIG:** *Previously* used. *Now:* INIS trial proved no survival benefit; routine use is contraindicated.
    - **G-CSF/GM-CSF:** Routine use not recommended; reserved only for severe, refractory neonatal alloimmune neutropenia with concurrent sepsis.

Prevention

- **Intrapartum Antibiotic Prophylaxis (IAP):** Penicillin/Ampicillin for GBS-positive mothers or unknown status with risk factors (ROM >18h, maternal fever >100.4°F, preterm labor).
- **CLABSI Bundles:** Strict aseptic central line insertion, daily review of line necessity, early enteral feeding.

Exam Summary: Must-Write Points

- **Kaiser EOS Calculator:** Replaces traditional categorical risk algorithms (reduces antibiotic overuse in ≥34w infants).
- **Multiplex PCR & MALDI-TOF:** Game-changers for rapid pathogen identification and resistance gene detection.
- **Biomarkers:** PCT and nCD64 are superior to CRP for early diagnosis and guiding stewardship.
- **HeRO Monitor:** Early detection of LOS via abnormal heart rate variability.
- **Stewardship:** Strict discontinuation of antibiotics at 36-48h if cultures are negative.
- **Adjuncts:** Pentoxifylline is beneficial in preterm sepsis; IVIG is explicitly *not* recommended.

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21. Approach to bleeding neonate

Subject: Neonatology

Initial Assessment

- **Cardinal Rule:** Differentiate the "Sick" neonate from the "Well" neonate (determines etiology and urgency).
- **Primary Survey:** Assess airway, breathing, circulation, and signs of hypovolemic shock (tachycardia, poor perfusion, hypotension).

Etiology

1. The "Sick" Neonate

- **DIC:** Sepsis, severe birth asphyxia (HIE), extreme prematurity, NEC, shock.
- **Liver Failure:** Gestational alloimmune liver disease (GALD), severe TORCH infections, metabolic disorders (Galactosemia, Tyrosinemia).
- **Consumptive Thrombocytopenia:** Sepsis, Kasabach-Merritt syndrome (giant hemangioma), massive thrombosis.

2. The "Well" Neonate

- **Swallowed Maternal Blood:** Swallowed during delivery or from cracked maternal nipples during breastfeeding.
- **Vitamin K Deficiency Bleeding (VKDB):**
    - *Early (<24 hrs):* Maternal drugs (Phenytoin, Phenobarbital, Rifampin, Warfarin).
    - *Classic (2–7 days):* Inadequate milk intake, failure to receive prophylactic Vit K.
    - *Late (2–12 weeks):* Exclusively breastfed, undiagnosed cholestasis/malabsorption.
- **Immune Thrombocytopenia:**
    - *Neonatal Alloimmune Thrombocytopenia (NAIT):* Maternal antibodies against fetal platelet antigens (HPA-1a most common); mother has *normal* platelets.
    - *Maternal ITP/SLE:* Transplacental autoantibodies; mother has *low* platelets.
- **Inherited Coagulopathies:** Hemophilia A/B (Factor VIII/IX), von Willebrand disease (rarely presents in neonatal period), Factor XIII deficiency (umbilical stump bleeding).

Clinical Features

- **Type of Bleed:**
    - *Petechiae/Purpura/Mucosal:* Platelet defect or vascular fragility.
    - *Deep hematoma/Joints/Umbilical stump/Post-circumcision:* Coagulation factor deficiency.
    - *Oozing from puncture sites/Widespread bleeding:* DIC.
- **Maternal History:** Anticonvulsants/anti-TB drugs (Early VKDB), low platelets (ITP), previous sibling with bleeding (NAIT, Hemophilia).

Diagnostic Approach

1. Bedside/Initial Tests

- **Apt Test (Alkali Denaturation Test):** Differentiates maternal vs. fetal blood in GI bleed. Add 1% NaOH to bloody stool/vomitus. Fetal Hb resists denaturation (stays pink); Adult Hb denatures (turns yellow/brown).
- **CBC & Peripheral Smear:** Assess platelet count, morphology (schistocytes in DIC), and WBC (sepsis).

2. Coagulation Profile (PT, aPTT, Fibrinogen)

- *Note: Neonatal physiological reference ranges are longer than adults (especially aPTT in preterms).*
- **Pattern Analysis:**
    - **Prolonged PT/aPTT + Low Platelets + Low Fibrinogen:** DIC.
    - **Prolonged PT/aPTT + Normal Platelets:** VKDB (Factors II, VII, IX, X) or Liver disease.
    - **Normal PT + Prolonged aPTT + Normal Platelets:** Hemophilia A/B, severe vWD.
    - **Normal PT/aPTT + Low Platelets:** NAIT, Maternal ITP, Sepsis (early).
    - **Normal PT/aPTT + Normal Platelets + Bleeding:** Factor XIII deficiency, platelet function defect (Glanzmann), swallowed maternal blood.

Management

1. Resuscitation & Supportive Care

- NPO, secure IV access.
- Treat hypovolemic shock: Normal Saline bolus (10-20 mL/kg), followed by O negative packed RBCs (10-15 mL/kg) if severe blood loss.
- Empiric Therapy: Administer **Vitamin K 1 mg IV/SC** immediately while awaiting lab results.

2. Targeted Blood Products

- **Fresh Frozen Plasma (FFP):** 10–15 mL/kg for DIC, liver disease, or severe VKDB with active bleeding.
- **Cryoprecipitate:** 1-2 units/kg if Fibrinogen < 100 mg/dL (DIC).
- **Platelet Transfusion (IAP/NNF 2023 Guidelines):**
    - < 25,000/microL: Prophylactic in stable neonates.
    - < 50,000/microL: Active bleeding, sick neonate, or minor surgery.
    - < 100,000/microL: Major surgery (e.g., neurosurgery) or active CNS bleeding.

3. Specific Etiology Management

- **NAIT:** Transfuse washed maternal platelets or HPA-1a/5b negative matched platelets. IVIG (1 g/kg/day for 2 days) to neonate.
- **Hemophilia:** Specific recombinant factor replacement.
- **DIC:** Treat underlying cause (antibiotics for sepsis, cooling for HIE).

Prevention

- **Routine Vitamin K Prophylaxis (WHO/IAP):**

  - Birth weight > 1500g: 1 mg IM at birth.
  - Birth weight < 1500g: 0.5 mg IM at birth.
- **Antenatal:** IVIG to mothers with known history of NAIT in previous pregnancies.

Exam Summary

- **Sick vs Well:** Crucial first step; Sick = DIC/Sepsis; Well = VKDB, NAIT, Hemophilia.
- **Apt Test:** Alkali denaturation; pink = fetal blood, yellow/brown = maternal blood.
- **Coag Patterns:** Low Plt + Prolonged PT/aPTT = DIC; Normal Plt + Prolonged PT/aPTT = VKDB.
- **NAIT Clue:** Mother has normal platelets; firstborn can be affected; severe neonatal thrombocytopenia.
- **Empiric Rx:** Always give 1 mg Vit K IV/SC to any bleeding neonate pending investigations.

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22. Necrotizing enterocolitis

Subject: Neonatology

Definition

- Acquired, life-threatening gastrointestinal emergency of the neonate characterized by ischemic and inflammatory necrosis of the bowel (primarily terminal ileum and proximal colon).

Risk Factors

- **Prematurity:** Inverse relationship with gestational age and birth weight (highest risk in ELBW/VLBW).
- **Enteral Feeding:** Formula feeding (risk is 6–10x higher compared to exclusive human milk).
- **Ischemic/Hypoxic Insults:** Perinatal asphyxia, severe RDS, PDA, congenital heart disease, umbilical catheterization.
- **Microbial Dysbiosis:** Prolonged empiric antibiotics, H2 blockers.

Pathophysiology

- **Classic Tetrad:** Immature gut barrier + Enteral feeds + Dysbiosis + Hypoxic-ischemic insult.
- **Mechanism:** Insult triggers exaggerated inflammatory response via Toll-like receptor 4 (TLR-4) → breakdown of mucosal barrier → bacterial translocation → coagulative necrosis → gas production by bacteria in bowel wall (pneumatosis) → transmural necrosis and perforation.

Clinical Features

- **Onset:** Typically occurs in the 2nd to 3rd week of life in preterm infants (inversely proportional to gestational age; later onset in extreme preemies).
- **Gastrointestinal:**
  - Feeding intolerance (earliest sign)
  - Abdominal distension (most common sign)
  - Bilious gastric aspirates/emesis

- Grossly bloody stools (hematochezia)

- **Systemic:** Apnea, bradycardia, temperature instability, lethargy, poor perfusion.
- **Red Flags (Impending/Actual Perforation):** Abdominal wall erythema/bluish discoloration, palpable mass, fixed dilated loop, severe shock.

Diagnosis

- **Abdominal X-Ray (AXR):** *Gold Standard*. Requires AP and Left Lateral Decubitus views.
  - *Early:* Diffuse distension, asymmetric bowel loops, ileus.
  - *Definite:* **Pneumatosis intestinalis** (pathognomonic; bubbly/linear radiolucencies in bowel wall).
  - *Severe:* Portal venous gas (branching lucencies over the liver).
  - *Perforation:* Pneumoperitoneum (Football sign, Rigler sign, falciform ligament sign).
- **Bowel Ultrasound (Point-of-Care USG):**
  - *Emerging standard:* Highly sensitive for early detection.
  - Findings: Bowel wall thickening/thinning, absent peristalsis, absent perfusion on color Doppler (necrosis), intramural gas (echogenic dots).
- **Laboratory Findings:**
  - *Hematology:* Severe thrombocytopenia (rapid drop indicates bowel gangrene), neutropenia, elevated CRP/Procalcitonin.
  - *Biochemistry:* Refractory metabolic acidosis, hyponatremia.
  - *Microbiology:* Blood and stool cultures (commonly *E. coli*, *Klebsiella*, *Clostridium*).

Staging (Modified Bell's Criteria)

- **Stage I (Suspected):** Mild systemic signs, feeding intolerance. AXR shows non-specific ileus.
- **Stage II (Definite):**
  - *IIA:* Mildly ill + Pneumatosis intestinalis.
  - *IIB:* Moderately ill + Metabolic acidosis/Thrombocytopenia + Portal venous gas.
- **Stage III (Advanced):**
  - *IIIA:* Severe shock, DIC, intact bowel.
  - *IIIB:* Pneumoperitoneum (Bowel perforation).

Management

- **Medical Management (Bell's Stage I, II, and IIIA):**
  - **NPO:** Immediately stop all enteral feeds.
  - **Decompression:** Insert large-bore double-lumen (Replogle) orogastric tube on continuous low suction.
  - **IV Antibiotics:** Broad-spectrum for 7–14 days (e.g., Ampicillin + Gentamicin + Metronidazole/Clindamycin for anaerobic coverage).

    - **Supportive:** TPN, strict fluid/electrolyte management, correct acidosis, inotropes for shock, platelet transfusions.

- **Surgical Management:**
    - **Absolute Indication:** Pneumoperitoneum (Stage IIIB).
    - **Relative Indications:** Clinical deterioration despite maximal medical therapy, fixed dilated loop on serial AXRs, abdominal wall erythema, portal venous gas.
    - **Procedures:**
        - *Primary Peritoneal Drainage (PPD):* Bedside procedure; preferred for extremely unstable, ELBW (<1000g) infants as a temporizing measure.
        - *Exploratory Laparotomy:* Resection of necrotic bowel with creation of proximal enterostomy and distal mucous fistula (standard of care for stable infants). Primary anastomosis is rarely performed due to risk of leak.

Complications

- **Early:** Septic shock, DIC, massive hemorrhage.
- **Late:**
    - **Intestinal Strictures:** (10-20%) Most common late complication; typically occurs in the colon 2-3 weeks post-recovery. Suspect if feeding intolerance recurs.
    - **Short Bowel Syndrome:** Leading to malabsorption and TPN dependence.
    - **TPN-associated Cholestasis.**
    - **Neurodevelopmental Impairment:** Significant risk of cerebral palsy and cognitive delays due to systemic inflammatory response.

Prevention

- **Exclusive Human Milk Feeding:** Breast milk (especially colostrum) provides secretory IgA, lactoferrin, and growth factors. Use pasteurized donor human milk if mother's milk is unavailable.
- **Feeding Protocols:** Standardized, slow advancement of enteral feeds (though recent trials suggest rapid advancement does not increase NEC risk, standard protocols reduce incidence).
- **Antenatal Corticosteroids:** Accelerates gut maturation.
- **Probiotics:**
    - *AAP 2021 Update:* Routine use of probiotics in ELBW infants is **NOT** recommended due to the risk of probiotic-associated sepsis and lack of FDA-regulated pharmaceutical-grade products.

Exam Summary

- **Classic Triad:** Abdominal distension + Bilious aspirates + Bloody stools in a premature neonate.
- **Pathognomonic Sign:** Pneumatosis intestinalis on AXR.
- **Absolute Surgical Indication:** Pneumoperitoneum (Bell's Stage IIIB).

- **Best Prevention:** Exclusive human milk feeding.
- **Most Common Late Complication:** Intestinal strictures (requires contrast enema prior to stoma closure).

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23. Role of probiotics in neonates and children

Subject: Neonatology

Definition & Basics

- **Probiotics:** Live microorganisms that confer a health benefit to the host when administered in adequate amounts.
- **Prebiotics:** Nondigestible food ingredients (e.g., oligosaccharides) that selectively stimulate beneficial gut bacteria.
- **Synbiotics:** Synergistic combination of pro- and prebiotics.
- **Core Principle:** Efficacy is highly **strain-specific** and **disease-specific**; effects cannot be generalized across different species or strains.

Mechanisms of Action

- **Barrier Enhancement:** Upregulates tight junction proteins (claudins, occludins) and increases mucin secretion.
- **Competitive Exclusion:** Competes with pathogens for binding sites and nutrients on intestinal epithelium.
- **Antimicrobial Production:** Secretes bacteriocins, defensins, and short-chain fatty acids (SCFAs) lowering luminal pH.
- **Immune Modulation:** Stimulates Secretory IgA (sIgA) production, enhances regulatory T-cells (Tregs), and shifts Th2 (allergic) to Th1 response.

Neonatal Applications

- **Necrotizing Enterocolitis (NEC) Prevention:**
    - Reduces incidence of Stage ≥2 NEC, late-onset sepsis (LOS), and all-cause mortality in preterm infants.
    - *Strains:* Combination of *Bifidobacterium infantis*, *B. lactis*, and *Lactobacillus acidophilus* shows highest efficacy.
    - **AAP 2021 Update:** Cautions *against* routine use in extremely preterm (<1000g) infants due to lack of FDA-regulated pharmaceutical-grade products and risk of probiotic-associated sepsis.
    - **ESPGHAN 2020:** Conditionally recommends specific strains for NEC reduction if high-quality products are locally available.
- **Enteral Feeding:** Reduces time to reach full enteral feeds.
- **Infantile Colic:**
    - *Lactobacillus reuteri* (DSM 17938) significantly reduces crying time in **exclusively breastfed** infants.

- Ineffective in formula-fed infants.

Pediatric Applications

- **Acute Gastroenteritis (AGE):**
  - Reduces duration of diarrhea by ~24 hours if started early.
  - *First-line strains: Lactobacillus rhamnosus* GG (LGG) and *Saccharomyces boulardii*.
- **Antibiotic-Associated Diarrhea (AAD) Prevention:**
  - Co-administration with antibiotics reduces AAD risk.
  - *First-line strains: LGG* or *S. boulardii*.
- **Clostridioides difficile Infection (CDI):**
  - *S. boulardii* is used as an adjunct to standard antibiotics to prevent recurrence.
- **Irritable Bowel Syndrome (IBS):**
  - Improves global symptoms and abdominal pain (specifically *LGG* and *VSL#3* multi-strain).
- **Allergy & Atopy:**
  - Maternal (prenatal) and infant (postnatal) supplementation may reduce the incidence of atopic dermatitis (eczema).
  - No proven benefit for asthma or allergic rhinitis prevention.

Highly Tested Strain-Specific Associations

- **LGG:** AGE, AAD prevention.
- **Saccharomyces boulardii:** AAD, *C. difficile* diarrhea (Note: it is a yeast, not affected by antibiotics).
- **Lactobacillus reuteri:** Infantile colic (breastfed).
- **VSL#3 (8-strain mixture):** Ulcerative colitis (pouchitis maintenance), IBS.
- **Bifidobacterium + Lactobacillus combinations:** NEC prevention in preterms.

Contraindications & Red Flags

- **Central Venous Catheters:** High risk of fungemia (*S. boulardii*) or bacteremia.
- **Immunocompromised State:** Primary immunodeficiencies, active chemotherapy, post-transplant.
- **Structural Heart Disease:** Risk of endocarditis.
- **Short Bowel Syndrome:** Risk of D-lactic acidosis (from *Lactobacillus* species) and bacterial overgrowth.
- **Critically Ill/ICU Patients:** Risk of transmigration across compromised gut barrier.

Exam Summary

- **Rule of Thumb:** Probiotic efficacy is strictly **strain-specific** and **dose-dependent**.

- **AAP 2021 Trap:** Routine use in ELBW (<1000g) is currently *not* recommended by AAP due to fatal probiotic-sepsis reports from contaminated non-FDA regulated supplements.
- **Must-know matches:** *L. reuteri* = breastfed colic; *S. boulardii* = *C. diff*/AAD; *LGG* = AGE.
- **Major Contraindication:** Never give *S. boulardii* (yeast) to a child with a central line (risk of fatal fungemia).
- **Mechanism Buzzwords:** Competitive exclusion, SCFA production, sIgA stimulation, tight junction enhancement.

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24. Role of prenatal diagnosis in prevention of pediatric diseases

Subject: Neonatology

Definition & Goals

- **Definition:** Detection of structural, genetic, metabolic, or hematologic fetal abnormalities before birth.
- **Goals:** Enable informed decision-making, facilitate in-utero therapy, optimize delivery timing/location, and prepare for immediate postnatal resuscitation.

Indications for Prenatal Diagnosis

- Advanced maternal age (≥35 years)
- Previous child with chromosomal/genetic/metabolic disorder
- Parents are known carriers of a genetic trait (e.g., Thalassemia, SMA)
- Abnormal maternal serum screening or fetal ultrasound
- History of recurrent miscarriages
- Teratogen exposure (drugs, radiation, TORCH infections)

Diagnostic Modalities

- **Non-Invasive Screening:**
    - *First Trimester (11–13 weeks):* Combined test (Nuchal Translucency + PAPP-A + free β-hCG).
    - *Second Trimester (15–20 weeks):* Quadruple screen (AFP, hCG, Estriol, Inhibin-A).
    - *NIPT (Cell-free DNA):* **ACOG 2020 Update:** Recommended as an option for *all* pregnant women; highest sensitivity/specificity for Trisomies 21, 18, 13 and sex chromosome aneuploidies.
- **Non-Invasive Imaging:**
    - Targeted USG (Level II anomaly scan at 18–20 weeks).
    - Fetal Echocardiography (18–22 weeks) for structural heart defects.
    - Fetal MRI: For complex neurosonography (e.g., corpus callosum agenesis) and airway assessment.
- **Invasive Diagnostic (Confirmatory):**

- *Chorionic Villus Sampling (CVS):* 10–13 weeks (risk of limb reduction defects if done <10 weeks).
- *Amniocentesis:* 15–20 weeks (gold standard for karyotyping/microarray).
- *Cordocentesis (PUBS):* >18 weeks (rapid karyotype, fetal anemia assessment).

Role in Prevention & Management (Core)

1. Primary Prevention (Avoidance of Disease)

- **Preimplantation Genetic Testing (PGT):** IVF selection of unaffected embryos for known carrier parents (e.g., Cystic Fibrosis, Duchenne Muscular Dystrophy).
- **Medical Termination of Pregnancy (MTP):** Option offered for lethal anomalies (e.g., anencephaly, bilateral renal agenesis) or severe debilitating conditions (e.g., Trisomy 13/18, Tay-Sachs).
  - *Update (India):* MTP Amendment Act 2021 allows termination up to 24 weeks for severe anomalies; >24 weeks requires State Medical Board approval.

2. In-Utero Medical Therapy

- **Congenital Adrenal Hyperplasia (CAH):** Maternal dexamethasone starting <9 weeks prevents virilization of an affected female fetus.
- **Fetal Arrhythmias (SVT/Atrial Flutter):** Maternal administration of digoxin, flecainide, or sotalol.
- **Fetal Hypothyroidism/Goiter:** Intra-amniotic thyroxine injections to prevent airway obstruction and cretinism.
- **Neonatal Alloimmune Thrombocytopenia (NAIT):** Maternal IVIG and corticosteroids to prevent fetal intracranial hemorrhage.
- **Neural Tube Defects (NTDs):** Periconceptional folic acid (400 mcg/day or 4 mg/day for high-risk) is the ultimate prenatal prevention.

3. In-Utero Surgical Interventions

- **Twin-Twin Transfusion Syndrome (TTTS):** Fetoscopic laser photocoagulation of placental anastomoses.
- **Myelomeningocele (Spina Bifida):** Open or fetoscopic repair at 19–25 weeks. *(MOMS Trial: Halves the need for VP shunt and improves motor outcomes).*
- **Lower Urinary Tract Obstruction (LUTO):** Vesicoamniotic shunting for posterior urethral valves to prevent Potter sequence (pulmonary hypoplasia).
- **Congenital Diaphragmatic Hernia (CDH):** FETO (Fetoscopic Endoluminal Tracheal Occlusion) promotes lung growth.
- **Fetal Anemia (Rh Isoimmunization/Parvovirus):** Intrauterine blood transfusion via umbilical vein.

4. Optimization of Delivery & Postnatal Care

- **Tertiary Care Triage:** Planned delivery in a center with Level III/IV NICU and pediatric surgery (e.g., Gastroschisis, CDH).

- **EXIT Procedure (Ex Utero Intrapartum Treatment):** Maintenance of uteroplacental circulation while securing the fetal airway (e.g., large cervical teratoma, cystic hygroma).
- **Prostaglandin E1 (PGE1) Readiness:** Immediate postnatal infusion for prenatally diagnosed duct-dependent heart lesions (e.g., Transposition of Great Arteries, Hypoplastic Left Heart Syndrome) to prevent sudden cardiovascular collapse.
- **Avoidance of Trauma:** Planned elective Cesarean for massive fetal hydrocephalus, osteogenesis imperfecta, or large sacrococcygeal teratoma.

Ethical & Legal Pitfalls

- **PCPNDT Act (India):** Strict prohibition of prenatal sex determination to prevent female feticide.
- **Counseling:** Must be non-directive. Provide recurrence risks and connect parents with support groups.

Exam Summary: Must-Write Points

- **NIPT** is the most sensitive screening tool currently available for common aneuploidies.
- Prenatal diagnosis allows **in-utero medical therapy** (e.g., Dexamethasone for CAH, Digoxin for SVT).
- Allows **in-utero surgery** (e.g., Laser for TTTS, MOMS-protocol repair for Myelomeningocele).
- Enables the **EXIT procedure** for securing compromised fetal airways before cord clamping.
- Facilitates immediate postnatal life-saving interventions (e.g., **PGE1 for duct-dependent CHD**) and prevents unexpected catastrophic collapse in the delivery room.

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25. Diagnosis of fetal disease and prenatal diagnosis

Subject: Neonatology

Definition

- Identification of structural abnormalities, genetic syndromes, or physiological fetal compromises in utero.
- Divided into **Screening** (risk assessment) and **Diagnostic** (definitive confirmation) modalities.

Indications

- Advanced maternal age (≥35 years).
- Previous child with chromosomal anomaly, structural defect, or genetic disease.
- Parental carrier of genetic disorder (e.g., Thalassemia, balanced translocation).
- Abnormal maternal screening (biochemical or ultrasound).
- Maternal teratogen exposure (drugs, radiation, TORCH infections).
- Maternal disease (e.g., pre-gestational diabetes mellitus, SLE).

Non-Invasive Screening: Biochemical & cfDNA

- **First Trimester (11–13^{+6} weeks):**
    - *Dual Marker:* Pregnancy-Associated Plasma Protein A (PAPP-A) + free β-hCG.

- Combined with USG Nuchal Translucency (NT) for Trisomy 21 (T21), 18, 13 risk.

- **Second Trimester (15–20 weeks):**
  - *Quadruple Marker:* Maternal serum Alpha-Fetoprotein (MSAFP), β-hCG, Unconjugated Estriol (uE3), Inhibin-A.
  - *Pattern in T21:* High hCG/Inhibin-A; Low MSAFP/uE3 (Mnemonic: **HI** are **H**igh).
  - *High MSAFP:* Neural tube defects (NTD), abdominal wall defects, multiple gestation.
- **Non-Invasive Prenatal Testing (NIPT / cfDNA):**
  - *Timing:* From 10 weeks gestation.
  - *Mechanism:* Analyzes cell-free fetal DNA in maternal blood.
  - *Utility:* Highest sensitivity/specificity screening for T21, T18, T13, and sex chromosome aneuploidies.
  - *Caveat:* It is a *screening* test; positive results mandate invasive diagnostic confirmation.

Non-Invasive Imaging

- **Level I USG (11–13^{+6} weeks):** Viability, dating, chorionicity (twins), NT measurement, nasal bone presence.
- **Level II USG (18–22 weeks):** Targeted Imaging for Fetal Anomalies (TIFFA scan). Detailed structural survey.
- **Fetal Echocardiography (18–22 weeks):** Indicated for maternal pre-gestational DM, SLE, teratogen exposure, or suspicious routine USG.
- **Fetal Doppler:** Middle Cerebral Artery (MCA) peak systolic velocity (screens for fetal anemia/Rh isoimmunization); Umbilical artery (IUGR).
- **Fetal MRI:** Second/third trimester adjunct for brain anomalies (e.g., ventriculomegaly, corpus callosum agenesis), posterior fossa defects, and congenital diaphragmatic hernia (lung volume assessment).

Invasive Diagnostic Tests

- **Chorionic Villus Sampling (CVS):**
  - *Timing:* 10–13 weeks.
  - *Sample:* Placental tissue (reflects fetal genotype).
  - *Advantage:* Early diagnosis; allows earlier, safer termination if needed.
  - *Risk:* ~0.2% fetal loss; limb reduction defects if done <10 weeks. Cannot detect NTDs (no amniotic fluid).
- **Amniocentesis:**
  - *Timing:* 15–20 weeks.
  - *Sample:* Amniotic fluid (fetal desquamated cells, amniocytes).
  - *Utility:* Cytogenetics, amniotic fluid AFP/Acetylcholinesterase (for NTDs), viral PCR (CMV, Toxo).

  - *Risk:* ~0.1–0.3% fetal loss, PROM, chorioamnionitis.
- **Cordocentesis (Percutaneous Umbilical Blood Sampling - PUBS):**
  - *Timing:* >20 weeks.
  - *Sample:* Fetal blood from umbilical vein.
  - *Utility:* Rapid karyotyping, fetal Hb/hematocrit (anemia), fetal platelets (NAIT), specific IgM (infections).
  - *Risk:* Highest fetal loss rate (1–2%), cord hematoma, bleeding.

Advanced Genetic Analysis (Post-Invasive Procedure)

- **Karyotype:** Standard for numerical aneuploidies and large structural rearrangements. Turnaround: 1–2 weeks.
- **FISH (Fluorescence In Situ Hybridization):** Rapid (24–48 hours) for specific chromosomes (13, 18, 21, X, Y).
- **Chromosomal Microarray (CMA):**
  - *Update (ACOG/SMFM):* Recommended as **first-line** test for any fetus with structural anomalies on USG. Detects microdeletions/microduplications.
- **Whole Exome Sequencing (WES):** Used if CMA is non-diagnostic in a fetus with multiple structural anomalies.

Preimplantation Genetic Testing (PGT)

- Performed during IVF before embryo transfer (Day 5 blastocyst biopsy).
- *PGT-A:* Screens for Aneuploidy.
- *PGT-M:* Tests for specific Monogenic disorders (e.g., Cystic Fibrosis, Thalassemia).

Fetal Therapy & Management (Brief)

- **Medical:** Maternal dexamethasone for CAH (prevents virilization), anti-arrhythmics for fetal SVT (digoxin, flecainide).
- **Surgical:** Intrauterine transfusion (Rh isoimmunization), Laser photocoagulation (TTTS), open/fetoscopic spina bifida repair.
- **Termination:** Governed by local laws (e.g., India MTP Amendment Act 2021 allows termination up to 24 weeks for severe anomalies, and beyond 24 weeks with Medical Board approval).

Exam Summary: Must-Write Points

- **NIPT/cfDNA** is the most accurate *screening* test for common aneuploidies but requires invasive confirmation if positive.
- **CVS (10–13 wks)** allows early diagnosis but cannot detect NTDs; **Amniocentesis (15–20 wks)** is the standard diagnostic test.
- **Chromosomal Microarray (CMA)** is the current first-line genetic test for fetuses with structural ultrasound anomalies.
- Always distinguish clearly between *screening* (Dual/Quad marker, USG, NIPT) and *diagnostic* (CVS, Amnio, PUBS) modalities.

Infectious Diseases

26. Tuberculosis in children: limitations of diagnosis and management of extrapulmonary tuberculosis

Subject: Infectious Diseases

Definition & Etiology

- **Definition:** Tuberculosis involving organs other than the lung parenchyma (e.g., lymph nodes, pleura, CNS, abdomen, osteoarticular).
- **Etiology:** *Mycobacterium tuberculosis* complex.
- **Epidemiology:** Accounts for 20–30% of all pediatric TB cases; lymphadenitis is the most common EPTB site.

Pathophysiology

- **Mechanism:** Lymphohematogenous dissemination during primary pulmonary infection.
- **Seeding:** Bacilli lodge in highly vascular areas (Rich focus in CNS, subchondral bone, lymph nodes).
- **Activation:** Reactivation occurs due to immature immunity (age <5 years) or immunosuppression (HIV, malnutrition).

Clinical Features (Site-Specific)

- **Lymphadenitis:** Painless, progressively enlarging, matted cervical nodes; cold abscess or sinus tract formation.
- **CNS (TBM):** Prodrome (fever, irritability) → Meningitic phase (cranial nerve palsies [CN III, VI], vomiting) → Paralytic phase (coma, posturing).
- **Pleural:** Unilateral exudative effusion, pleuritic chest pain.
- **Abdominal:** "Doughy" abdomen, ascites, weight loss, intestinal strictures.
- **Osteoarticular:** Pott spine (gibbus deformity, paraplegia), monoarthritis (hip/knee).

Limitations of Diagnosis (Core Focus)

- **Paucibacillary Nature:** EPTB sites have extremely low bacterial loads; smear microscopy sensitivity is dismal (<10–20%).
- **Sample Acquisition:** Requires invasive, painful procedures (lumbar puncture, lymph node biopsy, joint aspiration); yielding adequate fluid volume in small children is difficult.
- **Molecular Test Limits:** Standard Xpert MTB/RIF has lower sensitivity in paucibacillary fluids (e.g., pleural fluid, CSF) compared to sputum.
- **Culture Delays:** Mycobacterial Growth Indicator Tube (MGIT) culture takes 2–6 weeks; treatment cannot be delayed in severe EPTB (e.g., TBM).
- **Biomarker Confounders:** Adenosine Deaminase (ADA) lacks specificity; false positives occur in pyogenic/viral infections and lymphomas.

- **Immunological Tests:** Mantoux/Tuberculin Skin Test (TST) and IGRA cannot differentiate latent TB infection (LTBI) from active EPTB; often falsely negative in severe EPTB due to anergy.
- **Imaging Non-specificity:** Ultrasound, CT, or MRI findings (e.g., basal exudates, ascites) are suggestive but never microbiologically confirmatory.

Diagnostic Approach (Overcoming Limitations)

- **WHO/IAP Latest Update: Xpert MTB/RIF Ultra** is the initial test of choice for CSF and tissue biopsies (higher sensitivity than standard Xpert for paucibacillary EPTB).
- **Histopathology:** Caseating granulomas on biopsy remain the gold standard when microbiology is negative.
- **Pleural/Ascitic Fluid:** Exudative, lymphocyte-predominant, high protein, ADA >40 IU/L.
- **CSF Analysis:** Cobweb coagulum, pleocytosis (100–500 cells, lymphocyte predominant), high protein (>100 mg/dL), low glucose (<40 mg/dL or <50% of blood glucose).

Management of EPTB

- **Principles:** Multidrug therapy, weight-band dosing, adherence support, adjunctive steroids for specific sites.
- **Regimens & Duration (WHO/NTEP Guidelines):**
    - **Standard EPTB (Lymph node, Pleural, Abdominal):** 6 months total.
        - Intensive Phase (IP): 2 months HRZE (Isoniazid, Rifampicin, Pyrazinamide, Ethambutol).
        - Continuation Phase (CP): 4 months HRE.
    - **Severe EPTB (CNS/TBM, Osteoarticular/Spine):** 12 months total.
        - Intensive Phase (IP): 2 months HRZE.
        - Continuation Phase (CP): 10 months HRE.
- **Adjunctive Corticosteroids:**
    - **Indications:** TBM and Tuberculous Pericarditis (mortality/morbidity benefit).
    - *Note:* Routine steroids are *no longer recommended* for pleural TB unless massive effusion causes severe respiratory distress.
    - **Dose:** Oral Prednisolone 2 mg/kg/day (or IV Dexamethasone 0.4 mg/kg/day) for 4 weeks, then taper over the next 4 weeks.
- **Surgical Interventions:**
    - **Lymph node:** Needle aspiration for fluctuant nodes (avoid I&D/excision to prevent chronic sinus tracts).
    - **CNS:** Ventriculoperitoneal (VP) shunt for communicating/obstructive hydrocephalus.
    - **Spine:** Decompression/stabilization if progressive neurological deficit, spinal instability, or lack of response to medical therapy.

Complications & Prognosis

- **Complications:** Hydrocephalus, stroke, intellectual disability (TBM); kyphosis, paraplegia (Pott spine); constrictive pericarditis; infertility (genital TB).
- **Prognosis:** Excellent for lymph node/pleural TB. Poor for TBM if treatment is delayed to Stage III (coma/paralytic phase).

Prevention

- **BCG Vaccine:** Highly effective (up to 80%) in preventing severe childhood EPTB (TBM and miliary TB).
- **TB Preventive Treatment (TPT):** Isoniazid for 6 months (6H) or Isoniazid + Rifapentine for 3 months (3HP) for all close pediatric contacts of infectious TB cases, after ruling out active disease.

Exam Summary: Must-Write Points

- **Major Diagnostic Limitation:** Paucibacillary nature combined with the need for invasive sampling makes microbiological confirmation rare.
- **Test of Choice:** Xpert MTB/RIF Ultra is preferred for CSF/tissue due to enhanced sensitivity.
- **Treatment Duration:** 6 months (2HRZE + 4HRE) for most EPTB; 12 months (2HRZE + 10HRE) for CNS and Bone TB.
- **Steroids:** Mandatory in TBM and TB pericarditis (Prednisolone 2 mg/kg/day for 4 weeks + 4 weeks taper).
- **Surgery Trap:** Never incise and drain a TB lymph node; aspirate only, to prevent chronic sinus formation.

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27. Drug resistant tuberculosis in children

Subject: Infectious Diseases

Definitions (WHO 2021 Updates)

- **Mono-resistant TB:** Resistance to one first-line anti-TB drug only.
- **Poly-resistant TB:** Resistance to >1 first-line drug, but *not* both Isoniazid (H) and Rifampicin (R).
- **MDR-TB:** Resistance to both Isoniazid (H) and Rifampicin (R).
- **RR-TB:** Rifampicin-resistant TB (managed identically to MDR-TB).
- **Pre-XDR-TB:** MDR/RR-TB + resistance to any Fluoroquinolone (FQ).
- **XDR-TB:** Pre-XDR-TB + resistance to at least one Group A drug (Bedaquiline or Linezolid). *(Update: Injectables removed from definition)*.

Risk Factors (When to Suspect)

- Close contact with a known MDR/RR-TB case (most common cause in children).
- Failure to improve clinically or radiologically after 2–3 months of first-line ATT.
- Sputum/gastric aspirate remains smear-positive after 2 months of ATT.

- Relapse, treatment failure, or treatment default.
- Child with TB living in a high MDR-TB prevalence setting.

Pathogenesis & Clinical Features

- **Pathogenesis:** Primarily transmitted from infectious adults; primary resistance is more common in children than acquired resistance. Pediatric TB is typically paucibacillary, making bacteriological confirmation difficult.
- **Clinical Features:** Identical to drug-susceptible TB but progressive.
- Unremitting fever, persistent cough, progressive weight loss/failure to thrive despite ATT.
- Worsening radiological signs (new consolidations, cavities, expanding lymphadenopathy, pleural effusions).

Diagnosis (WHO 2022 / NTEP Guidelines)

- **Specimen Collection:**
    - Gastric aspirate (fasting, 2–3 consecutive days).
    - Induced sputum (hypertonic saline).
    - **WHO 2022 Update:** Stool is now a validated, non-invasive sample for Xpert MTB/RIF in children.
    - Bronchoalveolar lavage (BAL), lymph node aspirate, or CSF for extrapulmonary TB.
- **Rapid Molecular Tests (First-line diagnostics):**
    - **CBNAAT (Xpert MTB/RIF) / Truenat:** Mandatory initial test for all pediatric TB suspects. Detects *M. tuberculosis* and Rifampicin resistance simultaneously (results in 2 hours).
- **Drug Susceptibility Testing (DST):**
    - **First-Line LPA (Line Probe Assay):** Detects H and R resistance mutations.
    - **Second-Line LPA:** Detects FQ resistance.
    - **Liquid Culture (MGIT):** Gold standard; required for phenotypic DST for newer drugs (Bedaquiline, Linezolid, Delamanid).
- **Clinical Diagnosis (Presumptive DR-TB):** If a child is symptomatic and in close contact with a proven DR-TB case, treat based on the *source case's DST pattern*, even if the child's samples are culture/Xpert negative.

Management (Current WHO & IAP/NTEP Principles)

- **Core Strategy:** Never add a single drug to a failing regimen. Use at least 4 effective drugs.
- **Major Update:** Injectable agents (Kanamycin, Amikacin, Capreomycin) are phased out due to severe ototoxicity. **All-oral regimens are the standard of care.**
- **Drug Grouping (WHO):**
    - **Group A (Include all 3):** Levofloxacin/Moxifloxacin, Bedaquiline, Linezolid.
    - **Group B (Add 1 or both):** Clofazimine, Cycloserine/Terizidone.

    - **Group C (Add to complete regimen):** Ethambutol, Delamanid, Pyrazinamide, PAS, Ethionamide.

- **Pediatric Age Updates (WHO 2022):**
    - **Bedaquiline (BDQ):** Now approved for *all* ages (Previously restricted to >6 years).
    - **Delamanid (DLM):** Now approved for *all* ages (Previously restricted to >3 years).
- **Standard Regimens:**
    - **Shorter All-Oral Regimen (9–11 months):** For MDR/RR-TB *without* FQ resistance or severe extrapulmonary disease.
        - *Intensive phase (4–6 months):* BDQ (for 6 mo) + Lfx/Mfx + Cfz + Z + E + H(high-dose) + Eto.
        - *Continuation phase (5 months):* Lfx/Mfx + Cfz + Z + E.
    - **Longer Individualized Regimen (18–20 months):** For Pre-XDR, XDR, or severe disseminated/CNS TB.
        - Constructed using all Group A drugs + 1-2 Group B drugs + Group C drugs to ensure at least 4 effective agents.

Monitoring & Complications

- **ECG Monitoring:** Mandatory at baseline and monthly. QTc prolongation is a major risk when combining BDQ, DLM, FQs, and Clofazimine (Stop if QTc >500 ms).
- **CBC Monitoring:** Biweekly, then monthly for Linezolid (risk of myelosuppression, anemia, thrombocytopenia).
- **Neurological:** Linezolid causes peripheral and optic neuropathy (limit duration to 6 months if possible). Cycloserine causes psychosis/seizures (give Pyridoxine).
- **Disease Complications:** Bronchiectasis, destroyed lung syndrome, cor pulmonale, death.

Prevention (TPT - Tuberculosis Preventive Treatment)

- **WHO/NTEP 2023 Update:** Asymptomatic child contacts of MDR/RR-TB patients must receive DR-TB preventive therapy after ruling out active disease.
- **Regimen:** Oral **Levofloxacin** daily for 6 months (often combined with Ethambutol depending on local guidelines/source DST).

Exam Summary

- **Definitions:** XDR-TB is now Pre-XDR + resistance to Group A drugs (Bedaquiline/Linezolid); injectables are no longer in the definition.
- **Diagnosis:** CBNAAT/Truenat is the mandatory first test. Stool Xpert is now validated for pediatric use.
- **Treatment:** All-oral regimens are standard. Injectables are obsolete due to hearing loss.
- **New Drugs:** Bedaquiline and Delamanid are now approved for *all* pediatric age groups.
- **Prophylaxis:** MDR-TB child contacts receive 6 months of Levofloxacin TPT.

28. ATT induced hepatitis in children

Subject: Infectious Diseases

Definition & Diagnostic Criteria

- **Drug-Induced Liver Injury (DILI)** secondary to first-line Anti-Tubercular Therapy (ATT).
- **Diagnostic Criteria (NTEP/WHO):**
    - ALT/AST >3× Upper Limit of Normal (ULN) **with** symptoms (anorexia, nausea, vomiting, abdominal pain) OR
    - ALT/AST >5× ULN **without** symptoms OR
    - Total Bilirubin >1.5 mg/dL (or clinical jaundice).
- *Trap:* Transient asymptomatic asymptomatic elevation of ALT (<3× ULN) is a common "adaptation" phenomenon (especially with Isoniazid) and does *not* require stopping ATT.

Etiology & Risk Factors

- **Culprit Drugs:** Pyrazinamide (Z) > Isoniazid (H) > Rifampicin (R).
- **Patient Risk Factors:**
    - Severe Acute Malnutrition (SAM) / Hypoalbuminemia.
    - Age <5 years or disseminated/severe TB.
    - Pre-existing liver disease (HBV, HCV, Wilson disease).
    - HIV co-infection or concurrent hepatotoxic drugs (e.g., Antiretrovirals, Acetaminophen).
    - Genetics: Slow acetylators (NAT2 gene polymorphism) accumulate toxic Isoniazid metabolites.

Pathophysiology

- **Isoniazid (H):** Hepatocellular necrosis via toxic metabolites (hydrazine and acetylhydrazine) binding to hepatic macromolecules.
- **Rifampicin (R):** Potent CYP450 enzyme inducer; accelerates production of toxic INH metabolites. Can also cause dose-independent cholestasis.
- **Pyrazinamide (Z):** Dose-dependent direct hepatocellular toxicity. Has the longest half-life and delayed recovery.

Clinical Features

- **Prodrome:** Anorexia (earliest sign), nausea, vomiting, unexplained lethargy, right upper quadrant pain.
- **Icteric Phase:** Scleral icterus, dark urine, pale stools, tender hepatomegaly.
- **Red Flags (Impending Acute Liver Failure):** Altered sensorium (encephalopathy), bleeding diathesis, shrinking liver span, hypoglycemia.

Diagnosis & Investigations

- **Liver Function Tests:** Total and direct bilirubin, ALT, AST, ALP, Serum Albumin.
- **Coagulation Profile:** PT/INR (most sensitive marker for acute synthetic dysfunction).

- **Rule Out Mimics:** Viral markers (IgM HAV, HBsAg, anti-HCV, IgM HEV), Dengue serology, Malaria smear.
- **Imaging:** USG Abdomen to rule out biliary obstruction, focal lesions, or pre-existing cirrhosis.

Management Algorithm (IAP/NTEP Guidelines)

- **1. Immediate Action:**
    - Stop *all* hepatotoxic drugs (H, R, Z) immediately upon clinical suspicion or lab confirmation.
- **2. Interim "Liver-Safe" Regimen:**
    - Do not leave severe TB untreated.
    - Start: **Streptomycin (S) + Ethambutol (E) + Fluoroquinolone (Levofloxacin/Moxifloxacin)**.
- **3. Monitoring:**
    - Clinical assessment and LFTs every 3–7 days.
    - Provide supportive care (IV fluids, dextrose for hypoglycemia, Vitamin K if PT prolonged).
- **4. Reintroduction Strategy:**
    - *Prerequisite:* Wait until symptoms resolve completely AND ALT <2× ULN AND Bilirubin normalizes.
    - *Method:* Sequential reintroduction, one drug at a time, spaced 3–7 days apart.
    - *Order of Reintroduction:* **Rifampicin → Isoniazid → Pyrazinamide**.
        - Start R (least hepatotoxic alone). If tolerated for 3-7 days, add H.
        - If H is tolerated, add Z.
    - *Modification:* If hepatitis was severe (ALF/encephalopathy), **do not** reintroduce Pyrazinamide. Continue modified regimen (e.g., 2HRE/7HR).

Complications

- Acute Liver Failure (ALF).
- Hepatic Encephalopathy.
- Acquired Coagulopathy.
- TB treatment failure, relapse, or acquired drug resistance due to treatment interruptions.

Prognosis

- Generally reversible if offending drugs are stopped promptly.
- Recovery from Pyrazinamide-induced hepatitis takes the longest.
- Progression to ALF carries a high mortality rate without liver transplantation.

Prevention

- **Baseline LFTs:** Mandatory for high-risk children (SAM, HIV, pre-existing liver disease) before starting ATT.

- **Dosing:** Strict adherence to weight-band dosing to prevent accidental overdose.
- **Counseling:** Educate parents to stop ATT and report immediately if the child develops vomiting, loss of appetite, or yellow eyes.

Exam Summary

- **Criteria:** Stop ATT if ALT >3× ULN with symptoms, ALT >5× ULN without symptoms, or Bilirubin >1.5 mg/dL.
- **Toxicity Rank:** Pyrazinamide > Isoniazid > Rifampicin.
- **Immediate Step:** Halt H, R, Z; start interim liver-safe regimen (S + E + Lfx).
- **Reintroduction:** Wait for ALT <2× ULN. Reintroduce sequentially: Rifampicin first, Isoniazid second. Avoid Pyrazinamide if prior hepatitis was severe.
- **Differentiation:** Do not stop ATT for asymptomatic, mild transaminitis (<3× ULN) as it reflects hepatic adaptation, primarily to Isoniazid.

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29. Scrub Typhus in children: clinical features and management

Subject: Infectious Diseases

Basics

- **Agent:** *Orientia tsutsugamushi* (an obligate intracellular Gram-negative bacterium).
- **Vector:** Larval stage (chigger) of Trombiculid mites.
- **Reservoir:** Rodents.
- **Epidemiology:** "Tsutsugamushi Triangle" (Asia-Pacific region, highly endemic in India, especially post-monsoon).

Pathophysiology

- **Inoculation:** Chigger bite → focal necrosis at bite site (eschar).
- **Dissemination:** Hematogenous and lymphatic spread.
- **Mechanism:** Targets endothelial cells and macrophages → widespread focal vasculitis and perivasculitis.
- **Consequence:** Increased capillary permeability, microvascular leakage, microinfarcts, and multiorgan dysfunction (MODS).

Clinical Features

- **Incubation Period:** 6–21 days.
- **Classic Triad:** Prolonged fever + Maculopapular rash + Eschar.
- **Fever:** High-grade, continuous, unresponsive to standard antipyretics or beta-lactams.
- **Eschar:**
    - Pathognomonic sign (seen in 20–50% of Indian children).

    - Painless, non-pruritic, punched-out ulcer with a black necrotic crust and erythematous halo.
    - **Exam Trap:** Must search hidden areas (groin, axilla, genitalia, behind ears, skin folds).
- **Rash:** Maculopapular, appears on day 4–5, starts on trunk and spreads to extremities.
- **Systemic Signs:** Regional lymphadenopathy (draining eschar site) progressing to generalized, hepatosplenomegaly.
- **Capillary Leak Signs:** Facial edema, pedal edema, ascites, pleural effusion.

Diagnosis

- **Basic Labs:**
    - Thrombocytopenia, leukopenia (early) or leukocytosis (late).
    - Transaminitis (elevated SGOT/SGPT), hypoalbuminemia.
    - Elevated CRP.
- **Serology:**
    - **IgM ELISA:** Investigation of choice in clinical practice. Highly sensitive/specific after day 5–7 of fever.
    - **IFA (Indirect Fluorescent Antibody):** Gold standard, but expensive and requires expertise.
    - **Weil-Felix Test:** Agglutination to *Proteus mirabilis* **OX-K** strain. Low sensitivity/specificity; historically significant but largely replaced by ELISA.
- **Molecular:** PCR of blood, buffy coat, or eschar tissue (useful in the first 5 days before antibodies form).

Management

- **First-Line Therapy:**
    - **Doxycycline:** 4.5 mg/kg/day in 2 divided doses (Max 200 mg/day).
    - **Update (AAP Red Book/IAP):** Doxycycline is the drug of choice for rickettsial diseases **even in children <8 years**. Short courses (<21 days) do not cause dental staining.
- **Alternative Therapy:**
    - **Azithromycin:** 10 mg/kg/day once daily (Max 500 mg/day).
    - *Indications:* Pregnant adolescents, known doxycycline allergy, or areas with documented *Orientia* doxycycline resistance (e.g., parts of Thailand/India).
- **Duration:** 7–10 days (or until at least 3 days after defervescence). Rapid defervescence within 48 hours of starting Doxycycline is highly suggestive of the diagnosis.
- **Severe/Complicated Cases (ICU):**
    - IV Doxycycline or IV Azithromycin.
    - IV Chloramphenicol (50–100 mg/kg/day) is a historical alternative for severe CNS disease.

- Supportive care for ARDS (mechanical ventilation) and shock (fluids, inotropes).

Complications

- **Pulmonary:** ARDS, interstitial pneumonia (most common cause of mortality).
- **Neurological:** Meningoencephalitis, seizures, cranial nerve palsies.
- **Renal:** Acute Kidney Injury (AKI).
- **Hematological:** Hemophagocytic Lymphohistiocytosis (HLH), DIC.
- **Cardiac:** Myocarditis.

Prognosis & Prevention

- **Prognosis:** Excellent with early treatment (defervescence in 24–48 hours). Mortality can reach 30% if untreated or complicated by ARDS/MODS.
- **Prevention:**
  - No vaccine available.
  - Avoid sitting/lying on bare ground or grass in endemic areas.
  - Use DEET-based insect repellents and permethrin-treated clothing.

Exam Summary

- **Buzzwords:** *Orientia tsutsugamushi*, chigger bite, painless black eschar in skin folds, Weil-Felix OX-K positive.
- **Pathology:** Endothelial invasion leading to generalized vasculitis and capillary leak.
- **Diagnosis:** IgM ELISA after day 5 of fever.
- **Treatment:** Doxycycline is first-line for all ages; rapid defervescence within 48h is characteristic. Azithromycin is the primary alternative.
- **Complications:** ARDS and meningoencephalitis are the primary causes of morbidity/mortality.

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30. Viral exanthems in children: clinical features and diagnosis, also briefly discuss measles and varicella

Subject: Infectious Diseases

VIRAL EXANTHEMS IN CHILDREN

Overview & Pathogenesis

- **Definition:** Widespread eruptive skin rash (exanthem) often accompanied by mucosal lesions (enanthem) occurring as a manifestation of a systemic viral infection.
- **Pathogenesis:** Results from either direct viral dissemination to the skin (e.g., Varicella, Enteroviruses) or an immune response/immune complex deposition in the skin (e.g., Measles, Parvovirus B19).

General Diagnostic Approach

- **Rash Morphology:** Maculopapular (Measles, Rubella), Vesicular (Varicella, HFMD), Petechial/Purpuric (Dengue, severe Enterovirus).
- **Rash Distribution:**
    - *Centrifugal* (spreads outward): Measles, Rubella.
    - *Centripetal* (concentrated on trunk): Varicella.
    - *Acral* (palms/soles): Hand-Foot-Mouth Disease (HFMD).
- **Fever-Rash Relationship:**
    - Rash *with* peak fever: Measles.
    - Rash *after* fever abruptly resolves: Roseola Infantum.

MEASLES (Rubeola / First Disease)

Etiology & Transmission

- **Agent:** RNA virus, *Paramyxoviridae* family (Morbillivirus).
- **Transmission:** Airborne respiratory droplets; highly contagious (R0 = 12–18).
- **Incubation:** 10–14 days.

Clinical Features

- **Prodrome (2–4 days):** High fever, and the "3 Cs": Cough, Coryza, Conjunctivitis.
- **Enanthem: Koplik spots** (pathognomonic) – 1mm grey-white "grains of sand" on an erythematous base on buccal mucosa opposite lower molars; appears 48h before rash, fades as rash peaks.
- **Exanthem:** Erythematous, maculopapular rash.
    - *Progression:* Cephalocaudal (starts at hairline/behind ears → face → trunk → extremities).
    - *Characteristics:* Confluent on face/trunk, discrete on extremities.
    - *Resolution:* Fades in the same order of appearance, leaving **branny desquamation** and brownish hyperpigmentation.

Diagnosis

- **Clinical:** Primarily clinical diagnosis in endemic areas.
- **Confirmation:** Measles-specific IgM antibodies in serum (detectable >3 days post-rash).
- **Molecular:** RT-PCR of throat/nasopharyngeal swab or urine.

Management

- **Supportive:** Antipyretics, hydration, nutritional support.
- **Specific Therapy: Vitamin A** (reduces morbidity, blindness, and mortality).
    - *Dosing (Days 1 and 2):* <6 months: 50,000 IU; 6–11 months: 100,000 IU; ≥12 months: 200,000 IU. Give a 3rd dose on Day 14-28 if clinical signs of Vitamin A deficiency exist.

Complications

- **Respiratory:** Pneumonia (Giant cell/Hecht pneumonia or secondary bacterial) – **most common cause of death**.
- **ENT:** Otitis Media (**most common overall complication**).
- **CNS:** Acute disseminated encephalomyelitis (ADEM), Subacute sclerosing panencephalitis (SSPE – late, fatal neurodegenerative complication occurring 7–10 years later).

Prevention

- **Vaccine:** Live-attenuated (MR or MMR).
    - *IAP/NIS Schedule:* 9 months, 15 months, and 4–6 years.

VARICELLA (Chickenpox)

Etiology & Transmission

- **Agent:** Varicella-Zoster Virus (VZV / HHV-3).
- **Transmission:** Aerosolized droplets and direct contact with vesicular fluid.
- **Incubation:** 14–21 days.

Clinical Features

- **Prodrome:** Mild fever, malaise, anorexia (1–2 days before rash).
- **Exanthem:**
    - *Distribution:* Centripetal (starts on trunk/scalp → spreads to face and extremities). Spares palms/soles.
    - *Evolution:* Macule → Papule → Vesicle ("dew drop on a rose petal") → Pustule → Crust.
    - *Pathognomonic:* **Pleomorphism** (lesions in all stages of development are present simultaneously). Highly pruritic.

Diagnosis

- **Clinical:** Classic pleomorphic rash.
- **Bedside:** Tzanck smear (shows multinucleated giant cells – low sensitivity/specificity).
- **Gold Standard:** PCR of vesicular fluid.

Management

- **Supportive:** Calamine lotion, oral antihistamines for pruritus. Daily bathing to prevent secondary infection.
- **Contraindication:** Avoid salicylates (Aspirin) due to risk of **Reye syndrome**. Avoid NSAIDs (increases risk of severe necrotizing skin infections).
- **Antiviral (Oral Acyclovir 20mg/kg/dose QID for 5 days):** Start within 24 hours of rash onset.
    - *Indications (AAP Guidelines):* Age >12 years, chronic cutaneous/pulmonary disease, long-term salicylate therapy, short, intermittent, or aerosolized corticosteroids.
    - *IV Acyclovir:* Immunocompromised patients, severe complications (pneumonia, encephalitis).

Complications

- **Skin:** Secondary bacterial infection (Group A Strep/Staph aureus) – **most common**.
- **CNS:** Acute cerebellar ataxia (1 in 4000; benign, self-resolving), Encephalitis.
- **Respiratory:** Varicella pneumonia (more common in adults and immunocompromised).

Prevention

- **Vaccine:** Live-attenuated (given at 15 months and 4-6 years per IAP).
- **Post-Exposure Prophylaxis (PEP):**
    - *Vaccine:* Within 3–5 days of exposure for susceptible healthy individuals.
    - *Varicella Zoster Immune Globulin (VZIG):* Within 10 days of exposure for high-risk individuals (immunocompromised, pregnant women, premature infants, newborns whose mothers developed varicella 5 days before to 2 days after delivery).

OTHER HIGH-YIELD EXANTHEMS (Brief Overview)

- **Rubella (German Measles):** Maculopapular rash lasting 3 days. Tender postauricular/suboccipital lymphadenopathy. Forschheimer spots (petechiae on soft palate). Risk of Congenital Rubella Syndrome (CRS).
- **Erythema Infectiosum (Fifth Disease):** Parvovirus B19. "Slapped cheek" appearance followed by a lacy, reticular rash on extremities. Can cause aplastic crisis in chronic hemolytic anemias (e.g., Sickle cell).
- **Roseola Infantum (Sixth Disease):** HHV-6 and HHV-7. High fever for 3–4 days; rash appears *only after* fever drops abruptly. Frequently associated with febrile seizures.
- **Hand, Foot, and Mouth Disease (HFMD):** Coxsackievirus A16, Enterovirus A71. Painful oral ulcers + vesicles on palms, soles, and buttocks.

EXAM SUMMARY (Must-Write Points)

- **Measles triad:** Cough, coryza, conjunctivitis + Koplik spots. Rash spreads cephalocaudally; desquamates.
- **Vitamin A:** Mandatory in measles management to reduce mortality and blindness.
- **Varicella hallmark:** Centripetal, pleomorphic rash (macules, vesicles, crusts simultaneously).
- **Acyclovir in Varicella:** Not for healthy children <12 years; reserved for teens, adults, and high-risk groups (start <24h).
- **Reye Syndrome warning:** Never use Aspirin for fever control in Varicella (or Influenza).
- **Roseola clue:** Rash appears *after* defervescence.

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31. Dengue classification clinical manifestations and laboratory diagnosis

Subject: Infectious Diseases

Basics & Etiology

- **Agent:** Dengue virus (DENV 1, 2, 3, 4); single-stranded RNA Flavivirus.
- **Vector:** *Aedes aegypti* (primary, day-biting, urban) and *Aedes albopictus*.
- **Incubation Period:** 3–14 days (typically 4–7 days).

WHO 2009 Classification *Previously classified as Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF), and Dengue Shock Syndrome (DSS). Now universally classified into 3 categories for better triage:*

- **Dengue without Warning Signs:** Fever with 2 of the following: nausea/vomiting, rash, aches/pains, tourniquet test positive, leukopenia.
- **Dengue with Warning Signs:** Requires strict observation and medical intervention.
- **Severe Dengue:** Defined by severe plasma leakage, severe bleeding, or severe organ impairment.

Clinical Manifestations (By Phase)

- **1. Febrile Phase (Days 1–3):**
    - Sudden onset high-grade fever (biphasic or "saddleback" pattern).
    - Severe headache, retro-orbital pain.
    - Myalgia and bone/joint pain ("Break-bone fever").
    - Transient macular/blanching rash.
    - Positive Tourniquet test (≥10 petechiae per square inch).
- **2. Critical Phase (Days 3–7):**
    - Begins at **defervescence** (temperature drops to 37.5–38°C); this is the most dangerous period.
    - Systemic vascular leak syndrome driven by endothelial dysfunction (not necrosis).
    - **Warning Signs (Must-write):**
        - Abdominal pain or tenderness.
        - Persistent vomiting.
        - Clinical fluid accumulation (pleural effusion, ascites).
        - Mucosal bleeding.
        - Lethargy, restlessness.
        - Liver enlargement >2 cm.
        - **Lab:** Concurrent ↑ Hematocrit (Hct) with rapid ↓ in Platelet count.
- **3. Recovery Phase (Days 7–10):**
    - Gradual reabsorption of extravascular fluid.
    - Classic rash: "Isles of white in a sea of red" (confluent erythematous rash with small spared islands).
    - Generalized pruritus, bradycardia, profound fatigue.

Severe Dengue Manifestations

- **Severe Plasma Leakage:** Leads to shock (DSS) or fluid accumulation with respiratory distress.
- **Severe Bleeding:** Evaluated by clinician (e.g., GI bleed, intracranial bleed).
- **Severe Organ Involvement:**
    - Liver: AST or ALT > 1000 U/L.
    - CNS: Impaired consciousness (Dengue encephalopathy).
    - Heart/Other: Myocarditis, acute kidney injury.

Laboratory Diagnosis

- **Specific Virological Tests (Timing is critical):**
    - **NS1 Antigen (ELISA/Rapid):** Test of choice for **Days 1–5**. Highly specific; confirms acute infection.
    - **RT-PCR:** Detects viral RNA (Days 1–5). Used for serotyping.
    - **IgM MAC-ELISA:** Becomes positive **after Day 5**. Test of choice in the late critical/recovery phase.
    - **IgG ELISA:** Indicates past infection. A high titer in the acute phase indicates a secondary dengue infection (highest risk for severe dengue).
- **Supportive Hematology & Biochemistry:**
    - **CBC:** Leukopenia (earliest sign) → Thrombocytopenia (<100,000/mm^3) → Rising Hematocrit.
    - **Hematocrit (Hct):** A rise of **≥20%** above baseline defines objective plasma leakage.
    - **Liver Function Tests:** Mild to moderate transaminitis; characteristically **AST > ALT**.
    - **Coagulation:** Prolonged aPTT/PT, hypofibrinogenemia in severe bleeding/DIC.
- **Imaging:**
    - **USG Abdomen: Gallbladder wall edema** (earliest sonographic sign of plasma leak), minimal ascites.
    - **Chest X-Ray:** Right-sided pleural effusion (most common).

Management Principles (Briefly)

- **Group A (Outpatient):** Adequate oral hydration (ORS), Paracetamol. *Contraindicated: NSAIDs, Aspirin, IM injections.*
- **Group B (Inpatient - Warning Signs):** Isotonic crystalloids (Normal Saline or Ringer's Lactate). Titrate IV fluids strictly to maintain urine output (0.5 ml/kg/hr) and stabilize Hct.
- **Group C (Severe Dengue/Shock):** Immediate fluid resuscitation (10–20 ml/kg bolus over 15–30 mins). Switch to Colloids (Dextran/Starch) if refractory. Blood transfusion only if significant overt or concealed bleeding (suspect if Hct drops without clinical improvement).

Complications

- Dengue Shock Syndrome (DSS).

- Hemophagocytic Lymphohistiocytosis (HLH) / Macrophage Activation Syndrome (MAS).
- Expanded Dengue Syndrome (unusual manifestations like transverse myelitis, Guillain-Barré syndrome, ARDS).

Exam Summary

- **Crucial transition:** The highest risk of shock occurs during *defervescence* (Days 3–4), not during peak fever.
- **Diagnostic trap:** Use NS1 Ag for Days 1–5; use IgM antibodies after Day 5.
- **Classic labs:** Leukopenia precedes thrombocytopenia; AST is typically higher than ALT.
- **Hallmark of severity:** Plasma leakage (evidenced by ≥20% Hct rise, ascites, pleural effusion, gall bladder wall edema), driven by secondary infection (antibody-dependent enhancement).

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32. Challenges of dengue vaccination

Subject: Infectious Diseases

Basics

- **Pathogen:** Dengue virus (DENV), *Flaviviridae* family, single-stranded RNA.
- **Serotypes:** 4 distinct serotypes (DENV 1–4).
- **Immunity:** Infection provides lifelong *homotypic* immunity (same serotype) but only transient (2–3 months) *heterotypic* immunity.

Immunological Challenges

- **Antibody-Dependent Enhancement (ADE):** The most critical hurdle. Non-neutralizing antibodies from a primary infection (or vaccination in a seronegative person) bind to a new serotype.
- **Mechanism of ADE:** Virus-antibody complex binds to Fcγ receptors on macrophages/monocytes → facilitates viral entry → massive viral replication → cytokine storm → Severe Dengue (DHF/DSS).
- **Vaccine as Primary Infection:** Vaccinating a seronegative individual sensitizes them; a subsequent wild-type infection acts as a "secondary" infection, triggering ADE.
- **Viral Interference:** In live-attenuated tetravalent vaccines, one serotype often replicates faster and dominates the immune response, leading to unbalanced protection.
- **Correlates of Protection:** Lack of a defined minimum neutralizing antibody titer that guarantees clinical protection.

Current Vaccines & Specific Hurdles

- **CYD-TDV (Dengvaxia - Sanofi):**
    - *Structure:* Recombinant yellow fever 17D backbone with DENV envelope proteins.
    - *Efficacy:* Poor against DENV-2.
    - *Major Trap:* Increased risk of severe dengue in seronegative children.
- **TAK-003 (Qdenga - Takeda) [WHO Prequalified 2024]:**

- *Structure:* Live-attenuated DENV-2 backbone with structural proteins of DENV 1, 3, 4.
- *Advantage:* Less risk to seronegatives; approved for ages ≥4 years.
- *Challenge:* Variable efficacy (high for DENV-1 & 2, much lower/uncertain for DENV-3 & 4).

Diagnostic & Operational Challenges

- **Pre-Vaccination Screening Strategy (WHO mandated for CYD-TDV):**
  - Must confirm past dengue infection before administering Dengvaxia.
  - *Hurdle:* Requires highly sensitive and specific point-of-care rapid diagnostic tests (RDTs).
  - *False Positives:* Vaccinating a false-positive (actually seronegative) puts them at risk of ADE.
- **Cross-Reactivity:** Flaviviruses (Zika, Japanese Encephalitis, Yellow Fever) cross-react on IgG serology, making accurate pre-screening difficult in endemic areas.
- **Age Restrictions:** Highest morbidity/mortality is often in infants and young children, but CYD-TDV is restricted to 9–45 years due to ADE risk in younger (predominantly seronegative) cohorts.
- **Waning Immunity:** Protection declines over time, potentially converting a protective antibody level into a sub-neutralizing level, theoretically increasing late ADE risk.

Current WHO / IAP Recommendations

- **CYD-TDV:** Recommended *only* in highly endemic areas for individuals 9–45 years with documented prior DENV infection (seropositive).
- **TAK-003:** WHO SAGE (2023) recommended introduction in settings with high dengue burden and transmission intensity for children aged 6–16 years (optimal age 9-12), without requiring pre-vaccination screening.

Exam Summary

- **Core problem:** Antibody-Dependent Enhancement (ADE) causes severe dengue if seronegative individuals are vaccinated and later naturally infected.
- **Formulation hurdle:** Achieving balanced, simultaneous tetravalent immunity without viral interference.
- **Screening hurdle:** Need for highly specific tests to exclude cross-reacting Flaviviruses before giving CYD-TDV.
- **Dengvaxia (CYD-TDV):** Yellow fever backbone; strictly for seropositives aged 9–45.
- **Qdenga (TAK-003):** DENV-2 backbone; pre-screening not required, approved ≥4 years, but shows variable efficacy across serotypes.

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33. Recent recommendations for treatment of chloroquine resistant malaria

Subject: Infectious Diseases

Basics & Mechanism

- **Definition:** Parasite survival/clearance failure despite standard chloroquine (CQ) therapy; universally expected in *P. falciparum* (Pf) and increasingly prevalent in *P. vivax* (Pv).
- **Mechanism:** Mutations in *PfCRT* (Chloroquine Resistance Transporter) gene in *P. falciparum*; *Pvmdr1* gene amplification in *P. vivax*.
- **Epidemiology:** CQ resistance in Pf is endemic globally (except parts of Central America/Caribbean). CQ-resistant Pv is prominent in Oceania, Southeast Asia, and parts of South America/India.

Clinical Clues

- **Uncomplicated:** Fever (tertian/quartan), chills, rigors, headache, myalgia, hepatosplenomegaly, mild anemia.
- **Severe (Red Flags):** Impaired consciousness (cerebral malaria), prostration, multiple convulsions, respiratory distress (ARDS), shock, clinical jaundice + vital organ dysfunction, significant bleeding.

Diagnosis

- **Microscopy:** Thick smear (quantification/parasitemia level), Thin smear (species identification).
- **Rapid Diagnostic Tests (RDT):**
    - Pf-specific: HRP-2 (Histidine-Rich Protein 2) – *Beware: HRP-2 gene deletions causing false negatives (emerging WHO update).*
    - Pan-species/Pv: pLDH (Plasmodium lactate dehydrogenase) or Aldolase.

Management: Uncomplicated CQ-Resistant Malaria

- **Standard of Care:** Artemisinin-based Combination Therapy (ACT) for 3 days.
- **WHO Recommended ACT Options:**
    - Artemether-Lumefantrine (AL) – *Most widely used globally.*
    - Artesunate-Amodiaquine (AS-AQ)
    - Artesunate-Mefloquine (AS-MQ)
    - Dihydroartemisinin-Piperaquine (DHA-PPQ)
    - Artesunate-Pyronaridine
- **CQ-Resistant *P. vivax*:** Treat acute attack with ACT (same as Pf) + Radical cure.
- **Radical Cure (Anti-relapse for Pv/Po):**
    - Primaquine: 0.25–0.5 mg/kg/day for 14 days.
    - *Mandatory:* G6PD testing prior to initiation to prevent severe hemolysis.
    - *Recent Update:* Tafenoquine (single dose) approved for ≥16 years (requires quantitative G6PD testing).

Management: Severe Malaria (All Species)

- **First-line:** Intravenous (IV) or Intramuscular (IM) Artesunate.

- **Dosing (WHO Update):**
    - Children < 20 kg: 3.0 mg/kg/dose.
    - Children ≥ 20 kg: 2.4 mg/kg/dose.
- **Schedule:** Administer at 0, 12, and 24 hours, then once daily until oral tolerance.
- **Step-down:** Must complete a full 3-day course of oral ACT once the child can swallow, even if 3 days of IV therapy were given.
- **Alternatives (if Artesunate unavailable):** IM Artemether or IV Quinine infusion (requires cardiac/glucose monitoring).

Special Populations & Updates

- **Infants < 5 kg:** ACTs are now recommended with dose optimization; AL is commonly used off-label with weight-band dosing.
- **Pregnancy (WHO 2022 Update):**
    - *Previously:* Quinine + Clindamycin in 1st trimester.
    - *Now:* ACT (specifically AL) is the preferred first-line treatment for uncomplicated Pf in the **first trimester**, matching 2nd/3rd trimester guidelines.
- **Chemoprophylaxis in CQ-Resistant Zones:** Atovaquone-Proguanil, Doxycycline (if >8 years), or Mefloquine. *CQ is contraindicated for prophylaxis in these regions.*

Complications

- Post-artesunate delayed hemolysis (PADH): Monitor hemoglobin 1–3 weeks post-treatment.
- Blackwater fever (massive intravascular hemolysis, hemoglobinuria, AKI).
- Hypoglycemia (disease-induced or quinine-induced hyperinsulinemia).

Prevention Updates

- **Vaccines (WHO Prequalified):**
    - RTS,S/AS01 (Mosquirix)
    - R21/Matrix-M (Recent addition, highly efficacious, lower cost).
    - *Indication:* Children living in regions with moderate to high Pf transmission.

Exam Summary

- **First-line uncomplicated:** Oral ACT (Artemether-Lumefantrine is standard) for 3 days.
- **First-line severe:** IV Artesunate (3 mg/kg for <20kg; 2.4 mg/kg for ≥20kg) at 0, 12, 24h → follow with full oral ACT course.
- **CQ-Resistant Vivax:** ACT for acute clearance + 14 days Primaquine (check G6PD!).
- **Major WHO Update:** ACT is now first-line even in the 1st trimester of pregnancy.
- **Trap:** Do not use monotherapy (Artesunate alone) for uncomplicated malaria to prevent artemisinin resistance.

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34. Enteric fever and nalidixic acid resistant salmonella

Subject: Infectious Diseases

Basics & Etiology

- **Pathogen:** *Salmonella enterica* serovar Typhi (most common) and Paratyphi A, B, C (Gram-negative bacilli).
- **Transmission:** Fecal-oral route (contaminated food and water).
- **Incubation period:** 10–14 days (range 3–21 days).

The NARST Concept (High-Yield)

- **Definition:** Nalidixic Acid Resistant *Salmonella Typhi*.
- **Mechanism:** Single point mutation in the *gyrA* gene (DNA gyrase).
- **Clinical Significance:** Serves as a surrogate marker for **Decreased Ciprofloxacin Susceptibility (DCS)**.
- **The Trap:** Isolates may appear "susceptible" to Ciprofloxacin on standard disc diffusion but will result in delayed clearance, prolonged fever, and **clinical treatment failure** if treated with standard doses of fluoroquinolones.
- **Update (CLSI):** Nalidixic acid disc testing is being phased out; current guidelines recommend testing directly for **Pefloxacin disc** or determining the **Ciprofloxacin MIC** (MIC ≥0.12 µg/mL indicates non-susceptibility).

Pathophysiology

- Ingestion → Crosses intestinal epithelium via M cells.
- Hypertrophy of Peyer's patches (terminal ileum).
- Phagocytosis by macrophages → Survives and multiplies intracellularly.
- Dissemination to Reticuloendothelial System (RES: liver, spleen, bone marrow) → **Primary bacteremia**.
- Re-enters bloodstream from RES → **Secondary bacteremia** (onset of clinical fever).

Clinical Features

- **Week 1 (Bacteremia):** Step-ladder pattern fever, headache, malaise, constipation (older children) or diarrhea (infants).
- **Week 2 (RES involvement):** Toxic look, relative bradycardia (Faget sign), coated tongue, hepatosplenomegaly.
- **Classic Rash:** Rose spots (blanching erythematous macules on the lower chest/abdomen) – appears late 1st week, lasts 2–3 days.
- **Week 3 (Complications):** Intestinal bleeding, perforation, encephalopathy.
- **Week 4:** Resolution or transition to chronic carrier state (gallbladder colonization).

Diagnosis

- **Blood Culture:** Gold standard. Highest yield in the 1st week (60-80%).

- **Bone Marrow Culture: Most sensitive** (>90%); remains positive up to 5 days even after starting antibiotics.
- **Stool/Urine Culture:** Yield increases in the 2nd and 3rd weeks.
- **Serology (Widal Test):** Historically used; detects O and H antibodies. High false-positive rate. Significant only if O titer >1:160 and H titer >1:320 in endemic areas. *Generally discouraged in modern practice.*
- **Typhidot:** Detects IgM/IgG against Outer Membrane Protein (OMP). Lacks specificity; not recommended by WHO for clinical decisions.
- **Lab Clues:** Leukopenia, eosinopenia (absence of eosinophils is a classic clue), mild transaminitis.

Management

Empiric therapy must account for local NARST and Multi-Drug Resistant (MDR) prevalence.

- **Uncomplicated Enteric Fever (Outpatient):**
  - **NARST / Fluoroquinolone-resistant (Current First-line): Azithromycin** (10–20 mg/kg/day OD for 7 days) OR **Cefixime** (20 mg/kg/day divided BD for 10–14 days).
  - *Fully Susceptible (Rare now):* Ciprofloxacin (15 mg/kg/day divided BD for 5–7 days).
- **Severe / Complicated / Inpatient:**
  - **First-line: IV Ceftriaxone** (75–100 mg/kg/day divided BD for 10–14 days).
  - **XDR Typhoid (Resistant to Ceftriaxone - emerging strain):** IV Meropenem + Oral Azithromycin.
- **Adjunctive Corticosteroids:**
  - **Indication:** Severe toxemia, shock, or typhoid encephalopathy (delirium, obtundation).
  - **Regimen:** IV Dexamethasone (3 mg/kg initial dose, followed by 1 mg/kg q6h for 48 hours). Reduces mortality significantly in severe cases.

Complications

- **Gastrointestinal:** Intestinal perforation (typically terminal ileum, requires surgical repair + broad-spectrum coverage for anaerobes), GI hemorrhage.
- **Neurological:** Typhoid encephalopathy, meningitis, Guillain-Barré syndrome.
- **Cardiovascular:** Toxic myocarditis.
- **Hepatobiliary:** Acalculous cholecystitis, hepatitis.
- **Carrier State:** >1 year of shedding; treated with prolonged high-dose Amoxicillin or Ciprofloxacin (if susceptible), or cholecystectomy if gallstones present.

Prevention (IAP 2023/2024 Updates)

- **Typhoid Conjugate Vaccine (TCV):**
  - **Current IAP Recommendation:** Single dose administered at **6–9 months** of age (routinely given with 6-month vaccines).

    - Provides T-cell dependent immunity, mucosal immunity, and herd protection. No booster currently required.

- *Vi-Polysaccharide Vaccine (Older):* Only for >2 years of age; requires booster every 3 years. Superseded by TCV.

Exam Summary (Must-Write Points)

- **NARST:** Marker for decreased ciprofloxacin susceptibility (*gyrA* mutation); leads to clinical failure if treated with standard fluoroquinolones.
- **Diagnostic Gold Standard:** Blood culture in Week 1; Bone marrow culture is the most sensitive overall and unaffected by early antibiotics.
- **First-line for NARST:** Oral Azithromycin or Cefixime (uncomplicated); IV Ceftriaxone (severe/complicated).
- **Steroid Use:** IV Dexamethasone is life-saving but strictly reserved for severe toxemia or encephalopathy.
- **Prevention Update:** TCV is the vaccine of choice, given as a single dose starting at 6 months of age.

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35. Influenza virus infection in children: clinical features and management

Subject: Infectious Diseases

Basics & Etiology

- **Agent:** Influenza virus (Family *Orthomyxoviridae*); enveloped, segmented, negative-sense ssRNA.
- **Types:** A and B cause human epidemics; C causes mild illness.
- **Surface Antigens:** Hemagglutinin (HA) mediates cellular entry; Neuraminidase (NA) mediates viral release.
- **Mutation patterns:**
    - *Antigenic Drift:* Minor point mutations causing seasonal epidemics (Types A & B).
    - *Antigenic Shift:* Major genetic reassortment causing pandemics (Type A only).

Pathophysiology

- **Transmission:** Droplet, aerosol, and fomite contact.
- **Incubation period:** 1–4 days.
- **Mechanism:** Virus replicates in ciliated respiratory epithelium → cellular necrosis, desquamation, and intense cytokine release (interferons/TNF) causing systemic symptoms.

Clinical Features

- **Classic Presentation:** *Abrupt onset* of high fever (up to 40°C), severe myalgia, headache, chills, and extreme malaise.
- **Respiratory:** Non-productive cough, sore throat, and coryza (often peak after systemic symptoms).

- **Pediatric Specifics:**
    - *Infants:* Sepsis-like presentation, poor feeding, or isolated apnea.
    - *GI Symptoms:* Nausea, vomiting, diarrhea, and abdominal pain are significantly more common in children than adults.
    - *Young children:* Often present with croup or bronchiolitis-like picture.

Diagnosis

- **RT-PCR (Multiplex):** Gold standard; highest sensitivity and specificity (nasopharyngeal swab).
- **Rapid Antigen Tests (RIDTs):** High specificity but low-to-moderate sensitivity (a negative test *does not* rule out influenza).
- **Laboratory findings:** Uncomplicated cases show leukopenia and relative lymphocytosis. Leukocytosis suggests secondary bacterial infection.

Management

- **Supportive Care:** Adequate hydration, rest, and antipyretics (Paracetamol/Ibuprofen).
- **Contraindication:** Absolute avoidance of Aspirin/salicylates due to the risk of Reye syndrome.
- **Antiviral Indications (AAP/IAP guidelines):**
    - Any child hospitalized with suspected/confirmed influenza.
    - Severe, complicated, or progressive illness.
    - High-risk children: Age <2 years, chronic pulmonary disease (asthma), hemodynamically significant congenital heart disease, immunosuppression, neurodevelopmental disorders.
- **Antiviral Agents:**
    - *Oseltamivir (PO):* Drug of choice. Best if started within 48 hours of symptom onset (but indicated beyond 48 hours in severe/hospitalized cases). Treatment duration is 5 days.
    - *Zanamivir (Inhaled):* Alternative for age ≥7 years; avoid in asthma/reactive airway disease.
    - *Baloxavir marboxil (PO):* **Update (AAP 2023):** Cap-dependent endonuclease inhibitor approved as a single-dose treatment for otherwise healthy children ≥5 years.

Complications

- **Respiratory:**
    - *Acute Otitis Media:* Most common complication (up to 50% of young kids).
    - *Secondary Bacterial Pneumonia:* Classic exam association with *Staphylococcus aureus* (including MRSA) and *Streptococcus pneumoniae*. Suspect if biphasic fever occurs.
- **Musculoskeletal:** Benign acute childhood myositis (severe calf pain, refusal to walk, elevated CK); classically associated with Influenza B.
- **Neurologic:** Febrile seizures, Guillain-Barré Syndrome, and Acute Necrotizing Encephalopathy (ANE - rapid coma, bilateral thalamic lesions on MRI, poor prognosis).

- **Cardiac:** Myocarditis, pericarditis.

Prevention

- **Vaccination (IAP/AAP latest):** Annual Inactivated Influenza Vaccine (IIV) recommended for all children starting at 6 months of age.
- **Dosing Strategy:** Children aged 6 months to 8 years require **2 doses** (4 weeks apart) during their *first* vaccination season; thereafter, 1 dose annually.
- **Post-Exposure Prophylaxis (PEP):** Oseltamivir for 7 days; indicated only for high-risk, unvaccinated contacts exposed within the last 48 hours.

Exam Summary

- **Buzzwords:** *Abrupt* onset fever/myalgia, GI symptoms in kids, calf pain (myositis with Type B).
- **Trap:** Negative Rapid Antigen Test does *not* rule out flu; treat empirically if clinically suspected in high-risk patients.
- **Red Flag:** Biphasic fever (initial improvement followed by high fever/respiratory distress) = Secondary bacterial pneumonia (think *S. aureus*).
- **Treatment Rule:** Oseltamivir is most effective <48 hours, but never withhold it in a hospitalized/sick child regardless of symptom duration. No aspirin (Reye syndrome).

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36. Respiratory syncytial virus infection in children: clinical features and management

Subject: Infectious Diseases

Basics & Etiology

- **Pathogen:** Enveloped, single-stranded RNA virus (Family: *Paramyxoviridae*, Genus: *Pneumovirus*).
- **Subtypes:** Subtype A (more severe) and Subtype B.
- **Epidemiology:** Most common cause of acute bronchiolitis and viral pneumonia in infants <1 year.
- **Seasonality:** Peaks in winter and early spring.
- **Transmission:** Direct contact with respiratory secretions, fomites (highly contagious, survives hours on surfaces).

Pathophysiology

- **Invasion:** Replicates in nasopharyngeal epithelium → spreads to lower respiratory tract.
- **Injury:** Causes necrosis and sloughing of ciliated epithelial cells.
- **Obstruction:** Accumulation of sloughed cells, copious mucus, and submucosal edema → small airway narrowing.
- **Consequences:** Ball-valve mechanism leads to air trapping/hyperinflation; complete obstruction leads to patchy atelectasis and V/Q mismatch (hypoxia).

Clinical Features

- **Incubation:** 3–5 days.
- **Prodrome (URTI):** Rhinorrhea, congestion, mild cough, low-grade fever (1–3 days).
- **Progression (LRTI):** Worsening cough, tachypnea, dyspnea, poor feeding.
- **Examination:**
    - Tachypnea, chest retractions (subcostal, intercostal), nasal flaring, grunting.
    - Auscultation: Prolonged expiratory phase, widespread polyphonic wheeze, fine inspiratory crackles.
- **Red Flag Presentation: Apnea** (may be the *only* presenting sign in premature infants or neonates <2 months).

Diagnosis

- **Clinical:** Diagnosis is primarily clinical (based on age, season, and typical signs).
- **Virology:** Multiplex RT-PCR (Gold standard, highest sensitivity) or Rapid Antigen Detection Test (nasopharyngeal swab).
- **Chest X-Ray:** Routinely *not* recommended unless complications suspected. Classic findings: Hyperinflation, flattened diaphragms, peribronchial cuffing, patchy atelectasis (often mistaken for pneumonia).
- **Blood:** Mild lymphocytosis; CRP/Procalcitonin usually normal (helps rule out bacterial infection).
- **ABG/VBG:** Done in severe distress to assess hypercarbia ($PaCO_2$ >45 mmHg indicates impending failure).

Management

- **Supportive Care (Mainstay):**
    - **Oxygen:** Target SpO_2 >90% (AAP) or >92% (WHO/IAP). Use nasal prongs or face mask.
    - **Hydration:** Frequent small feeds. If respiratory rate >60/min or severe distress → NBM, provide IV fluids or NG tube feeds.
    - **Airway Clearance:** Gentle nasal suctioning before feeding/inhalations.
- **Respiratory Support (Escalation):**
    - High-Flow Nasal Cannula (HFNC) for moderate-severe distress to provide mild PEEP.
    - CPAP or Intubation/Mechanical ventilation for severe apnea, refractory hypoxia, or hypercarbia.
- **Medications (What NOT to do per AAP/IAP):**
    - **Salbutamol/Epinephrine:** Not routinely recommended (trial only if strong atopic/asthma family history).
    - **Corticosteroids:** Systemic or inhaled are *contraindicated* (no proven benefit).
    - **Antibiotics:** Only if secondary bacterial infection is proven (e.g., concurrent AOM).
    - **Hypertonic Saline (3%):** May be used for hospitalized infants >24 hours to improve mucociliary clearance (AAP 2014 advises against use in ED).

- **Specific Antiviral: Ribavirin** (aerosolized) – rarely used, reserved *only* for severe disease in highly immunocompromised hosts (e.g., post-HSCT).

Complications

- Apnea and respiratory failure.
- Secondary bacterial infections (Acute Otitis Media is most common; bacterial pneumonia is rare).
- Hyponatremia (SIADH) in severe cases.
- Long-term: Increased risk of recurrent post-bronchiolitis wheezing and childhood asthma.

Prevention (High-Yield Updates)

- **General:** Hand hygiene, avoiding sick contacts, cohorting in hospitals.
- **Immunoprophylaxis:**
    - **Palivizumab:** Short-acting monoclonal antibody. Given IM monthly (max 5 doses) during RSV season. *Indications:* Preterm <29 weeks, chronic lung disease of prematurity (CLD), hemodynamically significant congenital heart disease (CHD).
    - **Update (AAP/CDC 2023): Nirsevimab** – Long-acting monoclonal antibody. Recommended as a *single* IM dose for *all* infants <8 months entering their first RSV season (replaces Palivizumab where available).
    - **Update (FDA/CDC 2023): Maternal Vaccine** – RSVpreF (Abrysvo) given to pregnant women at 32–36 weeks gestation to protect infants via transplacental antibodies.

Exam Summary

- **Classic Triad:** Infant <1 year + winter season + preceding coryza progressing to wheeze/crackles.
- **Red Flag:** Apnea in neonates/preemies is a classic presentation of RSV, even without respiratory distress.
- **Management trap:** Steroids, bronchodilators, and antibiotics are *not* indicated; supportive care (O2 + hydration) is the gold standard.
- **CXR buzzwords:** Hyperinflation, peribronchial cuffing, patchy atelectasis.
- **Cutting-edge prevention:** Nirsevimab (single dose for all infants) and maternal RSV vaccine at 32-36 weeks.

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37. Enterovirus infection and non polio enteroviruses

Subject: Infectious Diseases

Basics

- **Virology:** *Picornaviridae* family; small, non-enveloped, positive-sense single-stranded RNA (+ssRNA) viruses.
- **Classification:** Includes Polioviruses (3 serotypes) and Non-Polio Enteroviruses (NPEV: Coxsackievirus A & B, Echoviruses, and newer numbered Enteroviruses like EV-A71, EV-D68).

- **Epidemiology:** Predominantly summer and early autumn seasonality in temperate climates.
- **Transmission:** Fecal-oral (primary), respiratory droplets, vertical (peripartum), and fomites.

Pathophysiology

- **Entry:** Fecal-oral or respiratory route.
- **Primary Replication:** Pharynx and lower GI tract lymphoid tissue (tonsils, Peyer patches).
- **Minor Viremia:** Spread to reticuloendothelial system (cervical and mesenteric lymph nodes).
- **Major Viremia:** Dissemination to target organs (CNS, heart, skin, muscle).
- **Shedding:** Respiratory tract (1–3 weeks) and stool (up to 8 weeks).

Clinical Syndromes (Organ-Specific)

- **Non-specific:** Undifferentiated febrile illness (most common presentation in infants).
- **Mucocutaneous:**
    - *Hand-Foot-Mouth Disease (HFMD):* Vesicles on palms, soles, buttocks, and oral mucosa (Coxsackie A16, EV-A71).
    - *Herpangina:* Painful vesicles/ulcers confined to the *posterior* pharynx and soft palate (Coxsackie A).
- **Neurological:**
    - *Aseptic Meningitis:* NPEVs are the most common cause of viral meningitis in children.
    - *Encephalitis:* Especially EV-A71 (often brainstem encephalitis).
    - *Acute Flaccid Myelitis (AFM):* Polio-like anterior horn cell injury (EV-D68, EV-A71).
- **Musculoskeletal:**
    - *Pleurodynia (Bornholm Disease / Devil's Grip):* Sudden, spasmodic pleuritic chest/abdominal pain (Coxsackie B).
- **Cardiovascular:**
    - *Myocarditis/Pericarditis:* Leading viral cause; presents with heart failure, arrhythmias (Coxsackie B).
- **Ocular:**
    - *Acute Hemorrhagic Conjunctivitis:* Sudden onset, subconjunctival hemorrhage (EV-D70, Coxsackie A24).
- **Neonatal Disease:**
    - *Sepsis-like syndrome:* Severe multi-organ failure.
    - *Hepatic necrosis & coagulopathy:* Classic for Echovirus 11.
    - *Severe myocarditis:* Classic for Coxsackie B.

High-Yield Specific Viruses

- **EV-A71:** Associated with severe HFMD complicated by rhombencephalitis (brainstem encephalitis) leading to fatal neurogenic pulmonary edema.

- **EV-D68:** Associated with severe severe asthma-like respiratory illness and Acute Flaccid Myelitis (AFM). *CDC 2023:* High index of suspicion required for AFM in children with sudden limb weakness following respiratory illness.

Diagnosis

- **Clinical:** Diagnosis is primarily syndromic (e.g., classic HFMD or Herpangina).
- **Nucleic Acid Amplification (PCR):** Gold standard.
    - *CSF PCR:* Rapid, highly sensitive for meningitis/encephalitis.
    - *Respiratory/Throat swabs:* Highest yield in first week (crucial for EV-D68).
    - *Stool PCR:* Prolonged shedding makes it sensitive, but implies recent infection, not necessarily current systemic disease.
- **CSF Analysis:** Pleocytosis (neutrophilic early -> lymphocytic later), normal/slightly low glucose, mildly elevated protein.

Management

- **General:** Primarily supportive (hydration, antipyretics, analgesia).
- **Specific Antivirals:** None currently FDA-approved (Pleconaril and Pocapavir are investigational).
- **Intravenous Immunoglobulin (IVIG):**
    - *Indications:* Severe neonatal sepsis-like disease, severe EV-A71 encephalitis, and chronic enteroviral meningoencephalitis in patients with agammaglobulinemia (XLA).
- **Milrinone & IVIG:** Often used in EV-A71 induced brainstem encephalitis with autonomic instability / pulmonary edema.

Complications & Prognosis

- **Complications:** Dilated cardiomyopathy (post-Coxsackie B), permanent flaccid paralysis (AFM), nail shedding (onychomadesis 1-2 months post-HFMD).
- **Prognosis:** Excellent for most self-limiting syndromes; guarded for neonatal sepsis, severe myocarditis, and EV-A71 brainstem encephalitis.

Prevention

- **Hygiene:** Strict handwashing (soap and water preferred over alcohol sanitizers as non-enveloped viruses are somewhat alcohol-resistant).
- **Vaccines:** Inactivated EV-A71 vaccines are available and approved in China (not currently FDA/EMA approved). No vaccines for other NPEVs.

Exam Summary: Must-Write Buzzwords

- **Coxsackie A:** "A" for **A**limentary/Skin -> Herpangina (posterior pharynx), HFMD.
- **Coxsackie B:** "B" for **B**ody/Heart -> **B**ornholm disease (Pleurodynia), Myocarditis.
- **EV-A71:** Severe HFMD + Brainstem encephalitis + Neurogenic pulmonary edema.
- **EV-D68:** Severe respiratory distress + Acute Flaccid Myelitis (AFM).
- **Neonatal Echovirus 11:** Fulminant hepatic necrosis with severe coagulopathy.

- **Aseptic Meningitis:** Most common viral cause; CSF PCR is the diagnostic test of choice.

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38. Helicobacter pylori infection

Subject: Infectious Diseases

Basics

- **Organism:** Gram-negative, microaerophilic, flagellated, spiral bacillus
- **Key Enzyme:** Abundant urease production (vital for survival in gastric acid)
- **Transmission:** Fecal-oral, oral-oral, or gastric-oral; primarily acquired during early childhood (<5 years)
- **Epidemiology:** High prevalence in developing nations; associated with overcrowding and lower socioeconomic status

Pathophysiology

- **Survival:** Urease converts urea to ammonia and bicarbonate, creating a localized neutral microenvironment
- **Motility:** Flagella enable penetration through the viscous gastric mucus layer
- **Adherence:** Binds to gastric epithelial cells via BabA and SabA adhesins
- **Virulence Factors:**
    - **CagA (Cytotoxin-associated gene A):** Injected into host cells; disrupts junctions, highly associated with peptic ulcer disease (PUD) and malignancy
    - **VacA (Vacuolating cytotoxin A):** Induces host cell apoptosis and vacuolation
- **Host Response:** Triggers robust IL-8 release, causing intense neutrophilic and mononuclear infiltration (chronic active gastritis)

Clinical Features

- **Asymptomatic:** Majority of infected children have asymptomatic chronic gastritis
- **Gastrointestinal:**
    - Epigastric pain (classic: waking at night, relieved/worsened by food)
    - Nausea, vomiting, early satiety
    - Hematemesis or melena (if complicated by PUD)
- **Extraintestinal Associations:**
    - Refractory Iron Deficiency Anemia (IDA)
    - Chronic Immune Thrombocytopenic Purpura (ITP)
    - Growth faltering (indirectly via dyspepsia/poor intake)

Indications for Testing (ESPGHAN/NASPGHAN 2017 Guidelines)

- **Primary Rule:** Goal is to diagnose *disease* (e.g., PUD), not merely infection
- **Indications:** Suspected PUD, unexplained refractory IDA, chronic ITP

- **Contraindications:** Do *not* test for *H. pylori* in children with functional abdominal pain
- **Exam Trap:** "Test-and-treat" strategy (using non-invasive tests to diagnose and treat without endoscopy) is standard in adults but **NOT recommended** in children

Diagnosis

- **Prerequisite:** Stop PPIs 2 weeks and antibiotics/bismuth 4 weeks prior to any testing
- **Invasive (Gold Standard for Initial Diagnosis):**
    - Upper GI Endoscopy with multiple biopsies (antrum and corpus)
    - *Positive Diagnosis requires:* Positive histology PLUS either positive Rapid Urease Test (RUT) or positive culture
    - *Macroscopic clue:* Antral nodularity (highly specific for *H. pylori* in children)
    - *Culture:* Recommended to determine antibiotic susceptibility before treatment
- **Non-Invasive (Used for Eradication Confirmation):**
    - **Urea Breath Test (13C-UBT):** Highly sensitive and specific; preferred test for proof of cure
    - **Stool Antigen Test (SAT):** Monoclonal ELISA only (polyclonal is inaccurate); acceptable alternative to UBT
    - **Serology (IgG): Obsolete** in pediatrics; cannot distinguish past from current infection

Management

- **Duration:** Always **14 days** in children (improves eradication rates over 7 or 10 days)
- **First-Line (Known Susceptibility):**
    - High-dose PPI + Amoxicillin + Clarithromycin (if susceptible) OR
    - High-dose PPI + Amoxicillin + Metronidazole (if susceptible)
- **First-Line (Unknown Susceptibility / High Clarithromycin Resistance Area):**
    - **Bismuth Quadruple Therapy:** PPI + Bismuth salts + Metronidazole + Tetracycline (if >8 years) or Amoxicillin (if <8 years)
    - **Non-Bismuth Concomitant Therapy:** PPI + Amoxicillin + Metronidazole + Clarithromycin
- **Pediatric Dosing Clues:** High-dose PPI (e.g., Omeprazole 1.5–2.5 mg/kg/day divided BID) is crucial for antibiotic efficacy
- **Follow-up:** Confirm eradication at least 4–8 weeks after completing therapy using UBT or SAT

Complications

- Peptic Ulcer Disease (gastric or duodenal)
- Upper GI bleeding / Perforation
- Gastric adenocarcinoma (rare in childhood, long-term risk)
- Gastric MALT (Mucosa-Associated Lymphoid Tissue) lymphoma (can regress completely with *H. pylori* eradication)

Prognosis & Prevention

- Excellent prognosis with confirmed eradication
- Reinfection rate is higher in children from developing countries but generally low (<2-5% per year) in developed nations
- Prevention relies on improved sanitation, safe water supply, and reducing household crowding (no vaccine currently available)

Exam Summary

- **Pathogenesis:** Gram-negative spiral rod; urease-positive (neutralizes acid); CagA/VacA toxins.
- **Pediatric Rule:** "Test-and-treat" is NOT recommended; do not test children with functional abdominal pain.
- **Gold Standard Diagnosis:** Endoscopy with biopsy (requires positive histology + positive RUT/culture).
- **Treatment:** Always 14 days; requires high-dose PPI + 2 or 3 antibiotics (tailored to susceptibility).
- **Eradication Check:** Use 13C-UBT or monoclonal SAT 4-8 weeks post-treatment (never serology).

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39. Septic shock in children: management and recent advances

Subject: Infectious Diseases

Definition

- **Sepsis (Update - Phoenix Criteria 2024):** Life-threatening organ dysfunction caused by a dysregulated host response to infection. Diagnosed by a Phoenix Sepsis Score ≥2 (evaluates respiratory, cardiovascular, coagulation, and neurologic systems). Replaces old SIRS-based criteria.
- **Septic Shock:** Sepsis with severe cardiovascular dysfunction (requiring vasoactive drugs, or presenting with profound hypotension/inadequate perfusion despite adequate fluid resuscitation).

Etiology

- **Neonates:** Group B *Streptococcus*, *E. coli*, *Listeria monocytogenes*, HSV.
- **Infants/Children:** *S. pneumoniae*, *N. meningitidis*, *S. aureus* (MRSA/MSSA), *E. coli*, *Klebsiella*.
- **Immunocompromised:** *Pseudomonas aeruginosa*, fungi (*Candida*, *Aspergillus*).

Pathophysiology

- Pathogen-associated molecular patterns (PAMPs) activate Toll-like receptors (TLRs).
- Massive release of pro-inflammatory cytokines (IL-1, IL-6, TNF-α).
- Endothelial injury leads to severe capillary leak and intravascular hypovolemia.
- Microvascular thrombosis occurs due to tissue factor activation (leading to DIC).
- Myocardial depression occurs secondary to cytokines and mitochondrial dysfunction.

Clinical Features

- **Cold Shock (Most common in children):** Tachycardia, prolonged capillary refill time (CRT >2 sec), weak/thready pulses, mottled/cool extremities, narrow pulse pressure.
- **Warm Shock:** Tachycardia, "flash" CRT (<1 sec), bounding pulses, warm/flushed extremities, wide pulse pressure.
- **Systemic Signs:** Altered mental status (irritability/lethargy), tachypnea, oliguria (<1 mL/kg/hr).
- **Late/Ominous Sign:** Hypotension (children maintain BP via extreme vasoconstriction until impending arrest).

Diagnosis

- **Bedside:** Vitals, CRT, pulse quality, Glasgow Coma Scale (GCS).
- **Biomarkers:** Lactate (trend is more important than absolute value), CRP, Procalcitonin.
- **Microbiology:** Blood cultures (draw *before* antibiotics, but do not delay administration >45 mins), urine/CSF cultures if indicated.
- **Organ Dysfunction Labs:** CBC (thrombocytopenia), Coagulation profile (PT, aPTT, fibrinogen, D-dimer), LFTs, KFTs, ABG/VBG (metabolic acidosis, base deficit).
- **Imaging:** Bedside echocardiography (assess fluid responsiveness, IVC collapsibility, myocardial contractility).

Management (The First-Hour Bundle)

- **Airway/Breathing:** 100% high-flow oxygen. Early intubation if increased work of breathing, hemodynamic instability, or GCS <8. Use Ketamine (maintains hemodynamics) for induction.
- **Access:** Establish IV or Intraosseous (IO) access within 5 minutes.
- **Fluid Resuscitation (Update - SSC 2020 Guidelines):**
    - *If ICU backup available:* 10–20 mL/kg boluses over 5–10 mins. Reassess after each bolus. Max 40–60 mL/kg. Stop if signs of fluid overload (hepatomegaly, crackles, gallop) appear.
    - *If NO ICU backup (and hypotensive):* 10–20 mL/kg boluses, max 40 mL/kg.
    - *If NO ICU backup (and normotensive):* **Do not bolus.** Give maintenance fluids only.
    - *Fluid Choice:* Balanced crystalloids (Plasmalyte/Ringer's Lactate) are preferred over Normal Saline to prevent hyperchloremic metabolic acidosis and AKI.
- **Antimicrobial Therapy:** Administer broad-spectrum IV antibiotics within 1 hour of recognition (e.g., Ceftriaxone + Vancomycin).
- **Vasoactive Agents (Update - SSC 2020 Guidelines):**
    - Initiate if shock persists after 40–60 mL/kg of fluids (or earlier if fluid overload signs appear).
    - *Cold Shock:* **Epinephrine** (0.05–0.3 mcg/kg/min).
    - *Warm Shock:* **Norepinephrine** (0.05–0.5 mcg/kg/min).
    - *Route:* Start via peripheral IV or IO immediately; do not wait for central line placement.

- **Corticosteroids:** IV Hydrocortisone (2 mg/kg/dose Q6H) *only* for fluid-refractory, catecholamine-resistant shock (suspected critical illness-related corticosteroid insufficiency - CIRCI).
- **Source Control:** Drain abscesses, remove infected central lines/catheters within 6–12 hours.

Recent Advances & Paradigm Shifts

- **Phoenix Sepsis Criteria (2024):** Shifts focus from systemic inflammation (SIRS) to quantifiable organ dysfunction, specifically validated for pediatric populations globally.
- **Demise of Dopamine:** *Previously:* Dopamine was first-line. *Now:* Epinephrine or Norepinephrine are strongly preferred due to lower mortality and fewer arrhythmias.
- **Restrictive Fluid Strategy:** Influenced by the FEAST trial; routine aggressive fluid boluses (60 mL/kg) are no longer recommended in resource-limited settings without mechanical ventilation capabilities due to increased mortality from respiratory failure.
- **Peripheral Vasoactives:** Early initiation of dilute peripheral epinephrine/norepinephrine is now standard, preventing delayed shock reversal.
- **Adjunctive Therapies:** Vitamin C, Thiamine, and Steroid (HAT) combination therapy has been proven *ineffective* in recent pediatric RCTs and is not recommended. Extracorporeal Membrane Oxygenation (ECMO) is increasingly used for refractory shock.

Complications

- Multiple Organ Dysfunction Syndrome (MODS).
- Acute Respiratory Distress Syndrome (ARDS).
- Acute Kidney Injury (AKI).
- Disseminated Intravascular Coagulation (DIC).
- Critical illness polyneuropathy/myopathy.

Prognosis

- Mortality ranges from 5–10% in healthy children to >30% in immunocompromised or delayed-presentation cases.
- Every 1-hour delay in antibiotic administration significantly increases the odds of mortality.

Prevention

- Routine immunizations (Pneumococcal, Hib, Meningococcal).
- Strict adherence to CLABSI (Central Line-Associated Bloodstream Infection) and CAUTI care bundles in the ICU.
- Early recognition using Pediatric Early Warning Scores (PEWS).

Exam Summary

- **Phoenix Criteria (2024):** Sepsis is now defined by a Phoenix Score ≥2 (organ dysfunction), abandoning SIRS criteria.

- **Fluids:** Use balanced crystalloids (RL/Plasmalyte). Bolus 10-20 mL/kg only if ICU backup is available or if hypotensive. Stop for hepatomegaly/crackles.
- **Inotropes:** Epinephrine (Cold Shock) or Norepinephrine (Warm Shock) are first-line. Start peripherally/IO; **Dopamine is obsolete.**
- **Golden Hour:** IV/IO access in 5 mins, fluids in 15 mins, antibiotics in 1 hour, inotropes in 60 mins.
- **Hypotension is a late sign:** Children maintain BP via intense vasoconstriction; rely on tachycardia, altered sensorium, and CRT for early diagnosis.

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40. Pathophysiology of shock and newer monitoring approaches

Subject: Infectious Diseases

Definition

- State of acute energy failure due to inadequate tissue perfusion, resulting in an imbalance between oxygen delivery (DO2) and oxygen demand (VO2), leading to cellular dysoxia.

Etiology (Pediatric Context)

- **Distributive:** Sepsis (most common in ID), anaphylaxis, neurogenic.
- **Hypovolemic:** Gastroenteritis, hemorrhagic, third-spacing (dengue).
- **Cardiogenic:** Viral myocarditis, arrhythmias.
- **Obstructive:** Cardiac tamponade, tension pneumothorax.

Pathophysiology (Sepsis/Infectious Focus)

- **Trigger:** Pathogen-Associated Molecular Patterns (PAMPs) and Damage-Associated Molecular Patterns (DAMPs) bind to host Toll-Like Receptors (TLRs).
- **Inflammatory Cascade:** Massive release of pro-inflammatory cytokines (TNF-α, IL-1, IL-6) leading to a "cytokine storm."
- **Endothelial Dysfunction:** Shedding of endothelial glycocalyx causes profound capillary leak and third-spacing.
- **Microcirculatory Failure:** Nitric oxide overproduction causes vasoplegia; simultaneous activation of coagulation causes microthrombi (DIC) and shunting (bypassing capillary beds).
- **Macrocirculatory Failure:**
    - *Cold Shock:* Severe compensatory vasoconstriction + myocardial depression.
    - *Warm Shock:* Profound peripheral vasodilation + high cardiac output.
- **Cellular/Mitochondrial Dysfunction:** "Cytopathic hypoxia" where cells cannot use oxygen even if delivered, forcing anaerobic glycolysis and massive lactate production.
- **Compensation:** Sympathetic nervous system activation (tachycardia) and RAAS activation (oliguria).

Clinical Features

- **Compensated Shock:** Tachycardia, altered sensorium, oliguria, normal blood pressure (BP is maintained by intense vasoconstriction).
- **Uncompensated (Hypotensive) Shock:** Fall in systolic BP (late and ominous sign in pediatrics).
- **Cold Shock (Classic Pediatric Sepsis):** Cold/mottled extremities, delayed capillary refill time (CRT >2 secs), narrow pulse pressure, weak pulses.
- **Warm Shock:** Warm extremities, flash CRT, wide pulse pressure, bounding pulses.

Newer Monitoring Approaches (High-Yield)

- **Point-of-Care Ultrasound (POCUS):** Replaces static CVP. Assesses fluid responsiveness (IVC collapsibility/distensibility index), myocardial contractility, and identifies fluid overload (B-lines on lung ultrasound).
- **Near-Infrared Spectroscopy (NIRS):** Non-invasive continuous monitoring of regional tissue oxygenation (rSO2) in cerebral, renal, and splanchnic beds. Drop in rSO2 precedes systemic hypotension.
- **Advanced Hemodynamic Monitors:**
    - *USCOM (Ultrasound Cardiac Output Monitor):* Non-invasive Doppler at suprasternal notch to measure stroke volume and cardiac output.
    - *PiCCO / EV1000:* Minimally invasive pulse-contour analysis for continuous cardiac output and extravascular lung water.
- **Veno-Arterial pCO2 Gap (ΔpCO2):** Difference between central venous and arterial pCO2. A gap >6 mmHg indicates inadequate cardiac output/tissue flow.
- **Dynamic Lactate Clearance:** Serial lactate monitoring. *Goal:* >10–20% decrease in serum lactate within the first 2–4 hours of resuscitation.
- **Microcirculation Imaging (Emerging):** Sidestream Dark Field (SDF) imaging allows direct bedside visualization of sublingual capillary flow.

Management (Surviving Sepsis Campaign 2020 Updates)

- **Recognition:** Initiate bundle within 1 hour of recognizing septic shock.
- **Fluid Resuscitation:**
    - *Update:* 10–20 mL/kg balanced crystalloids (Plasmalyte/Ringer's) over 5–20 mins.
    - *No ICU Access:* Restrictive fluid strategy without boluses (if no hypotension) to prevent mortality from fluid overload. Stop fluids if hepatomegaly or crackles develop.
- **Vasoactive Agents:**
    - *First-line:* Epinephrine (preferred in cold shock) or Norepinephrine (preferred in warm shock).
    - *Update:* Start peripherally if central access is delayed; do not wait.
- **Antimicrobials:** Broad-spectrum IV antibiotics within 1 hour.
- **Source Control:** Drain abscesses, remove infected lines.
- **Corticosteroids:** IV Hydrocortisone ONLY for fluid-refractory, catecholamine-resistant shock.

Complications

- Multiple Organ Dysfunction Syndrome (MODS).
- Acute Respiratory Distress Syndrome (ARDS).
- Acute Kidney Injury (AKI) requiring continuous renal replacement therapy (CRRT).
- Disseminated Intravascular Coagulation (DIC).

Prognosis

- Mortality highly dependent on timely recognition. Every hour delay in antibiotics/vasoactives increases mortality by ~8%.
- Refractory shock with persistent hyperlactatemia carries a >50% mortality rate.

Exam Summary

- **Must-Write Definition:** Shock is cellular energy failure, not just low BP; hypotension is a late, decompensated sign in children.
- **Pathophysiology Core:** Endothelial glycocalyx shedding + mitochondrial cytopathic hypoxia + microvascular thrombosis.
- **Modern Monitoring:** Shift from static (CVP) to dynamic (POCUS, IVC variability, Lactate clearance, NIRS, USCOM).
- **SSC 2020 Trap:** Fluid boluses are now restricted (10-20 ml/kg) and contraindicated in settings without mechanical ventilation if hypotension is absent.
- **Vasoactives:** Start Epinephrine/Norepinephrine early, via peripheral line if needed, rather than drowning the child in fluids.

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41. Prevention of mother to child transmission of HIV

Subject: Infectious Diseases

Definition & Goals

- **PMTCT:** Comprehensive strategy to prevent transmission of HIV from an infected mother to her child.
- **Goal:** Reduce vertical transmission from 15–45% (without intervention) to <1% (with effective intervention).
- **Transmission Timing:** In utero (25–30%), Intrapartum (60–70% - highest risk), Postpartum via breastfeeding (10–15%).

Maternal Antenatal Care (ANC)

- **Screening:** Universal opt-out HIV testing for all pregnant women at first visit; repeat in 3rd trimester if high risk.
- **"Treat All" Strategy:** Initiate lifelong Antiretroviral Therapy (ART) immediately, regardless of CD4 count or clinical stage.
- **WHO/NACO Updated First-Line:** Tenofovir (TDF) + Lamivudine (3TC) + Dolutegravir (DTG).

- *Update:* DTG is now preferred in pregnancy (neural tube defect risk concerns have been resolved).

- **Monitoring:** Maternal Viral Load (VL) testing at 32–36 weeks to determine delivery mode and infant risk.

Intrapartum Management

- **Standard Precautions:** Universal precautions for all deliveries.
- **Mode of Delivery (based on VL at 36 weeks):**
  - **VL <1,000 copies/mL:** Normal Vaginal Delivery (NVD) permitted.
  - **VL >1,000 copies/mL or Unknown:** Elective Lower Segment Cesarean Section (LSCS) at 38–39 weeks (before onset of labor/rupture of membranes).
- **Avoid (Obstetric Traps):** Artificial rupture of membranes (prolonged ROM >4 hours increases risk), episiotomy, fetal scalp electrodes, instrumental delivery (forceps/vacuum).
- **Medical Prophylaxis:** IV Zidovudine (AZT) during labor if maternal VL >1,000 copies/mL or unknown (infusion started 3 hours prior to elective LSCS or at onset of labor).

Neonatal Prophylaxis (Risk-Stratified)

- **Low-Risk Infant:** (Mother on ART >24 weeks, VL <1000, >80% adherence)
  - Give daily **Nevirapine (NVP)** drops for **6 weeks**.
- **High-Risk Infant:** (Mother on ART <24 weeks, VL >1000, incident HIV during pregnancy/lactation, or poor adherence)
  - Give dual prophylaxis: **Zidovudine (AZT) + Nevirapine (NVP)** for **6 weeks**.
  - *If breastfeeding:* Continue NVP for an additional 6 weeks (total **12 weeks** of NVP).

Infant Feeding Guidelines

- **First Choice:** Exclusive Breastfeeding (EBF) for first 6 months, followed by complementary feeding + continued breastfeeding up to 12–24 months (provided mother is fully virally suppressed on ART).
- **Alternative:** Exclusive Replacement Feeding (ERF) ONLY if **AFASS** criteria are met (Acceptable, Feasible, Affordable, Sustainable, Safe).
- **Absolute Contraindication:** Mixed feeding (breast milk + formula/water) in the first 6 months is strictly prohibited due to gut mucosal disruption and highest transmission risk.
- **Abrupt Weaning:** No longer recommended; transition gradually over 1 month.

Early Infant Diagnosis (EID)

- Maternal IgG antibodies cross placenta (persist up to 18 months); standard rapid tests are invalid for early infant diagnosis.
- **Test of Choice:** HIV-1 DNA PCR using Dried Blood Spot (DBS).
- **Testing Schedule (WHO/NACO):**
  - Birth (only in high-risk infants - optional in some guidelines).
  - **6 weeks** (First routine EID).

    - **6 months**.
    - **12 months**.
    - **6 weeks after complete cessation of breastfeeding**.
- **Confirmation:** Rapid HIV Antibody test at **18 months** (determines final HIV status).
- If any PCR is positive: Start infant ART immediately; send a second sample for confirmation, but do not delay treatment.

Additional Infant Care

- **Cotrimoxazole Preventive Therapy (CPT):** Start at 6 weeks of age for all HIV-exposed infants. Continue until HIV infection is definitively ruled out (after cessation of breastfeeding) to prevent *Pneumocystis jirovecii*.
- **Immunization:**
    - Give all routine vaccines including BCG at birth (infant is asymptomatic).
    - *Contraindication:* Avoid BCG and live vaccines (OPV, MMR) ONLY if the infant becomes severely immunosuppressed or symptomatic for HIV.

Exam Summary: Must-Write Points

- **Maternal ART:** Lifelong TDF + 3TC + DTG for all pregnant women ("Treat All").
- **Delivery Mode:** Elective LSCS at 38 weeks ONLY if maternal Viral Load >1000 copies/mL or unknown.
- **Infant Prophylaxis:** Low risk = NVP x 6 weeks; High risk = AZT + NVP x 6 weeks (extend NVP to 12 weeks if breastfeeding).
- **Feeding:** EBF for 6 months is preferred; Mixed feeding is strictly contraindicated.
- **Diagnosis:** HIV DNA PCR at 6 weeks, 6 months, 12 months; Antibody test at 18 months. Start CPT at 6 weeks.

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42. Chronic illness in childhood with emphasis on cystic fibrosis

Subject: Infectious Diseases

CHRONIC ILLNESS IN CHILDHOOD: OVERVIEW

- **Definition:** Condition lasting >3 months affecting normal activities, requiring frequent hospitalization/home health care.
- **Impact:** Affects physical growth, cognitive development, psychosocial well-being, and family dynamics.
- **Core Management:** Multidisciplinary team, catch-up growth nutrition, routine immunization (often plus pneumococcal/annual influenza), psychological support, and planned transition to adult care.

CYSTIC FIBROSIS (CF): IN-DEPTH

Genetics & Etiology

- **Inheritance:** Autosomal Recessive.
- **Gene:** *CFTR* (Cystic Fibrosis Transmembrane Conductance Regulator) on Chromosome 7q31.2.
- **Most common mutation:** F508del (Class II mutation – defective protein processing/folding).

Pathophysiology

- Defective CFTR protein → impaired chloride secretion and enhanced sodium absorption (via ENaC) across epithelial cells.
- **Result:** Depleted airway surface liquid → thick, dehydrated, viscous mucus.
- **Consequences:** Mucociliary dysfunction → chronic infection/inflammation → tissue destruction (bronchiectasis, pancreatic destruction, biliary cirrhosis).

Clinical Features

- **Neonatal:** Meconium ileus (classic buzzword, 15-20%), prolonged neonatal jaundice, "salty tasting baby".
- **Respiratory:** Chronic wet/productive cough, recurrent wheeze, nasal polyps, chronic pansinusitis.
- **Gastrointestinal:** Pancreatic exocrine insufficiency (steatorrhea, foul-smelling greasy stools), Failure to Thrive (FTT), rectal prolapse.
- **Genitourinary:** Congenital Bilateral Absence of Vas Deferens (CBAVD) → male infertility (>95%); reduced female fertility (thick cervical mucus).
- **Musculoskeletal:** Digital clubbing, hypertrophic osteoarthropathy.

Microbiology (Infectious Disease Focus)

- **Early childhood:** *Staphylococcus aureus* (often MRSA), *Haemophilus influenzae*.
- **Late childhood/Adults:** *Pseudomonas aeruginosa* (mucoid strains pathognomonic).
- **Red Flag Pathogen:** *Burkholderia cepacia* complex (associated with rapid decline and "cepacia syndrome"; contraindication for lung transplant in some centers).
- **Fungal:** *Aspergillus fumigatus* (risk of Allergic Bronchopulmonary Aspergillosis - ABPA), Nontuberculous Mycobacteria (NTM).

Diagnosis

- **Newborn Screening (NBS):** Elevated Immunoreactive Trypsinogen (IRT) from heel prick.
- **Sweat Chloride Test (Gold Standard):** Quantitative pilocarpine iontophoresis.
    - Positive (CF confirmed): ≥60 mmol/L.
    - Intermediate: 30–59 mmol/L (in infants ≤6 months) or 40–59 mmol/L (>6 months). Requires repeat and genetic testing.
    - Normal: <30 mmol/L (≤6 months) or <40 mmol/L (>6 months).
- **Genetic Testing:** CFTR mutation panel (confirms diagnosis if 2 disease-causing mutations found).

- **Nasal Potential Difference:** Used in atypical cases (shows more negative baseline and absent response to chloride-free solution).
- **Imaging:** HRCT Chest shows "Signet ring sign" (bronchiectasis), tram-tracking, mucus plugging.

Management: Respiratory

- **Airway Clearance Therapy (ACT):** Chest physiotherapy, positive expiratory pressure (PEP) devices, high-frequency chest wall oscillation.
- **Mucolytics:**
    - Dornase alfa (recombinant human DNase) cleaves extracellular DNA in sputum.
    - Inhaled hypertonic saline (7%) hydrates airway surface liquid.
- **Infection Control:**
    - *Pseudomonas eradication:* Inhaled tobramycin or colistin (often 28 days on/28 days off).
    - *Anti-inflammatory:* Oral Azithromycin (3x/week) for immunomodulatory effects in chronic *Pseudomonas* infection.
    - *Exacerbations:* IV antibiotics (dual anti-pseudomonal coverage, e.g., Ceftazidime + Amikacin) + intensified ACT.

Management: GI & Nutrition

- **Diet:** High-calorie, high-fat, high-protein diet (110–150% of normal RDA).
- **Enzymes:** Pancreatic Enzyme Replacement Therapy (PERT) with every meal/snack.
- **Vitamins:** Supplementation of fat-soluble vitamins (A, D, E, K).
- **Hydration:** Liberal salt intake, especially in hot weather.
- **Hepatobiliary:** Ursodeoxycholic acid for focal biliary cirrhosis.

Management: CFTR Modulators (Game Changers)

- *Target the underlying protein defect; highly mutation-specific.*
- **Ivacaftor:** Potentiator for Class III (gating) mutations (e.g., G551D).
- **Lumacaftor/Ivacaftor:** For homozygous F508del.
- **Elexacaftor/Tezacaftor/Ivacaftor (Trikafta):** Highly effective triple therapy.
    - *Update (FDA/Guidelines):* Now approved for patients aged ≥2 years with at least one F508del mutation (covers ~90% of CF population).

Complications

- **CF-Related Diabetes (CFRD):** Insidious onset, requires annual OGTT screening from age 10. *Treatment:* Insulin (oral hypoglycemics ineffective).
- **ABPA:** Worsening lung function, high IgE, positive Aspergillus serology. *Treatment:* Systemic steroids + Itraconazole.

- **Pulmonary:** Massive hemoptysis (may require bronchial artery embolization), spontaneous pneumothorax, cor pulmonale.
- **GI:** Distal Intestinal Obstruction Syndrome (DIOS) - treat with osmotic laxatives/Gastrografin enema.

Prognosis

- Historically fatal in early childhood.
- *Current:* Median predicted survival age is now >50 years in developed nations, largely driven by comprehensive center-based care and CFTR modulators.

EXAM SUMMARY: MUST-WRITE POINTS

- **Classic Triad:** Chronic sinopulmonary disease, pancreatic insufficiency, abnormally high sweat chloride.
- **Mutation:** *CFTR* gene, F508del most common; autosomal recessive.
- **Neonatal clues:** Meconium ileus, prolonged jaundice, elevated IRT on newborn screen.
- **Diagnosis cutoff:** Sweat chloride ≥60 mmol/L is diagnostic.
- **Microbiology shift:** *S. aureus* in early life → *P. aeruginosa* in adolescence/adulthood.
- **Modern Therapy:** Elexacaftor/Tezacaftor/Ivacaftor (Trikafta) for ≥2 years old with ≥1 F508del mutation drastically alters disease trajectory.

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43. Short notes on Zika virus, Ebola virus, Nipah virus, Avian Influenza virus

Subject: Infectious Diseases

ZIKA VIRUS

Etiology & Transmission

- **Agent:** RNA virus, *Flaviviridae* family.
- **Vector:** *Aedes* mosquitoes (*A. aegypti, A. albopictus*).
- **Transmission:** Mosquito bite, vertical (transplacental/intrapartum), sexual contact, blood transfusion.

Clinical Features

- **Acquired Infection:** 80% asymptomatic. Mild, self-limiting (2–7 days).
- **Classic Tetrad:** Low-grade fever, pruritic maculopapular rash (descending), non-purulent conjunctivitis, arthralgia.
- **Congenital Zika Syndrome (CZS):**
    - Severe microcephaly with partially collapsed skull.
    - Thin cerebral cortices with subcortical calcifications.
    - Ocular anomalies (macular scarring, focal pigmentary retinal mottling).

    - Congenital contractures (arthrogryposis).
    - Early marked hypertonia and extrapyramidal involvement.
- **Complication:** Guillain-Barré Syndrome (GBS) in older children/adults.

Diagnosis

- **Virology:** RT-PCR in serum (up to 7 days) and urine (up to 14 days).
- **Serology:** Zika IgM ELISA (Note: high cross-reactivity with Dengue/other flaviviruses; requires Plaque Reduction Neutralization Test [PRNT] for confirmation).

Management & Prevention

- **Treatment:** Strictly supportive (hydration, rest).
- **Red Flag:** Do NOT use NSAIDs or Aspirin until Dengue is ruled out (risk of hemorrhage). Use paracetamol.
- **Prevention:** Vector control, avoiding travel to endemic areas during pregnancy, safe sex practices (virus persists in semen).

EBOLA VIRUS

Etiology & Transmission

- **Agent:** RNA virus, *Filoviridae* family.
- **Reservoir:** Fruit bats.
- **Transmission:** Direct contact with infected blood/body fluids (including breast milk, semen, sweat) or contaminated fomites. Highly infectious post-mortem.

Clinical Features

- **Incubation:** 2–21 days.
- **"Dry" Phase (Early):** Abrupt high fever, severe asthenia, myalgia, headache.
- **"Wet" Phase (Days 3–5):** Severe watery diarrhea, nausea, vomiting (leading to massive volume loss).
- **Hemorrhagic Phase:** Melena, hematemesis, petechiae, oozing from venipuncture sites.
- **Complications:** Hypovolemic shock, Disseminated Intravascular Coagulation (DIC), Multi-Organ Dysfunction Syndrome (MODS).

Diagnosis

- **Testing:** RT-PCR of blood/body fluids (requires Biosafety Level 4 [BSL-4] handling).

Management & Prevention

- **Supportive:** Aggressive IV fluid and electrolyte resuscitation (improves survival significantly).
- **Specific Therapy (FDA Approved updates):** Monoclonal antibodies—**Inmazeb** (atoltivimab, maftivimab, odesivimab) or **Ebanga** (ansuvimab-zykl).
- **Prevention:** rVSV-ZEBOV vaccine (**Ervebo**) for outbreak ring vaccination; strict PPE and safe burial practices.

NIPAH VIRUS (NiV)

Etiology & Transmission

- **Agent:** RNA virus, *Paramyxoviridae* family (*Henipavirus* genus).
- **Reservoir:** *Pteropus* fruit bats. Amplifying hosts: Pigs.
- **Transmission:** Consumption of contaminated raw date palm sap, contact with infected animals, direct human-to-human transmission (droplet/contact).

Clinical Features

- **Incubation:** 4–14 days.
- **Presentation:** Rapid clinical deterioration.
    - Acute respiratory infection (mild to severe ARDS).
    - Acute Encephalitis: Fever, headache, altered sensorium, focal neurological deficits, seizures, progressing to coma within 24–48 hours.
- **Late Complication:** Relapsing or late-onset encephalitis (months to years after initial exposure).
- **Mortality:** Extremely high (40–75%).

Diagnosis

- **Testing:** RT-PCR (throat swab, CSF, urine, blood) handled under BSL-4.
- **Serology:** IgM and IgG ELISA in CSF/serum.

Management & Prevention

- **Treatment:** Intensive supportive care (mechanical ventilation, seizure control).
- **Antivirals:** Ribavirin is used empirically but lacks proven efficacy.
- **Experimental:** Monoclonal antibody **m102.4** (compassionate use).
- **Prevention:** Boil date palm sap before consumption, wash/peel fruits, strict hospital infection control.

AVIAN INFLUENZA VIRUS (Bird Flu)

Etiology & Transmission

- **Agent:** *Orthomyxoviridae*, Influenza A virus (Primary strains: **H5N1, H7N9**).
- **Reservoir:** Wild aquatic birds and domestic poultry.
- **Transmission:** Direct contact with infected poultry, feces, or contaminated environments. Human-to-human transmission is currently rare and unsustained.

Clinical Features

- **Presentation:** Rapidly progressive severe viral pneumonia.
- **Symptoms:** High fever (>38°C), cough, dyspnea.

- **H5N1 Specifics:** Frequent GI symptoms (watery diarrhea, vomiting) preceding respiratory distress.
- **Complications:** ARDS, ventilator-associated pneumonia, pulmonary hemorrhage, multiorgan failure.

Diagnosis

- **Testing:** RT-PCR from respiratory tract. Lower respiratory tract specimens (BAL, tracheal aspirate) have higher yield than nasopharyngeal swabs.

Management & Prevention

- **Antivirals:** Neuraminidase inhibitors (**Oseltamivir** or Zanamivir) started ASAP, ideally within 48 hours.
    - *Note:* Severe cases often require higher doses or prolonged duration (e.g., 10 days) compared to seasonal influenza.
- **Supportive:** Lung-protective mechanical ventilation, ECMO for refractory hypoxemia.
- **Contraindication:** Avoid routine systemic corticosteroids (increases mortality and viral shedding).
- **Prevention:** Culling infected flocks, strict PPE for poultry workers. Vaccines are developed and stockpiled but not routinely administered.

EXAM SUMMARY: MUST-WRITE BUZZWORDS

- **Zika:** *Aedes* mosquito, microcephaly/subcortical calcifications, GBS, avoid NSAIDs (Dengue cross-reactivity).
- **Ebola:** Fruit bats, massive fluid loss ("wet phase"), hemorrhage, Inmazeb/Ebanga (mAbs), Ervebo vaccine.
- **Nipah:** *Pteropus* bats, raw date palm sap, rapidly fatal encephalitis + ARDS, relapsing encephalitis.
- **Avian Flu:** H5N1/H7N9, poultry contact, rapidly progressive viral pneumonia/ARDS, early Oseltamivir, lower respiratory sample for PCR.

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44. Short notes on important tropical infections in children in Nepal

Subject: Infectious Diseases

Overview Acute undifferentiated febrile illness (AUFI) is a major pediatric presentation in Nepal. The epidemiological landscape varies by geography (Terai vs. Hills/Mountains) and season (monsoon/post-monsoon). The highest-yield tropical infections include Enteric Fever, Scrub Typhus, Dengue, Visceral Leishmaniasis, and Japanese Encephalitis.

1. Enteric Fever (Typhoid/Paratyphoid)

- **Etiology:** *Salmonella enterica* serotypes Typhi and Paratyphi (A, B, C). Fecal-oral transmission.
- **Clinical:** Step-ladder pattern fever, toxic appearance, relative bradycardia, coated tongue, hepatosplenomegaly, abdominal pain, constipation (early) followed by diarrhea. Rose spots (rarely seen in dark skin).

- **Complications:** Intestinal perforation/hemorrhage (3rd week), toxic encephalopathy.
- **Diagnosis:**
    - Blood culture: Gold standard (highest yield in 1st week).
    - Widal test: Poor sensitivity/specificity; requires paired sera showing 4-fold rise (rarely practical).
    - Typhidot (IgM/IgG): Rapid but limited diagnostic value.
- **Management:**
    - Uncomplicated: Oral Azithromycin (20 mg/kg/day for 7 days) or Cefixime.
    - Severe/Complicated: IV Ceftriaxone (75–100 mg/kg/day for 10–14 days).
    - *Note:* High rates of fluoroquinolone resistance in Nepal; empiric ciprofloxacin is no longer recommended.
- **Prevention:** Typhoid Conjugate Vaccine (TCV) is now included in Nepal's National Immunization Program (NIP) at 15 months.

2. Scrub Typhus

- **Etiology:** *Orientia tsutsugamushi*. Vector: Chigger (larva of Trombiculid mite). Rapidly emerging across Nepal.
- **Clinical:** High fever, severe headache, myalgia, generalized lymphadenopathy, maculopapular rash.
- **Pathognomonic Sign:** Eschar (painless, punched-out necrotic ulcer with black crust) at the bite site (axilla, groin, skin folds).
- **Complications:** Capillary leak syndrome leading to ARDS, acute kidney injury (AKI), meningoencephalitis, myocarditis.
- **Diagnosis:**
    - Scrub Typhus IgM ELISA (Test of choice).
    - Weil-Felix test (OXK positive): Poor sensitivity/specificity, largely obsolete but historically tested.
- **Management:**
    - Drug of choice: Doxycycline (4.4 mg/kg/day divided BD for 7–10 days). *AAP/Nelson Update:* Doxycycline is safe and recommended even in children <8 years for short courses.
    - Alternative: Azithromycin (10 mg/kg/day) if Doxycycline is contraindicated.

3. Dengue Fever

- **Etiology:** Flavivirus (DENV 1–4). Vector: *Aedes aegypti* and *Aedes albopictus*. Major outbreaks post-monsoon.
- **Clinical Phases:**
    - *Febrile:* High fever, retro-orbital pain, severe myalgia ("break-bone fever"), positive tourniquet test.

- *Critical (Days 3–7):* Defervescence marks the onset of capillary leak.
- *Warning Signs:* Abdominal pain, persistent vomiting, mucosal bleed, lethargy, hepatomegaly >2cm, rising hematocrit (Hct) with rapid drop in platelets.
- *Recovery:* Reabsorption of fluids, "isles of white in a sea of red" rash, bradycardia.

- **Diagnosis:**
  - Days 1–5: NS1 Antigen (ELISA/Rapid).
  - After Day 5: Dengue IgM ELISA.
- **Management:** Strictly per WHO 2009 guidelines.
  - Group A (No warning signs): Oral rehydration, paracetamol. *Strictly avoid NSAIDs/Aspirin*.
  - Group B (Warning signs): Isotonic IV crystalloids (RL/NS) guided by Hct and urine output.
  - Group C (Severe Dengue/Shock): Fluid resuscitation, blood transfusion if concealed bleeding.

4. Visceral Leishmaniasis (Kala-azar)

- **Etiology:** *Leishmania donovani*. Vector: Sandfly (*Phlebotomus argentipes*). Highly endemic in the Terai region.
- **Clinical:** Prolonged fever (>2 weeks), massive splenomegaly, hepatomegaly, severe cachexia/weight loss, darkening of skin ("Kala-azar").
- **Labs:** Pancytopenia, reversal of albumin/globulin ratio (hypergammaglobulinemia).
- **Diagnosis:**
  - rK39 Rapid Diagnostic Test: Field test of choice (high sensitivity/specificity).
  - Bone marrow/Splenic aspirate: Demonstration of LD (Leishman-Donovan) bodies (Gold standard).
- **Management:**
  - First-line (Nepal/WHO guidelines): Liposomal Amphotericin B (Single IV dose of 10 mg/kg).
  - Alternative: Miltefosine (oral, 28 days) or Paromomycin.
- **Complication:** Post-Kala-azar Dermal Leishmaniasis (PKDL) can occur months/years after treatment (macular/nodular rash, acts as a disease reservoir).

5. Japanese Encephalitis (JE)

- **Etiology:** Flavivirus. Vector: *Culex tritaeniorhynchus*. Amplifying host: Pigs and Ardeid birds. Endemic in Terai, spreading to valleys.
- **Clinical:**
  - Prodrome: Fever, headache, vomiting.
  - Encephalitic phase: Seizures, altered sensorium, focal neurological deficits.

- *Classic clue:* Extrapyramidal signs (mask-like facies, rigidity, tremors, choreoathetosis).

- **Diagnosis:** CSF JE IgM ELISA (Test of choice). CSF shows lymphocytic pleocytosis, normal/slightly low sugar.
- **Management:** Purely supportive (airway, seizure control, management of raised ICP).
- **Prevention:** Live-attenuated JE vaccine (SA 14-14-2 strain) given at 12 months in Nepal's NIP.

Exam Summary: Must-Write Points

- **Enteric Fever:** Step-ladder fever + relative bradycardia; Ceftriaxone/Azithromycin are drugs of choice; TCV now in Nepal EPI at 15 months.
- **Scrub Typhus:** Look for the pathognomonic **eschar**; treat aggressively with **Doxycycline** (even if <8 years old).
- **Dengue:** Monitor for capillary leak during defervescence (Days 3-7); rising Hct + dropping platelets = warning sign; strictly avoid NSAIDs.
- **Kala-azar:** Endemic in Terai; massive splenomegaly + pancytopenia; diagnose with **rK39**; treat with single-dose **Liposomal Amphotericin B**.
- **Japanese Encephalitis:** Encephalitis with **extrapyramidal/Parkinsonian features**; diagnose via CSF IgM; prevented by SA 14-14-2 vaccine at 12 months.

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45. Polio evaluation and eradication strategy

Subject: Infectious Diseases

Basics & Current Status

- **Agent:** Poliovirus (Enterovirus, single-stranded RNA).
- **Serotypes:** 1, 2, and 3.
- **Global Status (WHO Update):**
  - WPV2 eradicated (2015).
  - WPV3 eradicated (2019).
  - WPV1 remains endemic in only 2 countries: Pakistan and Afghanistan.
- **India Status:** Certified Polio-free on March 27, 2014 (last case: Jan 13, 2011, Howrah).

Clinical Evaluation (AFP)

- **AFP Definition:** Any child <15 years with acute onset flaccid paralysis/weakness, or any person of any age where polio is suspected.
- **Classic Polio Features:**
  - **Onset:** Acute (1–4 days), usually with fever.
  - **Tone/Reflexes:** Flaccid, deep tendon reflexes (DTRs) absent/diminished.
  - **Distribution:** Asymmetrical, proximal muscles > distal, legs > arms.

  - **Sensation:** Intact (hallmark distinguishing it from neuropathies).
  - **Progression:** No progression after 3–4 days of onset.
- **Differentials:** Guillain-Barré Syndrome (symmetrical, sensory involvement, afebrile), Transverse Myelitis (sensory level, bowel/bladder involvement), Traumatic Neuritis (gluteal IM injection history).

Diagnostic Evaluation

- **Stool Sampling (Gold Standard):**
  - **Timing:** 2 samples collected 24–48 hours apart, within 14 days of paralysis onset.
  - **Quantity:** 8–10 grams (thumb size).
  - **Transport:** Reverse cold chain (2–8°C) to WHO-accredited lab.
- **Viral Isolation:** Cultured on specific cell lines (L20B and RD cells).
- **Intratypic Differentiation (ITD):** PCR used to differentiate Wild Poliovirus (WPV) from Vaccine-Derived Poliovirus (VDPV) or Sabin-like strains.
- **CSF Analysis:** Non-specific; shows aseptic meningitis picture (pleocytosis, normal glucose, slightly elevated protein).

Eradication Strategy (Core Pillars)

- **1. Routine Immunization (RI):** High coverage (>90%) with OPV/IPV in the national schedule.
- **2. Supplementary Immunization Activities (SIAs):** National Immunization Days (NIDs) and Sub-NIDs (Pulse Polio) targeting all children <5 years, regardless of previous immunization status.
- **3. Surveillance:**
  - **AFP Surveillance:** Active case finding, 60-day follow-up of AFP cases for residual weakness.
  - **Environmental Surveillance:** Testing sewage/wastewater for poliovirus shedding (crucial for detecting silent transmission of VDPV/WPV).
- **4. Mop-Up Operations:** Massive, rapid, localized house-to-house immunization in high-risk areas within 4 weeks of detecting a new WPV/cVDPV case.

Polio Endgame Strategy (2022–2026 Updates)

- **Goal:** Eradicate all polioviruses (WPV and VDPV).
- **The "Switch" (April 2016):** Global synchronized withdrawal of tOPV (trivalent) and replacement with bOPV (bivalent: types 1 & 3) to stop cVDPV2 (circulating vaccine-derived poliovirus type 2).
- **IPV Introduction:** To maintain immunity against Type 2 following the switch.
  - **Current NIS India:** Fractional IPV (fIPV) 0.1 mL intradermally at 6 weeks, 14 weeks, and 9 months.
- **Novel OPV2 (nOPV2):**
  - **Update:** First vaccine authorized under WHO Emergency Use Listing (EUL).

- **Use:** Deployed specifically for cVDPV2 outbreaks.
- **Advantage:** Genetically more stable than Sabin OPV2; significantly lower risk of reverting to neurovirulence.

Complications & Prognosis

- **Bulbar Polio:** Involvement of cranial nerves (IX, X, XI, XII); risk of respiratory compromise and dysphagia (requires mechanical ventilation).
- **Post-Polio Syndrome (PPS):** New onset weakness, fatigue, and muscle atrophy occurring 15–40 years after acute paralytic polio. Pathophysiology: Premature exhaustion of enlarged motor units.

Exam Summary

- **Must-Write Definition:** AFP is acute onset flaccid paralysis in <15 yrs; Polio is asymmetrical, proximal > distal, with intact sensation.
- **Stool Protocol:** 2 samples, 24-48h apart, within 14 days, reverse cold chain (2-8°C).
- **The "Switch":** April 2016 shift from tOPV to bOPV to eliminate cVDPV2.
- **Current Strategy:** High RI + SIAs + AFP/Environmental Surveillance + Mop-up.
- **Latest Updates:** WPV1 only remaining endemic strain; use of nOPV2 for cVDPV2 outbreaks; fIPV schedule at 6w, 14w, 9m (India).

Respiratory System

1. Bronchial asthma diagnosis and management based on GINA guidelines

Subject: Respiratory System

Definition

- Heterogeneous disease characterized by chronic airway inflammation
- Defined by history of respiratory symptoms (wheeze, shortness of breath, chest tightness, cough) that vary over time and in intensity
- Associated with variable expiratory airflow limitation

Etiology & Triggers

- **Host factors:** Genetic predisposition (atopy), obesity, prematurity
- **Triggers:** Viral infections (RSV, Rhinovirus—most common in <5 years), aeroallergens (dust mites, pollen, pet dander), exercise, cold air, smoke, strong odors

Pathophysiology

- **Early phase (Minutes):** Allergen exposure → IgE cross-linking on mast cells → Degranulation (histamine, leukotrienes) → Acute bronchoconstriction
- **Late phase (Hours):** Eosinophil and Th2 lymphocyte infiltration → Mucosal edema, mucus hypersecretion

- **Chronic:** Airway remodeling (subepithelial fibrosis, smooth muscle hypertrophy, angiogenesis) due to poor control

Clinical Features

- **Classic tetrad:** Wheeze, cough, shortness of breath, chest tightness
- **Pattern:** Worse at night or early morning, triggered by exercise/viral infections
- **Signs of severity (Red Flags):** Inability to complete sentences, "silent chest" (no wheeze due to severe obstruction), cyanosis, paradoxus (>15 mmHg drop in systolic BP during inspiration), altered sensorium

Diagnosis (GINA Criteria)

- **Clinical History:** Variable symptoms, documented trigger associations
- **Spirometry (Children >5 years):**
    - Demonstrates obstructive pattern: FEV1/FVC ratio reduced (<0.80 in adults, often <0.90 in children)
    - **Reversibility testing (Gold Standard):** Post-bronchodilator increase in FEV1 >12% (and >200 mL in >12 years)
- **Peak Expiratory Flow Rate (PEFR):** Diurnal variability >13% over 2 weeks confirms diagnosis
- **Bronchoprovocation testing:** Fall in FEV1 >20% with methacholine/histamine or >10% with exercise
- **Allergy testing:** Skin prick test or specific IgE (RAST) to identify triggers (supportive, not diagnostic)

Management: Chronic Asthma (GINA 2023/2024 Updates)

- *GINA Paradigm Shift:* SABA-only treatment is no longer recommended for adults and adolescents due to risk of severe exacerbations.

1. Adolescents (>12 years) & Adults:

- **Track 1 (Preferred): MART (Maintenance and Reliever Therapy)**
    - *Step 1 & 2:* As-needed low-dose ICS-Formoterol
    - *Step 3:* Low-dose ICS-Formoterol maintenance + as-needed ICS-Formoterol
    - *Step 4:* Medium-dose ICS-Formoterol maintenance + as-needed ICS-Formoterol
    - *Step 5:* Add LAMA (Tiotropium) / Biologics (Omalizumab for high IgE, Mepolizumab for eosinophilic) / refer to specialist
- **Track 2 (Alternative):** Regular ICS + as-needed SABA (only if Track 1 unavailable/patient stable)

2. Children (6–11 years):

- *Step 1:* Low-dose ICS taken whenever SABA is taken
- *Step 2:* Daily low-dose ICS + PRN SABA
- *Step 3:* Low-dose ICS-LABA OR medium-dose ICS + PRN SABA (MART with very-low-dose ICS-formoterol is also an option here)

- *Step 4:* Medium-dose ICS-LABA OR refer for expert advice
- *Step 5:* Phenotypic assessment ± Biologics (Omalizumab)

3. Children (≤5 years):

- *Step 1:* PRN SABA
- *Step 2:* Daily low-dose ICS + PRN SABA
- *Step 3:* Double 'low-dose' ICS + PRN SABA
- *Step 4:* Continue double ICS + refer to specialist (consider adding LTRA)

Management: Acute Exacerbation

- **Mild/Moderate:**
  - SABA via MDI with spacer (4-10 puffs every 20 mins for 1 hour)
  - Oral Prednisolone (1-2 mg/kg/day for 3-5 days)
  - Target SpO2 93-95%
- **Severe (SpO2 <92%, PEF <50%):**
  - Oxygen therapy
  - Nebulized SABA + Ipratropium bromide
  - Systemic corticosteroids (IV Hydrocortisone or oral Prednisolone)
  - Consider IV Magnesium Sulfate (single dose 40-50 mg/kg over 20 mins)
- **Life-threatening (Impending arrest):**
  - Prepare for intubation/mechanical ventilation
  - IV Salbutamol or IV Aminophylline infusion

Complications

- Status asthmaticus (refractory acute exacerbation)
- Air leak syndromes (Pneumothorax, pneumomediastinum)
- Irreversible airway remodeling (chronic airflow limitation)
- Steroid toxicity (if overusing oral steroids/high-dose ICS): growth suppression, cataracts, osteopenia

Prognosis & Prevention

- **Prognosis:** Excellent with adherence to ICS; many children <5 years with viral-induced wheeze outgrow symptoms by school age.
- **Prevention:** Strict allergen avoidance, smoking cessation (parents), routine immunization (Influenza, Pneumococcal), treat comorbidities (Allergic rhinitis, GERD, obesity). Assess inhaler technique at every visit.

Exam Summary (Must-Write Points)

- **Definition:** Variable expiratory airflow limitation + chronic inflammation.
- **Diagnosis:** Post-bronchodilator FEV1 reversibility >12%.
- **GINA 2024 Update:** SABA monotherapy is obsolete in >12y; ICS-Formoterol (MART) is the preferred Track 1 reliever and maintenance.
- **Children <5y:** Step 2 starts with daily low-dose ICS; LTRA is an alternative but ICS is superior.
- **Acute Severe Rx:** O2 + SABA/Ipratropium nebs + Systemic Steroids + IV MgSO4.
- **Red Flags:** Silent chest and altered sensorium mandate immediate PICU escalation.

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2. Step up and step down therapy in asthma

Subject: Respiratory System

Basics

- **Goal:** Achieve good symptom control and minimize future risk (exacerbations, fixed airflow limitation, medication side effects).
- **Strategy:** Continuous cycle of Assess → Adjust (Step up/down) → Review.
- **Assessment Tools:** GINA symptom control tool (past 4 weeks), Asthma Control Test (ACT), spirometry.

Prerequisites Before Step-Up

- *Never step up blindly.* Always evaluate the "4 Ts":
    - **Technique:** Check inhaler/spacer technique.
    - **Taking it (Adherence):** Verify medication compliance.
    - **Triggers:** Assess ongoing environmental exposures (allergens, smoke, viral infections).
    - **Traits (Comorbidities):** Rule out/treat allergic rhinitis, GERD, obesity, vocal cord dysfunction.

Step-Up Therapy (GINA 2024 Updates)

- **Types of Step-Up:**
    - **Sustained:** For persistently poor control (assess after 2–3 months).
    - **Short-term:** For 1–2 weeks during viral infections or seasonal allergen exposure.
    - **Day-to-day:** Automated step-up via MART (Maintenance And Reliever Therapy) using ICS-Formoterol.
- **Adolescents (≥12 years) - Track 1 (Preferred):**
    - *Update:* SABA monotherapy is strictly contraindicated due to severe exacerbation risk.
    - **Steps 1 & 2:** As-needed low-dose ICS-Formoterol.
    - **Step 3:** Low-dose maintenance ICS-Formoterol + as-needed ICS-Formoterol (MART).
    - **Step 4:** Medium-dose maintenance ICS-Formoterol + as-needed ICS-Formoterol (MART).

    - **Step 5:** Add LAMA (Tiotropium) + phenotypic assessment for Biologics (Omalizumab, Mepolizumab, Dupilumab).

- **Children (6–11 years):**
    - **Step 1:** As-needed SABA + low-dose ICS (taken simultaneously).
    - **Step 2:** Daily low-dose ICS + as-needed SABA.
    - **Step 3:** Low-dose ICS-LABA (MART preferred if using Formoterol) OR Medium-dose ICS.
    - **Step 4:** Medium-dose ICS-LABA + refer for expert advice.
    - **Step 5:** Add Tiotropium or biologic (e.g., Anti-IgE/Omalizumab) + expert referral.
- **Preschoolers (≤5 years):**
    - **Step 1:** As-needed SABA.
    - **Step 2:** Daily low-dose ICS.
    - **Step 3:** Double 'low dose' ICS.
    - **Step 4:** Refer to specialist + consider addition of LTRA (Montelukast) or intermittent ICS.

Step-Down Therapy

- **Indications:** Symptoms well-controlled and lung function stable for **≥3 months**.
- **Contraindications for stepping down:** Ongoing respiratory infection, traveling, impending high-pollen season.
- **Methodology:**
    - Reduce ICS dose by **25–50%** at 2–3 month intervals.
    - If on ICS-LABA: Reduce ICS dose by 50%, continue LABA.
    - If on low-dose ICS: Switch to once-daily dosing.
    - *Red Flag:* **Never completely stop ICS** in a patient with an established asthma diagnosis (high risk of rebound exacerbation).

Monitoring & Prognosis

- Follow up 1–3 months after starting treatment, then every 3–12 months.
- Follow up within 1 week after an acute exacerbation.
- Monitor height yearly in children on long-term ICS (transient 1-2 cm reduction in final adult height may occur but is outweighed by severe asthma risks).

Exam Summary

- **Rule out pseudo-resistance:** Always check adherence and inhaler technique before stepping up.
- **GINA 2024 Paradigm Shift:** SABA-only treatment is obsolete for ≥12 years; as-needed ICS-Formoterol is the preferred reliever (Track 1).
- **MART Strategy:** Using ICS-Formoterol as both maintenance and reliever prevents exacerbations better than fixed-dose regimens.

- **Step-Down Rule:** Requires ≥3 months of strict control; reduce ICS by 25-50%; never stop ICS entirely.

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3. Management of acute severe asthma

Subject: Respiratory System

Definition & Grading

- **Acute Severe Asthma:** Severe exacerbation unresponsive to initial standard bronchodilator therapy; SpO2 < 92% on room air, PEFR < 50% predicted, inability to complete sentences.
- **Life-Threatening Asthma:** Presence of silent chest, cyanosis, poor respiratory effort, altered sensorium, or SpO2 < 92% despite oxygen therapy.

Etiology (Triggers)

- **Infections:** Viral URI (Rhinovirus, RSV, Influenza).
- **Allergens:** Pollen, dust mites, animal dander, mold.
- **Environmental:** Tobacco smoke, cold air, pollution.
- **Patient factors:** Poor compliance with inhaled corticosteroids (ICS), faulty inhaler technique.

Pathophysiology

- Acute bronchospasm + mucosal edema + thick mucus plugging.
- Leads to increased airway resistance and severe air trapping (hyperinflation).
- Results in V/Q mismatch, hypoxemia, and increased work of breathing (WOB).
- Eventual respiratory muscle fatigue leads to hypercapnia (Type 2 respiratory failure).

Clinical Features

- Severe dyspnea, tachypnea, tachycardia.
- Use of accessory muscles (sternocleidomastoid, intercostal retractions), tripod positioning.
- Loud biphasic wheeze (or ominous "silent chest" if airflow is critically low).
- Pulsus paradoxus (>20 mmHg drop in systolic BP during inspiration).
- Agitation progressing to lethargy/confusion (signs of hypercapnia/hypoxia).

Diagnosis & Investigations

- **Clinical Diagnosis:** Do not delay treatment for investigations.
- **Pulse Oximetry:** Continuous SpO2 monitoring.
- **PEFR:** < 50% of personal best or predicted (if child > 5 years and cooperative).
- **ABG:**
    - *Early:* Hypoxemia with respiratory alkalosis (low PaCO2).
    - *Trap:* A "normal" PaCO2 (35-45 mmHg) in a severely tachypneic child is a red flag for impending respiratory muscle fatigue.

- *Late:* Respiratory acidosis (high PaCO2).

- **CXR:** Not routine. Indicated only to rule out complications (pneumothorax, pneumomediastinum, pneumonia) or if unresponsive to therapy.
- **Serum Electrolytes:** Monitor for SABA-induced hypokalemia.

Management (Stepwise Algorithm)

- **1. Initial Resuscitation & Oxygenation**
  - Position propped up.
  - Target SpO2: 93–95% (children) via nasal prongs or face mask.
- **2. First-Line Pharmacotherapy (First Hour)**
  - **Inhaled SABA (Salbutamol):** Nebulized (2.5 mg if <20 kg; 5 mg if >20 kg) OR via pMDI with spacer (4–10 puffs). Give every 20 minutes for the first hour.
  - **Inhaled Anticholinergic (Ipratropium bromide):** 250 mcg (<20 kg) or 500 mcg (>20 kg) nebulized, mixed with SABA, every 20 minutes for 3 doses.
  - **Systemic Corticosteroids:** Give within 1 hour of presentation. Oral Prednisolone (1–2 mg/kg, max 40–50 mg) OR IV Hydrocortisone (4–5 mg/kg/dose) / IV Methylprednisolone (1–2 mg/kg/day).
- **3. Second-Line Therapy (Refractory/No improvement after 1 hour)**
  - **IV Magnesium Sulfate:** 40–50 mg/kg (max 2g) slow IV infusion over 20–30 minutes. Monitor BP (risk of hypotension).
  - **IV Bronchodilators:** IV Salbutamol or Terbutaline infusion (requires ICU monitoring for tachycardia/arrhythmias).
  - *Update (GINA 2024):* IV Aminophylline is rarely used/not recommended routinely due to narrow therapeutic index and toxicity.
- **4. Escalation & Respiratory Support (ICU)**
  - **NIV (HFNC or CPAP/BiPAP):** Used to stent airways and reduce WOB.
  - **Intubation & Mechanical Ventilation:**
    - *Indications:* Respiratory arrest, exhaustion, altered sensorium, refractory hypoxia/hypercapnia.
    - *Ventilator Strategy:* Permissive hypercapnia, low respiratory rate, prolonged expiratory time (low I:E ratio, e.g., 1:3 or 1:4) to prevent auto-PEEP, high peak inspiratory flow.
- **5. Supportive Care**
  - Maintain euvolemia (avoid fluid overload to prevent pulmonary edema).
  - Correct hypokalemia (due to frequent SABA use).

Complications

- Air leaks: Pneumothorax, pneumomediastinum, subcutaneous emphysema.
- Cardiopulmonary arrest, hypoxic-ischemic encephalopathy.

- Metabolic: Hypokalemia, lactic acidosis (from high-dose SABA).

Prognosis & Discharge Criteria

- **Discharge when:** Clinically stable, SpO2 > 94% on room air, PEFR > 70% predicted, sustained improvement for > 4 hours after last SABA dose.
- **Discharge Meds:** Complete a 3–5 day course of oral steroids.
- **Follow-up:** Step-up controller therapy (ICS).

Prevention

- Provide a written **Asthma Action Plan**.
- Verify and correct inhaler/spacer technique at every visit.
- Ensure adherence to daily controller medication (ICS).
- Administer annual Influenza and age-appropriate Pneumococcal vaccines.

Exam Summary (Must-Write Points)

- **Triad of 1st hour:** Oxygen (target 93-95%) + Nebulized Salbutamol/Ipratropium + Early systemic steroids.
- **Red Flag ABG:** Normal or rising PaCO2 in a severely breathless child indicates impending respiratory failure.
- **Red Flag Clinical:** "Silent chest" is a sign of critical airway obstruction, not improvement.
- **IV MgSO4:** Drug of choice for exacerbations refractory to 1st-hour treatment (dose: 40-50 mg/kg).
- **Ventilation rule:** Use low rate, long expiratory time, and permissive hypercapnia to avoid auto-PEEP and barotrauma.

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4. Type 2 asthma

Subject: Respiratory System

Definition

- Asthma endotype driven by Type 2 inflammatory pathways (Th2 cells and Type 2 Innate Lymphoid Cells [ILC2]).
- Encompasses two major phenotypes: Allergic (early-onset) and Eosinophilic (often later-onset, severe) asthma.

Pathophysiology

- **Triggers:** Allergens (dust mites, pollen) or viruses damage airway epithelium.
- **Alarmins:** Epithelium releases TSLP, IL-25, and IL-33.
- **Cellular Activation:** Activates Th2 cells (adaptive) and ILC2s (innate).
- **Key Cytokines:**

- **IL-4:** Promotes B-cell isotype switching to IgE.
- **IL-5:** Drives eosinophil proliferation, maturation, and survival.
- **IL-13:** Induces airway hyperresponsiveness, goblet cell hyperplasia (mucus), and airway remodeling.

Clinical Features

- **Onset:** Typically childhood-onset (classic allergic phenotype).
- **Atopic March:** Frequently coexists with allergic rhinitis, atopic dermatitis, and food allergies.
- **Triggers:** Symptoms predictably worsen with allergen exposure, viral infections, or exercise.
- **Treatment Response:** Characteristically highly responsive to Inhaled Corticosteroids (ICS).

Diagnostic Biomarkers

- *Essential for phenotyping severe asthma before starting biologics.*
- **Blood Eosinophils:** ≥150–300 cells/μL (indicates eosinophilic drive).
- **Sputum Eosinophils:** ≥2–3% (gold standard but difficult in pediatrics).
- **FeNO (Fractional exhaled Nitric Oxide):** ≥20 ppb in children (marker of IL-13 driven epithelial inflammation).
- **Allergy Testing:** Elevated total serum IgE; positive specific IgE (RAST) or skin prick test to aeroallergens.

Management (GINA 2024 Guidelines)

- **First-line:** ICS + Formoterol (MART - Maintenance and Reliever Therapy) is preferred across steps.
- **Add-on Therapy:** Leukotriene Receptor Antagonists (LTRA - Montelukast) target eosinophilic/allergic pathways.
- **Targeted Biologics (Severe, refractory T2 Asthma):**
  - **Anti-IgE (Omalizumab):** For severe allergic asthma; approved ≥6 years. Dosed by weight and total IgE.
  - **Anti-IL-5 (Mepolizumab):** For severe eosinophilic asthma; approved ≥6 years. (Benralizumab/Reslizumab typically ≥12 or ≥18 yrs).
  - **Anti-IL-4Rα (Dupilumab):** Blocks both IL-4 and IL-13; approved ≥6 years. Highly effective if coexisting severe eczema.
  - **Anti-TSLP (Tezepelumab):** Blocks upstream alarmin; approved ≥12 years. Useful for both T2-high and T2-low asthma.

Complications & Prognosis

- **Prognosis:** Generally excellent; most achieve control with low/medium dose ICS.
- **Complications:** Uncontrolled chronic T2 inflammation leads to irreversible airway remodeling (subepithelial fibrosis, smooth muscle hypertrophy).

Exam Summary: Must-Write Points

- **Core Cytokines:** IL-4 (IgE), IL-5 (Eosinophils), IL-13 (Mucus/Hyperresponsiveness).
- **Biomarkers:** High FeNO (≥20 ppb), High blood eosinophils (≥150/μL), High IgE.
- **First-line:** ICS is the cornerstone; highly effective in T2 asthma.
- **Biologics (Pediatric Cutoffs):** Omalizumab, Mepolizumab, and Dupilumab are all approved for age **≥6 years**.

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5. Acute respiratory distress syndrome in children definition and treatment recommendations

Subject: Respiratory System

Definition (PALICC-2 Criteria, 2023)

Pediatric Acute Respiratory Distress Syndrome (PARDS) is defined by the **2023 Pediatric Acute Lung Injury Consensus Conference (PALICC-2)** criteria:

- **Age:** Excludes perinatal-specific lung diseases.
- **Timing:** Within 7 days of a known clinical insult.
- **Origin of Edema:** Respiratory failure not fully explained by cardiac failure or fluid overload.
- **Imaging:** New infiltrates consistent with acute pulmonary parenchymal disease (Update: *Bilateral or unilateral* infiltrates are now accepted).
- **Oxygenation Criteria (Invasive Ventilation):** Based on Oxygenation Index (OI) or Oxygen Saturation Index (OSI).
    - *Mild:* OI 4 to <8 (or OSI 5 to <7.5)
    - *Moderate:* OI 8 to <16 (or OSI 7.5 to <12.3)
    - *Severe:* OI ≥16 (or OSI ≥12.3)
- **Oxygenation Criteria (Non-Invasive):**
    - CPAP/BiPAP ≥5 cmH2O: PaO2/FiO2 ≤300 or SpO2/FiO2 ≤264.
    - High Flow Nasal Cannula (HFNC): Included in PALICC-2 for specific age-based flow limits.

    (Formulas: OI = [MAP × FiO2 × 100] / PaO2; OSI = [MAP × FiO2 × 100] / SpO2)

Etiology

- **Direct Lung Injury:** Pneumonia (viral/bacterial), aspiration, pulmonary contusion, inhalation injury, near-drowning.
- **Indirect Lung Injury:** Sepsis (most common), severe trauma, massive transfusion (TRALI), pancreatitis, burns.

Pathophysiology

- **Exudative Phase (0-7 days):** Alveolar macrophage activation → Cytokine storm (IL-1, IL-6, TNF-α) → Endothelial/epithelial damage → Protein-rich fluid leaks into alveoli.

- **Surfactant Dysfunction:** Inactivation by plasma proteins → Alveolar collapse → Intrapulmonary shunting (V/Q mismatch) → Refractory hypoxemia.
- **Proliferative Phase (7-21 days):** Type II pneumocyte proliferation, early matrix deposition.
- **Fibrotic Phase (>21 days):** Extensive collagen deposition, structural remodeling, chronic lung disease (in survivors).

Clinical Features

- **Onset:** Acute severe dyspnea, tachypnea, grunting, severe retractions.
- **Hypoxemia:** Cyanosis refractory to standard oxygen therapy.
- **Auscultation:** Diffuse bilateral crackles/crepitations.
- **Systemic:** Signs of underlying cause (e.g., shock, fever) and evolving multiorgan dysfunction syndrome (MODS).

Diagnosis

- **ABG:** Severe hypoxemia (low PaO2), initially respiratory alkalosis → later respiratory acidosis + metabolic acidosis (tissue hypoxia).
- **Chest X-Ray / USG:** Diffuse patchy infiltrates, "white-out" lung, absence of cardiomegaly (differentiates from cardiogenic edema).
- **Echocardiography:** Normal LV function; useful to rule out congenital heart disease or assess for secondary pulmonary hypertension/RV dysfunction.

Management (PALICC-2 Recommendations)

1. Conventional Mechanical Ventilation (First-Line)

- **Lung Protective Ventilation (LPV):** Core strategy to prevent Ventilator-Induced Lung Injury (VILI).
- **Tidal Volume (Vt):** 4–6 mL/kg of *ideal body weight* (up to 8 mL/kg if compliance is preserved).
- **Plateau Pressure (Pplat):** Limit to ≤28 cmH2O (allow up to 30–32 cmH2O if chest wall compliance is reduced).
- **Driving Pressure:** Target <15 cmH2O (Pplat minus PEEP).
- **PEEP:** Titrate optimally using ARDSNet tables; high enough to prevent alveolar collapse (atelectrauma) but low enough to avoid overdistension (volutrauma).
- **Permissive Hypercapnia:** Allow PaCO2 to rise (even 60-80 mmHg) to maintain low Vt, provided pH remains >7.15 and no intracranial hypertension exists.

2. Escalation / Refractory Hypoxemia

- **Prone Positioning:** Strongly recommended for severe PARDS; maintain for ≥12–16 hours/day.
- **Neuromuscular Blockade (NMBA):** Early, short course (24-48 hours) to facilitate ventilation and eliminate patient-ventilator asynchrony in severe cases.
- **High-Frequency Oscillatory Ventilation (HFOV):** Rescue therapy if Pplat >28 cmH2O or failing conventional LPV.

- **Inhaled Nitric Oxide (iNO):** Not for routine use. Rescue therapy for documented Right Ventricular (RV) dysfunction or severe life-threatening hypoxemia.
- **ECMO:** V-V ECMO indicated for severe, potentially reversible PARDS refractory to all optimal medical/ventilator management.

3. Supportive Care

- **Fluid Management:** Conservative strategy *after* initial shock resuscitation. Aim for zero or negative fluid balance to reduce pulmonary edema.
- **Nutrition:** Early enteral nutrition preferred; use gastric tubes.
- **Sedation:** Goal-directed, avoiding over-sedation; use daily sedation vacations.

4. Pharmacotherapy

- **Corticosteroids:** Not routinely recommended for all PARDS. Consider only for specific triggers (e.g., severe PCP pneumonia, COVID-19 MIS-C) or refractory vasopressor-dependent shock.
- **Surfactant:** Routine exogenous surfactant is **not** recommended in PARDS.
- **Antibiotics:** Early empiric broad-spectrum coverage if sepsis/pneumonia is suspected.

Complications

- **Pulmonary:** Barotrauma (pneumothorax, pneumomediastinum), Ventilator-Associated Pneumonia (VAP), pulmonary fibrosis.
- **Systemic:** Multiorgan Failure (MOF), Critical illness myopathy/neuropathy, VTE.

Prognosis

- Mortality ranges from 15–30% (primarily driven by underlying cause/MODS rather than hypoxemia alone).
- Survivors often face long-term physical deconditioning, restrictive lung defects, and neurocognitive/psychological sequelae (Post-Intensive Care Syndrome - PICS).

💡 **Exam Summary (Must-Write Points)**

- **PALICC-2 2023 Update:** Unilateral infiltrates now accepted; severity classified by OI/OSI, not just PaO2/FiO2.
- **Formulas:** OI = (MAP × FiO2 × 100) / PaO2. Severe PARDS = OI ≥ 16.
- **Ventilation:** Lung Protective Strategy is paramount → Low Vt (4-6 mL/kg), limit Pplat (≤28 cmH2O), optimal PEEP, Permissive Hypercapnia (pH >7.15).
- **Fluid Strategy:** Conservative (keep lungs "dry") post-resuscitation.
- **Rescue Therapies:** Prone positioning (≥12 hrs/day), NMBA, HFOV, V-V ECMO.
- **Contraindicated/Not Routine:** Routine systemic steroids and exogenous surfactant are NOT recommended.

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6. Cystic fibrosis diagnosis and management

Subject: Respiratory System

Basics & Genetics

- **Inheritance:** Autosomal recessive.
- **Gene:** *CFTR* (Cystic Fibrosis Transmembrane Conductance Regulator) on chromosome 7q31.2.
- **Most Common Mutation:** F508del (Class II mutation: defective protein processing/trafficking).

Pathophysiology

- **Mechanism:** Defective cyclic AMP-dependent chloride channel.
- **Lungs/GI:** Decreased chloride secretion, increased sodium and water absorption → dehydrated, thick, viscous mucus.
- **Sweat Glands:** Defective chloride reabsorption → high salt content in sweat.
- **Consequence:** Luminal obstruction, chronic infection, exaggerated neutrophilic inflammation, and progressive tissue destruction.

Clinical Features

- **Neonatal:** Meconium ileus (pathognomonic), prolonged neonatal jaundice.
- **Respiratory:** Chronic productive cough, recurrent pneumonia (*S. aureus* in early childhood, *Pseudomonas aeruginosa* later), nasal polyps, chronic sinusitis.
- **Gastrointestinal:** Pancreatic exocrine insufficiency (steatorrhea, failure to thrive), rectal prolapse, Distal Intestinal Obstruction Syndrome (DIOS).
- **Genitourinary:** Congenital Bilateral Absence of Vas Deferens (CBAVD) causing obstructive azoospermia (>95% males).
- **Endocrine:** Cystic Fibrosis-Related Diabetes (CFRD) – typically peaks in adolescence.

Diagnosis

- **Diagnostic Criteria Formula:** Clinical symptom OR Positive Newborn Screen (NBS) OR Sibling with CF **PLUS** Evidence of CFTR dysfunction (Sweat test or Genetics or NPD).
- **Sweat Chloride Test (Gold Standard):**
    - Method: Pilocarpine iontophoresis.
    - Normal: <30 mmol/L.
    - Equivocal: 30–59 mmol/L (repeat test, do genetics).
    - Diagnostic: ≥60 mmol/L (on two separate occasions).
- **Genetic Testing:** Identification of two disease-causing *CFTR* mutations (in *trans*).
- **Nasal Potential Difference (NPD):** Used for atypical cases; shows more negative baseline potential and absent response to isoproterenol.
- **Supportive Investigations:**
    - **Newborn Screen:** High Immunoreactive Trypsinogen (IRT) on Guthrie card.

- **CXR/HRCT:** Hyperinflation, tram-track lines, signet-ring sign (bronchiectasis), upper lobe predominance.
- **Sputum Culture:** Classic pathogens (*P. aeruginosa, Burkholderia cepacia, S. aureus, H. influenzae*).
- **Stool:** Low fecal elastase (<200 µg/g) confirms pancreatic insufficiency.

Management: Respiratory

- **Airway Clearance Therapy (ACT):** Chest physiotherapy, positive expiratory pressure (PEP) devices, high-frequency chest wall oscillation.
- **Mucolytics:**
  - **Dornase alfa (rhDNase):** Cleaves extracellular DNA from necrotic neutrophils; reduces sputum viscosity.
  - **Hypertonic Saline (7%):** Hydrates airway surface liquid (osmotic effect).
- **Infection Control:**
  - **Eradication:** Aggressive treatment of first *Pseudomonas* isolate (inhaled tobramycin or colistin x 28 days).
  - **Chronic Suppression:** Inhaled tobramycin/aztreonam (alternating months) for chronic *Pseudomonas*.
  - **Anti-inflammatory:** Oral azithromycin (3x/week) reduces exacerbations and disrupts *Pseudomonas* biofilms.

Management: GI & Nutrition

- **Diet:** High-calorie, high-fat, high-protein (110–200% of normal daily requirements).
- **Pancreatic Enzyme Replacement Therapy (PERT):** Taken with all meals and snacks; dosed based on lipase units.
- **Vitamins:** Routine supplementation of fat-soluble vitamins (A, D, E, K).
- **Hepatobiliary:** Ursodeoxycholic acid (UDCA) for CF-associated liver disease to improve bile flow.

Management: CFTR Modulators (Highly Tested Updates)

- **Mechanism:** Targets the underlying protein defect rather than symptoms.
- **Ivacaftor (Potentiator):** For Class III (gating) mutations (e.g., G551D). Keeps channel open longer.
- **Lumacaftor/Tezacaftor (Correctors):** Help fold and traffic the F508del protein to the cell surface.
- **Elexacaftor/Tezacaftor/Ivacaftor (Triple Therapy / Trikafta):**
  - *Indication:* Patients with at least one F508del mutation (covers ~90% of CF population).
  - *FDA/AAP Update (2023):* Now approved for children aged **≥2 years**.

Complications & Escalation

- **Hemoptysis:** Stop NSAIDs/ACT; massive hemoptysis (>240 mL) requires bronchial artery embolization.
- **Pneumothorax:** Small (<20%) observe; large requires chest tube + pleurodesis.
- **Allergic Bronchopulmonary Aspergillosis (ABPA):** Suspect if sudden clinical decline + high IgE; treat with systemic steroids + itraconazole.
- **End-Stage Lung Disease:** Bilateral lung transplantation (improves survival, does not cure systemic CF).

Prognosis

- Life expectancy has improved dramatically (median survival >50 years in developed countries) due to early NBS, aggressive nutrition, and CFTR modulators.
- *Burkholderia cepacia* complex infection is a poor prognostic marker and a relative contraindication to lung transplant in some centers.

Exam Summary: High-Yield Must-Write Points

- **Defect:** *CFTR* gene (7q31.2), F508del mutation, defective Cl- channel.
- **Diagnosis:** Clinical/NBS + Sweat Chloride ≥60 mmol/L (Pilocarpine iontophoresis).
- **Neonatal Clue:** Meconium ileus (almost always CF).
- **Lung Pathogens:** *S. aureus* (infants) → *P. aeruginosa* (older children/adults).
- **Game-Changer Rx:** Elexacaftor/Tezacaftor/Ivacaftor (Triple therapy) for ≥1 F508del mutation, now approved for age ≥2 years.
- **GI Rx:** High-calorie diet + PERT + ADEK vitamins.

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7. Pleural effusion in children: diagnostic approach and management

Subject: Respiratory System

Definition

- Abnormal accumulation of fluid within the pleural space due to an imbalance between fluid formation and absorption.

Pathophysiology

- **Transudate:** Increased hydrostatic pressure or decreased oncotic pressure; intact capillaries.
- **Exudate:** Increased capillary permeability or impaired lymphatic drainage; damaged capillaries.

Etiology

- **Exudative (Most common in children):**
    - Infections: Parapneumonic (most common; *S. pneumoniae*, *S. aureus*, Group A *Streptococcus*), Tuberculosis (TB), Mycoplasma.
    - Malignancy: Lymphoma, Leukemia, Neuroblastoma.

- Autoimmune: Systemic Lupus Erythematosus (SLE), Juvenile Idiopathic Arthritis (JIA).
- Others: Pancreatitis, Uremia, Chylothorax (trauma, congenital).

- **Transudative:**
  - Congestive Heart Failure (CHF).
  - Hypoproteinemia: Nephrotic syndrome, Protein-losing enteropathy, Liver cirrhosis.

Clinical Features

- **Symptoms:** Pleuritic chest pain (worsens on inspiration), tachypnea, dyspnea, dry cough, high-grade fever (in parapneumonic effusion).
- **Signs:**
  - Inspection: Restricted chest wall movement on the affected side, fullness of intercostal spaces.
  - Palpation: Decreased vocal fremitus, apical impulse/trachea shifted to the contralateral side.
  - Percussion: Stony dullness.
  - Auscultation: Decreased or absent vesicular breath sounds, pleural friction rub (early stage).

Diagnostic Approach

- **1. Imaging:**
  - **Chest X-Ray (CXR):** PA/AP and Lateral views. Shows obliteration of costophrenic angle, meniscus sign, homogeneous opacity. Lateral decubitus detects small/free-flowing fluid (>10 mL).
  - **Chest Ultrasound (USG):** *Modality of choice* to confirm fluid, detect septations/loculations, measure pleural thickness, and guide thoracentesis.
  - **Contrast CT Chest:** Not routine. Indicated for suspected malignancy, parenchymal necrosis, lung abscess, or pre-surgical (VATS) mapping.
- **2. Thoracentesis (Diagnostic Tap):**
  - Indicated for all new effusions of unknown etiology, suspected empyema, or respiratory compromise.
  - Avoid if effusion is purely transudative (e.g., known nephrotic syndrome) without distress.
- **3. Pleural Fluid Analysis:**
  - **Light's Criteria (Diagnoses Exudate if ≥1 met):**
    - Pleural fluid protein / Serum protein > 0.5
    - Pleural fluid LDH / Serum LDH > 0.6
    - Pleural fluid LDH > 2/3 upper limit of normal serum LDH
  - **Biochemistry:**

        - pH < 7.2 (Strongest indicator for chest tube drainage).
        - Glucose < 40 mg/dL (Suggests empyema, TB, malignancy, or rheumatoid arthritis).
        - Adenosine Deaminase (ADA) > 40 U/L (Highly suggestive of TB).
        - Triglycerides > 110 mg/dL (Chylothorax).
    - **Cytology:**
        - Neutrophil predominance: Acute parapneumonic effusion, pulmonary infarction.
        - Lymphocyte predominance: TB, malignancy, viral infection.
    - **Microbiology:** Gram stain, Aerobic/Anaerobic culture, AFB smear/GeneXpert, Pneumococcal antigen test.

Management (Focus: Parapneumonic Effusion/Empyema)

- **Supportive Care:**
    - Supplemental oxygen for hypoxemia.
    - Adequate analgesia (NSAIDs/Paracetamol) to prevent splinting and atelectasis.
    - IV fluids and nutritional support.
- **Medical Therapy:**
    - **Empiric IV Antibiotics:** 3rd generation Cephalosporin (Ceftriaxone/Cefotaxime) + Clindamycin or Vancomycin/Linezolid (if MRSA suspected).
    - Duration: 2–4 weeks depending on clinical response and organism.
- **Interventional Step-up Approach (BTS/IAP Guidelines):**
    - **Step 1: Simple Thoracentesis.** For small, uncomplicated effusions.
    - **Step 2: Intercostal Chest Drain (ICD).**
        - *Indications:* Purulent fluid (pus), pH < 7.2, Glucose < 40 mg/dL, positive Gram stain/culture, or massive effusion causing respiratory compromise.
        - Small-bore pigtail catheters (10–14 Fr) are preferred over large-bore tubes.
    - **Step 3: Intrapleural Fibrinolytics.**
        - *Indicated for:* Loculated/septated empyema (USG proven) not draining via ICD.
        - *Agents:* Urokinase (40,000 units in normal saline) or Tissue Plasminogen Activator (tPA/Alteplase). Given twice daily for 3 days.
    - **Step 4: Video-Assisted Thoracoscopic Surgery (VATS).**
        - *Indicated for:* Failure of ICD + fibrinolytics after 48–72 hours, persistent sepsis, or thick pleural peel.
    - **Step 5: Open Thoracotomy & Decortication.**
        - Reserved for chronic, organized fibrothorax with trapped lung.

Complications

- Bronchopleural fistula.
- Tension pneumothorax / Pyopneumothorax.
- Lung abscess / Pneumatocele.
- Fibrothorax and trapped lung.
- Scoliosis (usually transient, secondary to pain/splinting).

Prognosis & Prevention

- **Prognosis:** Excellent in children compared to adults. Even with severe empyema, long-term pulmonary function usually returns to normal within 3–6 months.
- **Prevention:** Routine immunization with Pneumococcal Conjugate Vaccine (PCV) and *Haemophilus influenzae* type b (Hib) vaccine.

Exam Summary: Must-Write Points

- **Most common cause:** Parapneumonic effusion (*S. pneumoniae*).
- **USG Chest:** Modality of choice for septations and guiding tap; CT is NOT first-line.
- **Light's criteria:** Differentiates transudate vs exudate (Protein ratio >0.5, LDH ratio >0.6).
- **Absolute indications for ICD:** Pus, positive Gram stain, pH < 7.2, glucose < 40 mg/dL.
- **Loculated empyema management:** Small-bore ICD + Intrapleural Fibrinolytics (Urokinase/tPA) → VATS if fails.

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8. Bronchiectasis diagnostic approach and management

Subject: Respiratory System

Definition

- Irreversible, abnormal dilation and distortion of the bronchial tree due to structural wall destruction.

Etiology

- **Post-infectious (Most common in developing nations):** Tuberculosis, Adenovirus, Measles, Pertussis, severe pneumonia.
- **Mucociliary clearance defects:** Cystic Fibrosis (CF), Primary Ciliary Dyskinesia (PCD).
- **Immunodeficiency:** Common Variable Immunodeficiency (CVID), X-linked Agammaglobulinemia (XLA), Chronic Granulomatous Disease (CGD).
- **Aspiration:** Uncoordinated swallowing, severe GERD, neurodisability, retained foreign body.
- **Hypersensitivity:** Allergic Bronchopulmonary Aspergillosis (ABPA).
- **Congenital/Anatomical:** Williams-Campbell syndrome (cartilage defect), Mounier-Kuhn syndrome (tracheobronchomegaly), sequestration.

Pathophysiology

- **Cole's Vicious Cycle:** Initial insult → Impaired mucociliary clearance → Retained secretions → Chronic bacterial infection → Inflammatory response (neutrophil elastase release) → Airway wall destruction → Further dilation and impaired clearance.

Clinical Features

- **Classic symptom:** Chronic wet/productive cough lasting >8 weeks.
- **Sputum:** Purulent, often copious; worse in the morning.
- **Signs:** Digital clubbing, halitosis, poor weight gain/growth failure.
- **Auscultation:** Persistent coarse crackles, localized wheezing.
- **Exacerbations:** Increased cough, change in sputum volume/color, fever, dyspnea.

Diagnostic Approach

- **Imaging (Gold Standard):** High-Resolution Computed Tomography (HRCT) of the chest.
    - *Signet-ring sign:* Bronchus diameter > adjacent pulmonary artery.
    - *Tram-tracking:* Parallel thickened bronchial walls.
    - *Lack of tapering:* Bronchi visible within 1 cm of the pleura.
- **Initial Imaging:** Chest X-ray (shows ring shadows, honeycombing, volume loss, but low sensitivity).
- **Microbiology:** Deep throat swab or sputum culture (look for *H. influenzae*, *S. pneumoniae*, *Staph aureus*, *Pseudomonas aeruginosa*, NTM).
- **Etiological Workup (Must perform in all cases):**
    - *CF screen:* Sweat chloride test (first-line) ± CFTR genetics.
    - *Immune workup:* Serum IgG, IgA, IgM, IgE, and specific vaccine antibody responses.
    - *PCD screen:* Nasal Nitric Oxide (low in PCD) → ciliary biopsy/genetics.
    - *ABPA screen:* Total IgE, Aspergillus specific IgE/IgG.
    - *Anatomy/FB:* Flexible bronchoscopy (if localized disease on HRCT to rule out foreign body or structural anomaly).

Management

- **Airway Clearance Therapy (ACT) (Cornerstone):**
    - Daily chest physiotherapy, postural drainage, and percussion.
    - Positive Expiratory Pressure (PEP) devices (e.g., Acapella, Flutter).
    - *Mucoactive agents:* Nebulized hypertonic saline (3-7%) prior to ACT.
    - *Update/Trap:* Recombinant human DNase (Dornase alfa) is indicated in CF but **strictly contraindicated** in Non-CF bronchiectasis (increases exacerbations).
- **Antibiotic Therapy:**
    - *Acute Exacerbations:* 14-day course based on prior cultures (empirical: Amoxicillin-Clavulanate or Macrolide; Ciprofloxacin if *Pseudomonas* suspected).

  - *Eradication:* Aggressive treatment upon first isolation of *P. aeruginosa* (e.g., Nebulized Tobramycin/Colistin + Oral Ciprofloxacin for 1-3 months).
  - *Maintenance:* Long-term oral Azithromycin (3x/week) for immunomodulatory and antibacterial effects (indicated if ≥3 exacerbations/year).
- **Bronchodilators:** Only if concurrent airway hyperreactivity/asthma is documented.
- **Surgical Intervention:** Lobectomy/segmentectomy reserved for highly localized disease refractory to medical management or for life-threatening hemoptysis.
- **Hemoptysis Management:** Mild (treat exacerbation); Massive (Bronchial Artery Embolization [BAE] → surgery if BAE fails).

Complications

- Massive hemoptysis (from hypertrophied bronchial arteries).
- Cor pulmonale and pulmonary hypertension.
- Respiratory failure.
- Brain abscess, secondary amyloidosis (rare now).

Prevention

- Prompt treatment of lower respiratory tract infections.
- Foreign body removal without delay.
- Vaccination: Pneumococcal, Influenza, Measles, Pertussis.

Exam Summary

- **Cole's cycle:** Infection ↔ Inflammation ↔ Structural damage.
- **Diagnosis:** HRCT is the gold standard (look for *Signet-ring sign* and *Tram-tracking*).
- **Workup non-negotiables:** Sweat chloride, Immunoglobulins, Sputum culture.
- **Management triad:** Airway clearance (Hypertonic saline + PEP) + Antibiotics (exacerbation/eradication/maintenance) + Nutrition.
- **Trap:** Do NOT use rhDNase (Dornase alfa) in non-CF bronchiectasis.
- **Pseudomonas:** First isolation requires immediate, aggressive eradication therapy.

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8. Recurrent respiratory infections in children

Subject: Respiratory System

Definition

- **Recurrent Upper Respiratory Infections (URTI):** >6–8 episodes/year in young children (normal in daycare/school-aged).
- **Recurrent Lower Respiratory Infections (LRTI):** ≥2 episodes of pneumonia in a single year, or >3 episodes over any timeframe.
- **Recurrent Otitis Media:** ≥3 episodes in 6 months, or ≥4 episodes in 12 months.

Etiology & Classification Divided into four classic categories (The 50-30-10-10 Rule):

- **Normal child (50%):** Frequent viral URTIs due to daycare, older siblings, or passive smoking; normal growth and rapid recovery.
- **Atopy/Allergy (30%):** Asthma, allergic rhinitis; triggered by aeroallergens, family history positive.
- **Structural/Anatomical (10%):** Retained foreign body, tracheomalacia, vascular ring, adenoid hypertrophy, cleft palate.
- **Chronic Disease/Immunodeficiency (10%):**
    - *Mucociliary clearance:* Cystic Fibrosis (CF), Primary Ciliary Dyskinesia (PCD).
    - *Aspiration:* Severe GERD, H-type tracheoesophageal fistula (TEF), bulbar palsy.
    - *Immunodeficiency:* Primary (X-linked Agammaglobulinemia, CVID, IgA deficiency, SCID) or Secondary (HIV, malnutrition).

Clinical Clues & Red Flags

- **SPUR Criteria for Immunodeficiency: S**evere, **P**ersistent, **U**nusual organisms, **R**ecurrent.
- *Failure to thrive (FTT) + chronic diarrhea:* Suspect CF or severe Primary Immunodeficiency (PID).
- *Choking with feeds:* Suspect aspiration, GERD, or H-type TEF.
- *Situs inversus + chronic sinusitis:* Suspect Kartagener syndrome (PCD).
- *Unilateral foul-smelling nasal discharge:* Suspect retained foreign body.
- *Persistent localized wheeze/infiltrate in same lobe:* Suspect anatomical anomaly or foreign body.
- *Eczema + seasonal flares:* Suspect atopy/asthma.

Diagnosis: Stepwise Approach

- **Tier 1 (Initial Screening):**
    - Complete Blood Count (CBC) with differential (assess Absolute Neutrophil and Lymphocyte Counts).
    - Peripheral smear (Howell-Jolly bodies imply asplenia).
    - Quantitative Immunoglobulins (IgG, IgA, IgM, IgE).
    - Chest X-ray (CXR) AP and Lateral (hyperinflation, focal infiltrates, right-sided heart).
    - HIV serology (if risk factors).
- **Tier 2 (Specific Testing):**
    - *CF:* Sweat chloride test (>60 mEq/L is diagnostic).
    - *PCD:* Nasal nitric oxide (low in PCD), Saccharin test.
    - *Asthma:* Spirometry with bronchodilator reversibility (if >5 years old).
    - *Aspiration:* Barium swallow, 24-hour esophageal pH monitoring.

- *Immune function:* Specific vaccine antibody titers (Tetanus, Diphtheria, Pneumococcal).

- **Tier 3 (Advanced/Specialist):**
  - Flexible bronchoscopy (structural lesions, bronchoalveolar lavage).
  - High-Resolution CT (HRCT) chest (bronchiectasis, interstitial disease).
  - Flow cytometry (lymphocyte subsets: CD3, CD4, CD8, CD19, CD56).
  - Whole exome sequencing/Genetic panels.

Management

- **General/Supportive:**
  - Optimize nutrition (Vitamin A, Zinc, Vitamin D).
  - Strict avoidance of passive smoke and indoor air pollution (biomass fuels).
  - Temporary withdrawal from daycare (if safe and feasible).
- **Targeted Therapy:**
  - *Allergy/Asthma:* Inhaled corticosteroids (ICS), antihistamines, leukotriene receptor antagonists (LTRA).
  - *Anatomical/Foreign Body:* Rigid bronchoscopy for FB removal; surgical correction of anomalies.
  - *Cystic Fibrosis:* Chest physiotherapy, hypertonic saline, dornase alfa, CFTR modulators (e.g., Elexacaftor/Tezacaftor/Ivacaftor).
  - *Immunodeficiency:* Intravenous/Subcutaneous Immunoglobulin (IVIG/SCIG) replacement, prophylactic antibiotics (e.g., Cotrimoxazole), Hematopoietic Stem Cell Transplant (HSCT) for SCID.
  - *GERD:* Thickened feeds, upright positioning, PPIs (if erosive).

Complications

- Bronchiectasis (irreversible airway dilation).
- Growth retardation / Failure to thrive.
- Cor pulmonale (secondary to chronic hypoxia/pulmonary hypertension).
- Conductive hearing loss (due to recurrent AOM).

Prevention

- **IAP/AAP 2024 Vaccination Guidelines:** Ensure age-appropriate completion of National Immunization Schedule.
- *Special populations:* Annual Influenza vaccine (>6 months age), Pneumococcal vaccines (PCV15/20 or sequential PCV + PPSV23 for high-risk groups >2 years).
- Exclusive breastfeeding for the first 6 months of life.
- Good hand hygiene and cough etiquette.

Exam Summary: Must-Write Points

- *50-30-10-10 Rule:* 50% normal, 30% atopic, 10% structural, 10% immunodeficient/chronic disease.
- *Red Flags:* Use the **SPUR** mnemonic (Severe, Persistent, Unusual, Recurrent) to differentiate normal viral URTIs from underlying pathology.
- *Same Lobe vs. Different Lobes:* Recurrence in the *same* lobe suggests structural anomaly/foreign body; recurrence in *multiple/different* lobes suggests systemic disease (CF, PID, Asthma).
- *First-line investigations:* Always include CBC with ANC/ALC, IgG/IgA/IgM, and CXR.
- *Prevention:* Passive smoke avoidance, exclusive breastfeeding, and Pneumococcal/Influenza vaccination are critical interventions.

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9. Non cardiogenic pulmonary edema

Subject: Respiratory System

Definition

- Accumulation of protein-rich fluid in pulmonary interstitium and alveoli due to altered alveolar-capillary membrane permeability.
- Occurs with **normal** pulmonary capillary hydrostatic pressure (rules out left heart failure).

Etiology

- **Direct Lung Injury:**
  - Severe pneumonia (viral/bacterial)
  - Aspiration (gastric contents, meconium)
  - Toxic inhalation (smoke, chemicals)
  - Near-drowning
- **Indirect Lung Injury:**
  - Sepsis (most common cause of ARDS)
  - Multiple trauma / shock
  - Transfusion-Related Acute Lung Injury (TRALI)
  - Acute pancreatitis
- **Specific Syndromes:**
  - **Neurogenic Pulmonary Edema (NPE):** Post-seizures, head trauma, raised ICP (sympathetic surge).
  - **High Altitude Pulmonary Edema (HAPE):** Hypoxic pulmonary vasoconstriction.
  - **Re-expansion Pulmonary Edema:** Following rapid drainage of massive pleural effusion/pneumothorax.

Pathophysiology

- **Insult/Trigger:** Release of pro-inflammatory cytokines (TNF-α, IL-1, IL-6, IL-8).

- **Endothelial/Epithelial Injury:** Breakdown of the alveolar-capillary barrier.
- **Fluid Shift:** Leakage of protein-rich exudate into interstitium and alveoli.
- **Surfactant Dysfunction:** Alveolar flooding dilutes and inactivates surfactant.
- **Consequence:** Microatelectasis, decreased lung compliance, profound intrapulmonary shunting, and refractory hypoxemia.

Clinical Features

- **Symptoms:** Acute onset severe dyspnea, tachypnea, grunting, restlessness.
- **Signs:** Cyanosis (unresponsive to standard O2), intercostal retractions, diffuse bilateral crackles/crepitations.
- **Secretions:** Pink, frothy sputum (hallmark of alveolar flooding).
- **Absence of Heart Failure:** Normal JVP, no gallop rhythm, no hepatomegaly, normal peripheral perfusion.

Diagnosis

- **Chest X-ray:** Bilateral diffuse alveolar infiltrates ("white-out" lung), normal cardiothoracic ratio, absence of prominent Kerley B lines or pleural effusions (differentiates from cardiogenic).
- **Echocardiography (Crucial):** Normal left ventricular ejection fraction and normal structural anatomy (rules out cardiogenic etiology).
- **Arterial Blood Gas (ABG):** Severe hypoxemia (low PaO2), initially respiratory alkalosis → progresses to respiratory acidosis.
- **Pediatric ARDS (PALICC-2 2023 Criteria):**
    - Acute onset (within 7 days of clinical insult).
    - Oxygenation defect: Oxygenation Index (OI) ≥ 4 or SpO2/FiO2 ratio ≤ 264.
    - New infiltrates on imaging consistent with acute pulmonary parenchymal disease.
    - Edema not fully explained by cardiac failure or fluid overload.

Management

- **Treat Underlying Cause:** Source control (antibiotics for sepsis, stop offending transfusion in TRALI).
- **Respiratory Support (PALICC-2 Guidelines):**
    - **Non-invasive:** HFNC or CPAP/BiPAP for mild cases.
    - **Mechanical Ventilation:** Lung-protective strategy is mandatory.
    - **Tidal Volume (Vt):** Low (5–8 mL/kg predicted body weight) to prevent volutrauma.
    - **PEEP:** Titrate optimally (often high, 8–15 cm H2O) to recruit alveoli and prevent atelectrauma.
    - **Target:** Permissive hypercapnia (pH > 7.15-7.20 acceptable) and SpO2 88-92% (to minimize oxygen toxicity).
- **Fluid Management:**

- Conservative/restrictive fluid strategy once hemodynamic stability is achieved (aim for zero or negative fluid balance).
- Diuretics (Furosemide) if hemodynamically stable.

- **Adjunctive Therapies (Refractory Hypoxemia):**
  - **Prone Positioning:** Improves V/Q matching (minimum 12-16 hours/day).
  - **Neuromuscular Blockade:** Short-course (first 48 hrs) to minimize ventilator dyssynchrony.
  - **Inhaled Nitric Oxide (iNO):** Rescue therapy for severe oxygenation failure.
  - **ECMO:** V-V ECMO for reversible, life-threatening respiratory failure failing conventional support.
- **Specific Treatments:**
  - *HAPE:* Descent, oxygen, Nifedipine, Dexamethasone.
  - *NPE:* Reduce ICP, alpha-blockers (rarely needed, usually self-limiting).

Complications

- Ventilator-Associated Pneumonia (VAP).
- Barotrauma (Pneumothorax, pneumomediastinum).
- Pulmonary fibrosis (in fibrotic phase of ARDS).
- Right ventricular failure (acute cor pulmonale) due to high pulmonary vascular resistance.

Prognosis

- Overall mortality in pediatric ARDS is 10–20% (significantly lower than adults, but dependent on etiology).
- Sepsis-induced NCPE has a worse prognosis than trauma/TRALI.
- Survivors often have normal pulmonary function by 1 year, though mild restrictive defects may persist.

Exam Summary

- **Core defect:** Increased capillary permeability → Protein-rich exudate (normal LV function).
- **Top triggers:** Sepsis, pneumonia, aspiration, near-drowning, TRALI.
- **Key differentiator:** Normal heart size on CXR, normal LV function on Echo, no hepatomegaly.
- **Management triad:** Treat cause + Lung-protective ventilation (Low Vt, High PEEP) + Conservative fluids.
- **Rescue therapies:** Prone positioning, iNO, ECMO.

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10. Hemorrhagic pleural effusion

Subject: Respiratory System

Definition & Classification

- **Hemorrhagic Pleural Effusion:** Blood-stained pleural fluid with a pleural fluid hematocrit (Hct) **< 50%** of the peripheral blood Hct.
- **Hemothorax:** Gross blood in the pleural space with pleural fluid Hct **≥ 50%** of the peripheral blood Hct.

Etiology

- **Trauma (Most Common):** Iatrogenic (post-thoracentesis/central line), blunt or penetrating chest trauma.
- **Malignancy:** Lymphoma, leukemia, neuroblastoma, metastatic sarcomas.
- **Infection:** Tuberculosis (classic cause in endemic regions), severe necrotizing pneumonia (e.g., *Staphylococcus aureus*, *Streptococcus pneumoniae*).
- **Vascular/Infarction:** Pulmonary embolism (consider in hypercoagulable states like nephrotic syndrome).
- **Hematologic:** Coagulopathies, thrombocytopenia, sickle cell disease (acute chest syndrome).
- **Miscellaneous:** Uremia, acute pancreatitis, catamenial hemothorax (endometriosis in older adolescent females).

Pathophysiology

- **Direct Injury:** Mechanical disruption of intercostal, internal mammary, or pulmonary vessels.
- **Malignancy:** Tumor neo-angiogenesis, direct pleural invasion, or lymphatic obstruction.
- **Inflammation:** Severe pleural inflammation causing capillary leakage and microvascular necrosis (e.g., TB delayed hypersensitivity).

Clinical Features

- **Symptoms:** Dyspnea, tachypnea, pleuritic chest pain, cough.
- **Signs:** Decreased chest movement, stony dullness on percussion, decreased/absent breath sounds on the affected side.
- **Systemic Clues:**
    - *TB:* Chronic cough, fever, weight loss, night sweats.
    - *Malignancy:* Hepatosplenomegaly, lymphadenopathy, cachexia.
    - *Bleeding diathesis:* Petechiae, purpura, mucosal bleeding.

Diagnosis

- **Imaging:**
    - *CXR (PA/Lateral):* Blunting of costophrenic angle, meniscus sign, mediastinal shift.
    - *Chest USG:* Modality of choice to quantify fluid, detect loculations, and guide thoracentesis.
    - *CECT Chest:* Identifies underlying parenchymal lesions, tumors, or vascular anomalies.
- **Pleural Fluid Analysis (Diagnostic Thoracentesis):**

- *Gross Appearance:* Red/bloody. (Note: Just 1-2 mL of blood can make 1L of pleural fluid look bloody).
- *Hematocrit:* Mandatory to differentiate hemorrhagic effusion (<50% serum Hct) from hemothorax (>50% serum Hct).
- *Biochemistry:* Light's criteria (usually an exudate).
- *Microbiology:* Gram stain, culture, AFB smear, **CBNAAT/GeneXpert** (first-line for TB).
- *Cytology:* Malignant cells (send large volume for better yield).
- *Specific markers:* ADA (>40 U/L suggests TB).

- **Blood Investigations:** CBC, coagulation profile (PT/APTT/INR), peripheral smear.

Management

- **Supportive Care:** ABCs, supplemental oxygen, IV fluids/blood transfusion if hemodynamically unstable (rare in simple effusion, common in massive hemothorax).
- **Drainage (Therapeutic Thoracentesis / ICD):**
  - Indicated for respiratory compromise, massive effusions, or true hemothorax.
  - *Surgical Escalation (VATS/Thoracotomy):* Indicated for hemothorax with initial drainage >15 mL/kg or ongoing bleeding >2–3 mL/kg/hr for 3 consecutive hours.
- **Disease-Specific Therapy:**
  - *Tuberculosis:* Standard Anti-Tubercular Therapy (ATT) per latest NTEP/IAP guidelines (2HRZE + 4HRE). Routine steroids are *not* recommended.
  - *Malignancy:* Systemic chemotherapy; pleurodesis (e.g., talc, bleomycin) if recurrent and symptomatic.
  - *Infection:* IV antibiotics directed by culture/sensitivity.
  - *Coagulopathy:* Correct with FFP, platelets, or specific factor replacement prior to any drainage.

Complications

- Fibrothorax and pleural trapping (restrictive lung disease).
- Secondary empyema (superinfection of blood).
- Hypovolemic shock (if progressing to massive hemothorax).

Exam Summary

- **Key Distinction:** Hemorrhagic effusion (Pleural Hct <50% of serum) vs. Hemothorax (Pleural Hct ≥50% of serum).
- **Top 3 Pediatric Causes:** Trauma, Tuberculosis, Malignancy (Lymphoma/Neuroblastoma).
- **Diagnostic Musts:** USG-guided tap, CBNAAT for TB, Cytology for malignancy, Coagulation profile.
- **Management Red Flag:** Do not place an ICD in a bleeding diathesis without prior factor/platelet correction. Ongoing massive bleeding requires VATS/Thoracotomy.

11. Hygiene hypothesis and implications

Subject: Respiratory System

Definition

- **Core concept:** Proposed by David Strachan (1989); posits that reduced exposure to early childhood infections and environmental microbes increases the risk of allergic and autoimmune diseases.
- **Modern iteration:** "Old Friends" or "Microbiome" hypothesis (focuses on commensal flora and evolutionary microbial exposure rather than pathogenic infections).

Pathophysiology

- **Classic Immune Deviation (Th1/Th2 balance):**
  - Fetal immune system is naturally Th2-skewed (prevents maternal rejection).
  - Early microbial exposure stimulates Th1 response, balancing the system.
  - Lack of microbes → persistent Th2 predominance → IgE production and eosinophilia (allergic phenotype).
- **Regulatory T-cell (Treg) Defect:**
  - Microbial antigens (endotoxins, helminths) stimulate dendritic cells to induce Tregs.
  - Tregs secrete IL-10 and TGF-β → immune tolerance.
  - "Clean" environment → reduced Treg activity → failure of tolerance to harmless allergens.
- **Dysbiosis:** Disruption of gut/respiratory microbiome alters mucosal barrier integrity and local immune signaling.

Epidemiological Evidence

- **Protective factors (decreased atopy):**
  - *The "Farm Effect":* Growing up on a farm, exposure to livestock, unpasteurized milk (high endotoxin exposure).
  - Large family size and presence of older siblings.
  - Early day-care attendance (within first 6 months).
  - Early exposure to pets (especially dogs).
  - Vaginal delivery (exposure to maternal vaginal/fecal flora).
  - Breastfeeding (provides Human Milk Oligosaccharides to feed gut flora).
  - Helminthic infections (endemic areas have lower asthma rates).
- **Risk factors (increased atopy):**
  - Cesarean section delivery (colonization by hospital/skin flora).
  - Early, frequent, or broad-spectrum antibiotic use.
  - Urbanization, smaller family sizes, and strict indoor hygiene.

Clinical Implications

- **Antibiotic Stewardship:** Strict avoidance of unnecessary antibiotics in early infancy to preserve gut microbiome.
- **Delivery Practices:** Promoting vaginal delivery; cautious evaluation of "vaginal seeding" post-LSCS (currently under research, not routinely recommended due to infection risks).
- **Nutrition:** Exclusive breastfeeding for 6 months to establish healthy gut flora.
- **Environmental Advice:**
    - Do not recommend prophylactic pet removal for expecting parents.
    - Encourage outdoor play and natural environmental exposures.
- **Probiotics/Prebiotics:**
    - *WAO/AAP guidelines:* Suggest considering probiotics in pregnant/lactating women and high-risk infants to prevent *eczema*.
    - *GINA 2024 Update:* Routine use of probiotics/prebiotics is **not** recommended for the prevention of *asthma* or allergic rhinitis (insufficient evidence).

Outcomes of "Over-Hygiene"

- **The Atopic March:** Progression from Atopic Dermatitis (infancy) → Food Allergies → Allergic Rhinitis → Asthma (childhood).
- **Autoimmunity:** Parallel rise in Th1/Th17-mediated autoimmune diseases (Type 1 Diabetes, Inflammatory Bowel Disease, Multiple Sclerosis) in highly developed nations.

Exam Summary

- **Buzzwords:** Strachan, Th1/Th2 imbalance, Treg deficiency, "Old Friends" hypothesis, Farm Effect.
- **Mechanism:** Lack of early microbial exposure prevents immune tolerance, skewing immunity toward Th2 (allergic) pathways.
- **Key Protectors:** Vaginal delivery, breastfeeding, older siblings, farm living, early pet exposure.
- **Clinical Trap:** Probiotics show some benefit for preventing eczema but are *not* recommended by GINA for asthma prevention.
- **Actionable Implication:** Rational antibiotic use in infancy is the most critical modifiable factor for pediatricians.

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12. Preschool wheeze

Subject: Respiratory System

Definition

- Continuous, high-pitched musical sound during expiration in children < 5 years
- Affects up to 50% of children by 6 years of age

Phenotypes & Classification

Longitudinal Phenotypes (Tucson Children's Respiratory Study - TCRS):

- **Transient Early Wheeze:** Onset <3 years, resolves by 6 years; non-atopic; due to congenitally narrow airways; maternal smoking is a major risk factor
- **Persistent Wheeze:** Onset <3 years, persists >6 years; strongly associated with atopy, elevated IgE, and parental asthma
- **Late-Onset Wheeze:** Onset >3 years; often associated with mild atopy and viral infections

Symptom-Based Phenotypes (ERS Task Force):

- **Episodic Viral Wheeze (EVW):** Wheezing only during discrete viral upper respiratory tract infections (URTIs); asymptomatic between episodes
- **Multiple-Trigger Wheeze (MTW):** Wheezing during URTIs *and* between episodes (triggered by exercise, crying, laughter, allergens)

Etiology & Risk Factors

- **Viral Triggers:** Rhinovirus (highest risk for subsequent asthma), RSV, Parainfluenza, Human Metapneumovirus
- **Host Factors:** Prematurity, low birth weight, male gender (in infancy)
- **Environmental Factors:** Maternal smoking (in utero and postnatal), daycare attendance, indoor/outdoor air pollution

Pathophysiology

- Infant airways have smaller baseline caliber; minimal mucosal edema/secretions exponentially increase resistance (Poiseuille's Law)
- Deficient antiviral interferon (IFN-lambda) response leads to prolonged viral replication
- Viral damage to epithelium exposes sensory nerves, causing reflex bronchoconstriction and hyperresponsiveness

Clinical Features

- Expiratory wheeze, tachypnea, chest retractions, prolonged expiratory phase
- Cough (often worse at night or with exertion)
- Feeding difficulties or lethargy in severe exacerbations

Red Flags (Alternative Diagnoses)

- Neonatal onset or continuous/unremitting wheeze (Congenital structural anomalies, vascular rings, tracheomalacia)
- Failure to thrive, steatorrhea, clubbing (Cystic Fibrosis)
- Sudden onset with choking episode, unilateral wheeze (Foreign Body Aspiration)
- Recurrent wet/productive cough, situs inversus (Primary Ciliary Dyskinesia)
- Stridor, weak cry, feeding-related choking (Aspiration syndromes, TEF, vocal cord palsy)

Diagnosis & Risk Stratification

- **Clinical Diagnosis:** Based on history and physical examination

- **Investigations:** Routine CXR not indicated unless red flags are present; consider allergy testing (Skin prick/Specific IgE) in persistent wheeze
- **Modified Asthma Predictive Index (mAPI):** Used to predict future asthma in children <3 years with ≥4 wheezing episodes/year
    - **Major Criteria:** Parental history of asthma, physician-diagnosed atopic dermatitis, allergic sensitization to ≥1 aeroallergen
    - **Minor Criteria:** Allergic sensitization to milk/egg/peanut, wheezing unrelated to colds, blood eosinophilia ≥4%
    - **Positive mAPI:** 1 Major OR 2 Minor criteria (Predicts 7x higher risk of school-age asthma)

Management (GINA 2024 Guidelines for <5 Years)

Acute Exacerbation:

- **Mild-Moderate:** SABA (Salbutamol 100mcg: 2–6 puffs via MDI with valved holding chamber/spacer) every 20 mins for first hour
- **Severe:** Add Ipratropium bromide (250 mcg/dose), target SpO2 94-98% with oxygen, systemic corticosteroids (Oral Prednisolone 1-2 mg/kg/day for 3-5 days; max 20mg <2yrs, 30mg 2-5yrs)
- **Refractory:** IV Magnesium sulfate (50 mg/kg over 20 mins), IV Aminophylline/Salbutamol in PICU

Maintenance / Controller Therapy:

- **Step 1:** SABA PRN (for infrequent viral wheezing)
- **Step 2 (Initial Controller):** Daily low-dose Inhaled Corticosteroid (ICS) (e.g., Budesonide 200 mcg/day or Fluticasone propionate 100 mcg/day)
    - *Alternative Step 2:* Leukotriene Receptor Antagonist (Montelukast) OR intermittent high-dose ICS at onset of viral illness (if exacerbations are strictly viral)
- **Step 3:** Double 'low-dose' ICS daily
- **Step 4:** Continue Step 3 + Specialist referral (consider adding LTRA or intermittent ICS)
- *Note:* Assess adherence, inhaler technique, and environmental triggers before stepping up therapy.

Complications

- Acute respiratory failure requiring mechanical ventilation
- Air leak syndromes (pneumothorax, pneumomediastinum)
- Long-term airway remodeling (if persistent atopic wheeze is undertreated)

Prognosis

- Approximately 60% of preschool wheezers become asymptomatic by age 6
- Rhinovirus-induced wheezing combined with aeroallergen sensitization carries the highest risk for persistent school-age asthma

Prevention

- Absolute avoidance of environmental tobacco smoke
- Promote exclusive breastfeeding
- RSV immunoprophylaxis (Palivizumab or Nirsevimab) in eligible high-risk infants (prematurity, hemodynamically significant CHD, chronic lung disease of prematurity)

Exam Summary

- **TCRS Phenotypes:** Transient early (narrow airways, resolves by 6y) vs. Persistent (atopic, parental asthma) vs. Late-onset.
- **mAPI:** Crucial tool to predict asthma. Requires ≥4 wheeze episodes/yr + 1 Major (parent asthma, eczema, aeroallergen) OR 2 Minor (food allergy, eosinophilia ≥4%, non-viral wheeze).
- **Red Flags:** Neonatal onset, clubbing, FTT, unilateral signs, choking history.
- **GINA 2024 <5y Controller:** Step 2 first-line is daily low-dose ICS; alternatives include LTRA or intermittent ICS during viral URTIs.
- **Inhaler Technique:** Always prescribe MDI with a spacer/valved holding chamber (with mask for <3 years, mouthpiece for 3-5 years) – never nebulizers for routine maintenance.

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13. Ventilator settings and treatment in severe pneumonia

Subject: Respiratory System

Definition & Etiology

- **WHO Severe Pneumonia:** Cough/difficult breathing + central cyanosis, inability to breastfeed/drink, lethargy, convulsions, or severe chest indrawing.
- **Common Pathogens:** *S. pneumoniae*, *H. influenzae* type b, *S. aureus* (including MRSA), RSV, Influenza, Adenovirus.

Clinical & Diagnosis

- **Clinical:** Grunting, flaring, severe retractions, head nodding, cyanosis, altered sensorium.
- **Imaging:** CXR (lobar consolidation, multilobar infiltrates, pleural effusion, pneumatocele).
- **Labs:** ABG (Type 1 or Type 2 respiratory failure), CBC, CRP/Procalcitonin, Blood culture.
- **Microbiology:** Endotracheal aspirate (ETA) Gram stain/culture, BioFire/viral respiratory multiplex PCR.

Medical Management

- **Empirical Antibiotics:** IV Ceftriaxone or Cefotaxime (First-line).
- **MRSA Suspected:** Add IV Vancomycin, Linezolid, or Clindamycin (post-viral/influenza pneumonia with rapid cavitation).
- **Atypical Suspected:** Add IV/Oral Azithromycin.
- **Fluids:** Restrict to 80% maintenance initially (high risk of SIADH and pulmonary edema).
- **Steroids:** Not routinely recommended unless concomitant asthma/wheeze or refractory septic shock.

Indications for Intubation

- **Oxygenation failure:** SpO2 < 90–92% despite FiO2 > 60% on HFNC/CPAP.
- **Ventilation failure:** PaCO2 > 60 mmHg with pH < 7.20.
- **Clinical:** Exhaustion, recurrent apnea, altered sensorium (GCS < 8), hemodynamic instability.

Ventilator Settings (Lung Protective Strategy)

- **Goal:** Prevent Ventilator-Induced Lung Injury (VILI) using PALICC (Pediatric Acute Lung Injury Consensus Conference) guidelines.
- **Mode:** PRVC (Pressure Regulated Volume Control) or PC-SIMV (Pressure Control) with Pressure Support.
- **Tidal Volume (Vt):** 5–8 mL/kg (Ideal Body Weight). Reduce to 4–6 mL/kg if poor lung compliance (ARDS).
- **PEEP:** Start at 5–8 cm H2O. Titrate upwards (up to 10–15 cm H2O) using ARDSnet PEEP/FiO2 tables to recruit alveoli and prevent atelectrauma.
- **FiO2:** Start at 1.0 (100%), rapidly wean to maintain target SpO2 to avoid oxygen toxicity.
- **Respiratory Rate (RR):** Age-appropriate (e.g., Infant: 25–30, Child: 20–25). Adjust to maintain target pH.
- **Inspiratory Time (Ti):** Age-appropriate (Infants: 0.35–0.5s; Toddlers: 0.6–0.7s; Older children: 0.8–1.0s).
- **Target Pressures:** Keep Plateau Pressure (Pplat) < 28–30 cm H2O. Keep Driving Pressure (Pplat - PEEP) < 15 cm H2O.

Ventilation Targets & Monitoring

- **SpO2 Target:** 92–97% (Mild/Moderate disease); **88–92%** (if severe PARDS/high PEEP required).
- **Permissive Hypercapnia:** Allow PaCO2 50–70 mmHg provided pH remains > 7.20 (contraindicated in raised ICP).
- **Monitoring:** Continuous capnography (EtCO2), serial ABGs, daily CXR.

Refractory Hypoxemia Management

- **Neuromuscular Blockade:** IV Vecuronium/Rocuronium infusion to eliminate patient-ventilator dyssynchrony.
- **Prone Positioning:** Improves V/Q matching; do for 12–16 hours/day.
- **Advanced Modes:** High-Frequency Oscillatory Ventilation (HFOV) if Pplat > 30 cm H2O or Oxygenation Index (OI) > 16.
- **Inhaled Nitric Oxide (iNO):** Trial if documented severe pulmonary hypertension/right heart failure.
- **ECMO:** V-V ECMO for reversible severe respiratory failure failing conventional and HFOV support (OI > 40).

Complications

- **Pulmonary:** ARDS, necrotizing pneumonia, pneumatocele, pneumothorax (barotrauma), empyema.
- **Systemic:** Septic shock, MODS, SIADH, critical illness myopathy.

Prevention

- **Vaccines:** PCV (Pneumococcal conjugate), Hib, Annual Influenza vaccine.
- **Prophylaxis:** Palivizumab for RSV in high-risk preemies/CHD patients.

Exam Summary

- **Core Medical Rx:** IV Ceftriaxone + fluid restriction (80%); add Vancomycin if MRSA/necrotizing.
- **Ventilator Mode/Vt:** PRVC/PC; use lung-protective Tidal Volumes (5–8 mL/kg).
- **Pressures:** High PEEP for recruitment; strictly maintain Plateau Pressure < 28–30 cm H2O.
- **Targets:** Permissive hypercapnia (pH > 7.20) and lower SpO2 targets (88–92%) in severe ARDS.
- **Refractory Rx:** Prone positioning, paralysis, HFOV, and ECMO for failing conventional settings.

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14. Interstitial lung disease in children

Subject: Respiratory System

Definition & Concept

- Heterogeneous group of rare, complex respiratory disorders affecting the alveolar epithelium, pulmonary interstitium, and distal airways.
- Collectively termed **chILD** (Children's Interstitial Lung Disease).
- Pathology involves impaired gas exchange, restrictive lung physiology, and variable degrees of inflammation/fibrosis.

Etiology & Classification (ATS Guidelines)

Classification is heavily age-dependent.

Infancy (< 2 Years):

- **Diffuse Developmental Disorders:** Acinar dysplasia, Alveolar capillary dysplasia with misalignment of pulmonary veins (ACD/MPV) – *universally fatal without transplant*.
- **Growth Abnormalities:** Pulmonary hypoplasia, Chronic neonatal lung disease (BPD).
- **Surfactant Dysfunction Mutations:**
    - *SP-B* (fatal in infancy).
    - *SP-C, ABCA3, NKX2-1* (variable severity, NKX2-1 associated with brain-thyroid-lung syndrome).
- **Specific Conditions of Undefined Etiology:**
    - *Neuroendocrine cell hyperplasia of infancy (NEHI):* Classic "tachypnea + crackles", excellent prognosis.
    - *Pulmonary interstitial glycogenosis (PIG).*

Older Children (> 2 Years):

- **Systemic Disease-Associated:** Connective tissue diseases (SLE, JIA, Scleroderma), Systemic vasculitis.
- **Exposure-Related:** Hypersensitivity pneumonitis (e.g., pigeon breeder's lung), toxic inhalation.
- **Immune/Infectious:** Post-infectious (Adenovirus, Mycoplasma), Opportunistic infections in immunocompromised (PCP, CMV).
- **Diffuse Alveolar Hemorrhage:** Idiopathic pulmonary hemosiderosis, Goodpasture syndrome.
- **Idiopathic Interstitial Pneumonias (rare in kids):** Cryptogenic organizing pneumonia (COP), Non-specific interstitial pneumonia (NSIP).

Clinical Features (chILD Syndrome Criteria)

Diagnosis requires ≥3 of the following 4 criteria (in absence of known cause like CF or congenital heart disease):

- **Respiratory Symptoms:** Chronic cough, tachypnea, heavy breathing, exercise intolerance.
- **Physical Signs:** Retractions, digital clubbing, failure to thrive (FTT), fine end-inspiratory crackles (velcro-like).
- **Hypoxemia:** Resting, nocturnal, or exercise-induced (SpO2 < 90%).
- **Radiographic Abnormalities:** Diffuse infiltrates on CXR or HRCT.

Diagnosis & Investigations

- **Initial Bloods:** CBC, ESR/CRP, Autoimmune panel (ANA, ANCA, RF), Immunoglobulins, Sweat chloride (rule out CF).
- **Echocardiogram:** Mandatory to rule out structural heart disease and screen for Pulmonary Hypertension (PH).
- **Pulmonary Function Tests (PFTs):** Restrictive pattern (↓FVC, ↓TLC, normal/↑ FEV1/FVC ratio) and ↓DLCO.
- **Imaging:**
    - *CXR:* Bilateral diffuse reticular, nodular, or reticulonodular opacities.
    - *HRCT Chest (Gold Standard Imaging):* Ground-glass opacities, interlobular septal thickening, cysts, and honeycombing (indicates end-stage fibrosis). *Classic NEHI:* Ground-glass opacities in right middle lobe & lingula.
- **Bronchoalveolar Lavage (BAL):**
    - Rule out infection.
    - *Lipid-laden macrophages:* Chronic aspiration.
    - *Hemosiderin-laden macrophages:* Diffuse alveolar hemorrhage.
    - *PAS-positive milky effluent:* Pulmonary Alveolar Proteinosis (PAP).
- **Genetic Testing:** High-yield first-line diagnostic step in infants (surfactant protein panels).
- **Lung Biopsy:** Video-Assisted Thoracoscopic Surgery (VATS) or open biopsy. Definitive gold standard if genetics/BAL are non-diagnostic.

Management

Supportive Care:

- **Oxygen Therapy:** Maintain SpO2 > 92% (prevents pulmonary hypertension and improves growth).
- **Nutrition:** High-calorie supplementation (work of breathing ↑ metabolic demand).
- **Prevention:** Annual Influenza, Pneumococcal vaccines, RSV prophylaxis (Palivizumab) in infants, strict avoidance of environmental tobacco smoke.

Pharmacological Therapy:

- *Systemic Corticosteroids:* First-line for inflammatory/fibrotic ILD (IV Methylprednisolone pulses or long-term oral Prednisolone).
- *Hydroxychloroquine (HCQ):* Frequently used for surfactant mutations and forms of idiopathic chILD.
- *Macrolides (Azithromycin):* Used for immunomodulatory and anti-inflammatory effects.
- *Immunosuppressants:* Cyclophosphamide, Mycophenolate Mofetil, or Rituximab (specifically for CTD-associated ILD or vasculitis).
- *Whole Lung Lavage:* Specific curative/maintenance therapy for PAP.

Surgical Therapy:

- **Lung Transplantation:** Indicated for end-stage fibrotic lung disease, severe ABCA3/SP-B mutations, and ACD/MPV.

Complications & Prognosis

- **Complications:** Pulmonary hypertension, Cor pulmonale, spontaneous pneumothorax, chronic respiratory failure.
- **Prognosis:** Highly etiology-dependent.
    - *Excellent:* NEHI, PIG (often resolve with age).
    - *Poor/Fatal:* SP-B deficiency, ACD/MPV.
    - *Variable:* Surfactant C mutations, CTD-ILD.

Exam Summary: Must-Write Points

- **chILD Criteria:** Diagnosis requires $\ge$3 of: symptoms, signs (clubbing/FTT/crackles), hypoxemia, diffuse radiographic changes.
- **Infant vs. Older Child:** Surfactant mutations/developmental anomalies dominate infancy; systemic/connective tissue diseases dominate older children.
- **HRCT Chest:** Gold standard imaging; look for ground-glass opacities, septal thickening, and honeycombing.
- **Genetics before Biopsy:** Surfactant mutation panels (SP-B, SP-C, ABCA3, NKX2-1) should be sent in infants before proceeding to invasive VATS biopsy.
- **Treatment Triad:** Supportive (O2 + Nutrition) + Corticosteroids + Hydroxychloroquine/Macrolides.

15. Pulmonary hypertension in children

Subject: Respiratory System

Definition (Updated WSPH Guidelines)

- **Current Criteria:** Mean pulmonary arterial pressure (mPAP) **> 20 mmHg** at rest (Previously: > 25 mmHg) via Right Heart Catheterization (RHC).
- **Pre-capillary PH:** mPAP > 20 mmHg + Pulmonary Capillary Wedge Pressure (PCWP) ≤ 15 mmHg + Pulmonary Vascular Resistance Index (PVRI) ≥ 3 Wood units·m^2.
- **Post-capillary PH:** mPAP > 20 mmHg + PCWP > 15 mmHg.

Classification (WHO / Nice Groups)

- **Group 1 (PAH):** Idiopathic, heritable (*BMPR2* mutation), Congenital Heart Disease (L-to-R shunts, Eisenmenger), Connective Tissue Disease.
- **Group 2 (Left Heart Disease):** LV systolic/diastolic dysfunction, valvular disease (mitral/aortic).
- **Group 3 (Lung Disease/Hypoxia):** Bronchopulmonary dysplasia (BPD - most common in infants), Obstructive Sleep Apnea (OSA), Congenital Diaphragmatic Hernia (CDH), Interstitial lung diseases.
- **Group 4 (Obstruction):** Chronic Thromboembolic Pulmonary Hypertension (CTEPH).
- **Group 5 (Multifactorial/Unclear):** Sickle cell disease, Down syndrome (independent of CHD), metabolic disorders.

Pathophysiology

- **Endothelial Dysfunction:** Imbalance between vasodilators and vasoconstrictors.
- **↓ Vasodilators:** Nitric Oxide (NO), Prostacyclins.
- **↑ Vasoconstrictors:** Endothelin-1, Thromboxane A2.
- **Vascular Remodeling:** Smooth muscle hypertrophy, intimal proliferation, plexiform lesions (irreversible).
- **Consequence:** Increased RV afterload → RV hypertrophy → RV dilation → Cor Pulmonale (Right Heart Failure).

Clinical Features

- **Symptoms:** Exertional dyspnea (most common), fatigue, lethargy.
- **Red Flags:** Exertional syncope, chest pain, hemoptysis (indicate severe disease/low cardiac output).
- **Signs:**
    - Palpation: Left parasternal heave (RVH), palpable P2.
    - Auscultation: Loud/single P2, pansystolic murmur of Tricuspid Regurgitation (TR), early diastolic murmur of Pulmonary Regurgitation (Graham Steell murmur), RV S3/S4 gallop.
    - Right Heart Failure: Tender hepatomegaly, elevated JVP, peripheral edema, ascites.

Diagnosis

- **Screening (Echocardiography):**
    - Estimates Right Ventricular Systolic Pressure (RVSP) via TR jet velocity.
    - Assesses RV function, septal flattening ("D-shaped" left ventricle), and rules out structural CHD.
- **Gold Standard (Right Heart Catheterization):**
    - Mandatory for definitive diagnosis and treatment initiation.
    - **Acute Vasoreactivity Testing:** Done during RHC using inhaled NO, IV epoprostenol, or IV adenosine.
    - *Positive test:* Drop in mPAP ≥ 10 mmHg to an absolute value ≤ 40 mmHg with preserved cardiac output (indicates suitability for Calcium Channel Blockers).
- **Ancillary Testing:**
    - **ECG:** RVH, Right Axis Deviation, Right Atrial Enlargement (tall P pulmonale).
    - **CXR:** Prominent main pulmonary artery, peripheral "pruning" (oligemia), RV enlargement.
    - **Workup for etiology:** PFTs/Sleep study (Group 3), V/Q scan (Group 4), ANA/Genetic testing (*BMPR2*).

Management

1. General Measures

- Avoid strenuous physical exertion and high altitudes.
- Strict prevention of respiratory infections (Influenza, Pneumococcal, RSV prophylaxis).
- Supplemental oxygen (if hypoxic; target SpO2 > 92%).
- Diuretics (furosemide/spironolactone) for right heart failure/edema.
- Digoxin (select cases of RV failure).

2. Targeted Pharmacotherapy (Pathway-Specific)

- **Calcium Channel Blockers (CCBs):** Only for RHC vasoreactive-positive patients (Amlodipine, Diltiazem).
- **Nitric Oxide Pathway (PDE-5 Inhibitors):** Sildenafil, Tadalafil (First-line oral therapy).
- **Endothelin Pathway (ERAs):** Bosentan, Ambrisentan, Macitentan (Monitor LFTs monthly with Bosentan).
- **Prostacyclin Pathway:**
    - *Epoprostenol (IV continuous):* Gold standard for severe/WHO Functional Class IV.
    - *Others:* Treprostinil (IV/SC/Inhaled/Oral), Iloprost (Inhaled), Selexipag (Oral receptor agonist).
- *Note:* Combination therapy (e.g., Sildenafil + Bosentan) is now standard for moderate-to-severe disease.

3. Surgical / Interventional

- **Atrial Septostomy:** Creates a R-to-L shunt; decompresses failing RV at the expense of cyanosis (palliative bridge).
- **Potts Shunt:** Anastomosis between Left Pulmonary Artery and Descending Aorta (pediatric-specific alternative to septostomy).
- **Transplantation:** Bilateral lung or Heart-Lung transplant (definitive therapy for refractory cases).

Complications & Prognosis

- **Complications:** Refractory right heart failure, arrhythmias, massive hemoptysis, sudden cardiac death, pulmonary hypertensive crises (especially post-op).
- **Prognosis:** Historically poor (median survival < 1 year in infants without treatment). Significantly improved with modern targeted combination therapies, though still remains a progressive, incurable disease without transplant.

Exam Summary: Must-Write Points

- **Updated Definition:** mPAP > 20 mmHg (not 25) + PVRI ≥ 3 WU·m^2.
- **Etiology trap:** BPD is the most common cause of Group 3 PH in infants; *BMPR2* is the most common genetic mutation.
- **Classic Signs:** Exertional syncope + Loud P2 + RV Heave.
- **Diagnosis:** Echo is for screening; Right Heart Catheterization is the gold standard.
- **Vasoreactivity:** Must test during RHC; only positive responders get CCBs.
- **Drug Pathways:** PDE-5 inhibitors (Sildenafil), ERAs (Bosentan), Prostacyclins (Epoprostenol).
- **Pediatric Surgery:** Potts shunt (LPA to descending aorta) unloads the RV.

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16. Congenital Malformations of the Respiratory System

Subject: Respiratory System

Classification (Top-Down Approach)

- **Nasal:** Choanal atresia
- **Laryngeal:** Laryngomalacia, Laryngeal web, Laryngotracheal cleft
- **Tracheal:** Tracheoesophageal fistula (TEF), Tracheomalacia, Tracheal stenosis/agenesis
- **Pulmonary/Lower (Congenital Lung Malformations - CLM):** Congenital Pulmonary Airway Malformation (CPAM), Bronchopulmonary Sequestration (BPS), Congenital Lobar Emphysema (CLE), Bronchogenic cyst
- **Diaphragmatic:** Congenital Diaphragmatic Hernia (CDH)

Upper Airway Malformations (Key Highlights)

- **Choanal Atresia:** Bony/membranous septum between nose and pharynx.

  - *Bilateral:* Neonatal emergency; presents with **cyanosis relieved by crying** (paradoxical cyanosis). Inability to pass 8F catheter.
  - *Association:* CHARGE syndrome.
- **Laryngomalacia:** Most common congenital anomaly of the larynx; most common cause of infantile stridor.
  - *Pathophysiology:* Immature supraglottic cartilage collapses during inspiration.
  - *Diagnosis:* Flexible laryngoscopy shows **omega-shaped epiglottis**.
  - *Prognosis:* Self-limiting; peaks at 6 months, resolves by 18–24 months.
- **Tracheoesophageal Fistula (TEF):**
  - *Most common:* Type C (Proximal esophageal atresia with distal TEF).
  - *Clinical:* Drooling, choking/cyanosis on first feed, failure to pass NGT.
  - *Association:* VACTERL (evaluate with Echo, Renal USG, Spinal X-ray).

Congenital Lung Malformations (CLMs)

1. Congenital Pulmonary Airway Malformation (CPAM)

- *Previously:* Congenital Cystic Adenomatoid Malformation (CCAM).
- *Pathology:* Hamartomatous proliferation of terminal respiratory bronchioles.
- *Types (Stocker):*
  - Type 1: Large cysts (>2 cm) – Most common (70%), best prognosis.
  - Type 2: Small cysts (<2 cm) – Associated with renal/cardiac anomalies.
  - Type 3: Solid/microcystic – Often presents with fetal hydrops; poor prognosis.
  - Type 4: Distal acinar origin – High risk of Pleuropulmonary Blastoma (PPB).

2. Bronchopulmonary Sequestration (BPS)

- *Definition:* Mass of non-functioning lung tissue lacking normal communication with the tracheobronchial tree.
- *Hallmark:* Receives **systemic arterial blood supply** (usually descending aorta).
- *Intralobar (75%):* Shares visceral pleura of normal lung; venous drainage via pulmonary veins; presents later with **recurrent focal pneumonia**.
- *Extralobar (25%):* Has its own separate visceral pleura; venous drainage via systemic veins (azygos); presents in infancy/antenatally; associated with CDH.

3. Congenital Lobar Emphysema (CLE)

- *Pathophysiology:* Defective bronchial cartilage causes a **ball-valve effect** (air enters on inspiration, trapped on expiration).
- *Location:* Left Upper Lobe (LUL) > Right Middle Lobe (RML) > Right Upper Lobe (RUL).
- *Clinical:* Progressive respiratory distress in the first few weeks of life.

- *CXR:* Hyperlucent, overexpanded lobe with mediastinal shift away from the lesion.

4. Bronchogenic Cyst

- *Pathology:* Abnormal budding of the foregut; lined by ciliated respiratory epithelium and contains cartilage/mucous glands.
- *Location:* Mostly mediastinal (near the carina) or intrapulmonary.
- *Clinical:* Often asymptomatic; can cause airway compression (wheeze/stridor) or get infected.

Diagnosis of Lower Tract CLMs

- **Antenatal:**
  - *Fetal USG:* Echogenic lung mass. Monitor for polyhydramnios and **fetal hydrops** (indicates severe mediastinal shift and impending demise).
  - *Fetal MRI:* Delineates mass volume and precise anatomy.
- **Postnatal:**
  - *CXR:* Initial modality; shows cysts, hyperlucency, or radiopacities.
  - *CECT Chest with IV contrast:* **Gold standard**. Maps the exact anatomy, differentiates solid vs. cystic, and identifies aberrant systemic feeding vessels (crucial for BPS).

Management of Lower Tract CLMs

- **Antenatal Management:**
  - *No hydrops:* Expectant management; maternal steroids (improves fetal lung maturation and shrinks CPAM).
  - *Hydrops present:* Thoracoamniotic shunt (for large cysts), fetal resection, or EXIT (Ex Utero Intrapartum Treatment) procedure.
- **Postnatal Symptomatic:**
  - Resuscitation (ABCs), intubation/mechanical ventilation if needed.
  - Urgent surgical resection (lobectomy is preferred over segmentectomy to prevent recurrence).
- **Postnatal Asymptomatic:**
  - *Current Consensus:* Elective surgical resection between **3 to 6 months** of age.
  - *Rationale:* Prevents future recurrent infections and eliminates the risk of malignant transformation (e.g., CPAM to rhabdomyosarcoma or pleuropulmonary blastoma).

Complications of CLMs

- Recurrent localized pneumonias (especially Intralobar BPS).
- Pneumothorax (rupture of CPAM or CLE cysts).
- Pulmonary hypoplasia (due to mass effect in utero).

- Malignant transformation (CPAM Types 1 and 4).

Exam Summary: High-Yield Buzzwords

- **Bilateral Choanal Atresia:** Cyanosis relieved by crying; CHARGE syndrome.
- **Laryngomalacia:** Omega-shaped epiglottis; inspiratory stridor.
- **CPAM:** Hamartoma, Type 1 most common (large cysts); risk of Pleuropulmonary blastoma.
- **BPS:** Systemic arterial supply (aorta). Intralobar = recurrent pneumonia; Extralobar = separate pleura.
- **CLE:** Ball-valve mechanism; hyperlucent LUL/RML; mediastinal shift.
- **Gold Standard Investigation (Postnatal CLM):** CECT chest with contrast.

Neurology / CNS

17. Classification of epileptic seizures according to ILAE 2025

Subject: Neurology / CNS

Basics & Current Framework

- **Current Standard:** Clinical practice in 2024/2025 relies on the **ILAE 2017 Operational Classification of Seizure Types**, integrated with the **ILAE 2021 Neonatal Seizures** and **ILAE 2022 Epilepsy Syndromes** updates.
- **Core criteria:** Classification is based on three pillars:
    1. Origin of onset (Focal, Generalized, Unknown)
    2. Level of awareness (Aware, Impaired)
    3. First prominent sign (Motor, Non-motor)

1. Focal Onset Seizures

- Originates within networks limited to one hemisphere.
- **Awareness Level:**
    - *Focal Aware Seizure (FAS):* Consciousness intact (Previously: Simple partial).
    - *Focal Impaired Awareness Seizure (FIAS):* Consciousness impaired at any point (Previously: Complex partial).
- **Motor Onset:**
    - Automatisms (lip smacking, manual picking)
    - Atonic (focal loss of tone)
    - Clonic (rhythmic jerking)
    - Epileptic spasms (focal flexion/extension)
    - Hyperkinetic (pedaling, thrashing)

    - Myoclonic (irregular, brief jerks)
    - Tonic (sustained stiffening)
- **Non-Motor Onset:**
    - Autonomic (pallor, flushing, palpitations)
    - Behavior arrest (pausing, freezing)
    - Cognitive (déjà vu, aphasia, hallucinations)
    - Emotional (fear, agitation, gelastic/laughing)
    - Sensory (olfactory, visual, somatosensory)
- **Progression:**
    - *Focal to bilateral tonic-clonic:* Spreads to both hemispheres (Previously: Secondary generalized).

2. Generalized Onset Seizures

- Originates at some point within, and rapidly engages, bilaterally distributed networks. Awareness is typically impaired.
- **Motor Onset:**
    - Tonic-clonic (Previously: Grand mal)
    - Clonic
    - Tonic
    - Myoclonic
    - Myoclonic-tonic-clonic
    - Myoclonic-atonic (Classic in Doose syndrome)
    - Atonic (Drop attacks)
    - Epileptic spasms
- **Non-Motor Onset (Absence):**
    - Typical (Brief, 3 Hz spike-wave)
    - Atypical (Slower onset/offset, <3 Hz spike-wave)
    - Myoclonic absence
    - Eyelid myoclonia (Jeavons syndrome)

3. Unknown Onset Seizures

- Onset missed or obscured; classified by predominant feature until more data (EEG/video) is available.
- **Motor:** Tonic-clonic, Epileptic spasms.
- **Non-motor:** Behavior arrest.
- **Unclassified:** Inadequate information to categorize.

Pediatric Updates (ILAE 2021 & 2022)

- **Neonatal (2021):** Awareness is untestable; categorized strictly as Motor, Non-motor, or **Electrographic-only** (subclinical, heavily emphasized in neonates).
- **Syndromes (2022):** Grouped strictly by age of onset:
    - *Neonatal/Infant:* e.g., KCNQ2-DEE, West syndrome, Dravet syndrome.
    - *Childhood:* e.g., Childhood Absence Epilepsy (CAE), Lennox-Gastaut Syndrome (LGS), Rolandic Epilepsy (now: Self-limited epilepsy with centrotemporal spikes - SeLECTS).
    - *Adolescent/Adult:* e.g., Juvenile Myoclonic Epilepsy (JME).

Etiology (The 6 Pillars)

- Must be evaluated simultaneously with seizure type:
    1. **S**tructural (e.g., Cortical dysplasia, stroke)
    2. **G**enetic (e.g., SCN1A in Dravet)
    3. **I**nfectious (e.g., Neurocysticercosis, post-HSV)
    4. **M**etabolic (e.g., GLUT1 deficiency)
    5. **I**mmune (e.g., Anti-NMDA receptor encephalitis)
    6. **U**nknown

Clinical & Diagnostic Clues

- **History:** Aura = focal onset. Post-ictal confusion = typically FIAS or generalized motor.
- **EEG:** Essential for classifying Unknown -> Focal/Generalized.
- **Neuroimaging:** MRI Epilepsy Protocol (3T preferred) is mandatory for all focal seizures to rule out structural etiology.

Management (First-Line Approach)

- **Focal Seizures:** Levetiracetam, Lamotrigine, Oxcarbazepine, Carbamazepine.
- **Generalized Motor:** Valproate (avoid in adolescent females due to teratogenicity/PCOS), Levetiracetam, Lamotrigine.
- **Absence:** Ethosuximide (1st line), Valproate.
- **Contraindications:** Avoid Carbamazepine/Oxcarbazepine/Phenytoin in generalized epilepsies (can worsen Absence and Myoclonic seizures).

Prognosis & Complications

- **Status Epilepticus:** Risk highest in poorly controlled generalized tonic-clonic or focal to bilateral tonic-clonic seizures.
- **SUDEP (Sudden Unexpected Death in Epilepsy):** Highest risk in uncontrolled generalized tonic-clonic seizures, non-compliance, and nighttime seizures.

Exam Summary (Must-Write Points)

- **Terminology shifts:** "Simple partial" is now **Focal Aware**; "Complex partial" is now **Focal Impaired Awareness**; "Secondary generalized" is now **Focal to Bilateral Tonic-Clonic**.
- **Classification pillars:** Onset (Focal/Gen/Unknown) + Awareness + First prominent sign (Motor/Non-motor).
- **Neonatal caveat:** ILAE 2021 excludes "awareness" for neonates and introduces "Electrographic-only" as a distinct, critical seizure type.
- **Etiology:** Always list the 6 ILAE etiologic categories (Structural, Genetic, Infectious, Metabolic, Immune, Unknown) alongside the seizure type.

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18. Status epilepticus management

Subject: Neurology / CNS

Definition

- **Current ILAE Criteria:**
    - **Time 1 (T1 = 5 mins):** Time when a seizure is continuous and unlikely to stop spontaneously (indication to start treatment).
    - **Time 2 (T2 = 30 mins):** Time beyond which ongoing seizure causes long-term neuronal injury.
- **Operational Definition:** Continuous clinical/electrographic seizure lasting ≥5 minutes, OR ≥2 discrete seizures without complete recovery of consciousness in between.

Etiology

- **Febrile:** Prolonged febrile seizure (most common in 6 mo – 5 yr).
- **Infectious:** Meningitis, encephalitis, cerebral malaria.
- **Metabolic:** Hypoglycemia, hyponatremia, hypocalcemia, inborn errors of metabolism (IEM), pyridoxine deficiency (neonates).
- **Structural:** Trauma, stroke, tumor, hypoxic-ischemic encephalopathy (HIE).
- **Toxic/Pharmacologic:** Subtherapeutic anti-seizure medication (ASM) levels (most common in known epileptics), lead poisoning, drug intoxication.

Mechanism

- **Failure of termination:** Rapid internalization (downregulation) of inhibitory $GABA_A$ receptors at the synaptic membrane.
- **Promotion of maintenance:** Upregulation of excitatory NMDA/AMPA receptors.
- **Systemic shift:** Transition from compensated phase (hypertension, tachycardia, hyperglycemia) to decompensated phase (hypotension, hypoxia, hypoglycemia, acidosis).

Clinical Features

- **Convulsive SE:** Sustained rhythmic jerking, tonic posturing, loss of consciousness.
- **Non-convulsive SE (NCSE):** Altered sensorium, subtle facial twitching, nystagmus, unexplained coma (requires EEG for diagnosis).

- **Focal SE (Epilepsia partialis continua):** Continuous focal motor jerking with preserved consciousness.

Diagnosis

- **Bedside:** Capillary blood glucose (CBG) immediately, vital signs, ECG.
- **Labs:** Serum electrolytes (Ca, Mg, Na), ABG/VBG, CBC, CRP, LFT, RFT, ASM levels, toxicology screen.
- **Neuroimaging:** CT head (if trauma, raised ICP, or focal deficit) ⇒MRI brain (definitive).
- **Lumbar Puncture:** Defer if raised ICP signs; perform once stable if CNS infection suspected.
- **EEG:** Mandatory if paralyzed/intubated, or if NCSE is suspected (prolonged altered sensorium post-convulsion).

Stepwise Management

Goal: Stop seizure clinically and electrographically, prevent systemic complications.

Phase 1: Stabilization (0–5 mins)

- **A/B/C:** Position laterally, suction airway, high-flow O_2 (100%), bag-valve-mask if hypoventilating.
- **IV Access:** Secure 2 large-bore IV lines.
- **Hypoglycemia check:** If CBG < 60 mg/dL ⇒2 mL/kg of 25% Dextrose (or 5 mL/kg of 10% Dextrose) IV.

Phase 2: Early SE / First-Line Therapy (5–20 mins)

- **Drug of Choice:** Benzodiazepines (BZDs).
- **IV available:** Lorazepam 0.1 mg/kg (max 4 mg) slow IV over 2 mins.
- **IV not available:** Midazolam 0.2 mg/kg IM/buccal/intranasal, OR Diazepam 0.5 mg/kg per-rectal.
- *Action:* May repeat one dose of BZD after 5 minutes if seizure persists.

Phase 3: Established SE / Second-Line Therapy (20–40 mins)

- *Update (ConSEPT & EcLiPSE Trials):* Levetiracetam, Phenytoin, and Valproate show equal efficacy. Levetiracetam often preferred due to safety profile and lack of cardiotoxicity.
- **Option 1:** Levetiracetam 40–60 mg/kg IV over 10 mins (max 3000 mg).
- **Option 2:** Fosphenytoin 20 mg PE/kg IV over 10 mins (preferred over phenytoin due to less infusion site reaction/hypotension).
- **Option 3:** Phenytoin 20 mg/kg IV over 20 mins (max 1000 mg; requires cardiac monitoring; mix ONLY in Normal Saline).
- **Option 4:** Sodium Valproate 40 mg/kg IV over 10 mins (max 3000 mg). *Contraindicated in suspected IEM/mitochondrial disorders or age < 2 years with liver disease.*

Phase 4: Refractory SE / Third-Line Therapy (40–60+ mins)

- **Definition:** Seizure persists despite adequate doses of BZD and one second-line ASM.

- **Action:** Intubation, mechanical ventilation, and continuous EEG monitoring in PICU.
- **Infusions:**
    - Midazolam infusion: 0.2 mg/kg bolus ⇒1–2 mcg/kg/min infusion.
    - Thiopental infusion: 3–5 mg/kg bolus ⇒3–5 mg/kg/hr.
    - Propofol infusion: 1–2 mg/kg bolus ⇒2–10 mg/kg/hr (Caution: Propofol Infusion Syndrome in young children).

Complications

- **Neurologic:** Excitotoxic neuronal death, cerebral edema, permanent cognitive decline, subsequent epilepsy.
- **Systemic:** Aspiration pneumonia, neurogenic pulmonary edema, arrhythmias.
- **Metabolic/Renal:** Rhabdomyolysis ⇒myoglobinuria ⇒Acute Kidney Injury (AKI), hyperkalemia, severe lactic acidosis.

Prognosis & Prevention

- **Prognosis:** Primarily dictated by the underlying etiology (e.g., HIE/meningitis has worse outcomes than febrile SE). Mortality ranges from 3–10%.
- **Prevention:** Medication adherence counseling in known epileptics; rescue action plans (prescribing home buccal midazolam) for high-risk patients.

Exam Summary

- **T1/ T2 concept:** 5 minutes to treat, 30 minutes to permanent injury.
- **Receptor shift:** GABA downregulation, NMDA upregulation (why delayed BZDs fail).
- **First step:** Always check CBG (Hypoglycemia is the most easily reversible cause).
- **First-line:** IV Lorazepam (0.1 mg/kg) or IM/Buccal Midazolam (0.2 mg/kg).
- **Second-line:** IV Levetiracetam (40-60 mg/kg) or IV Fosphenytoin/Phenytoin (20 mg/kg).
- **Valproate trap:** Never give IV Valproate in a child < 2 years with suspected metabolic/mitochondrial disease or hepatopathy.

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19. Cerebral Palsy classification and management

Subject: Neurology / CNS

Definition

- Group of permanent, non-progressive disorders of movement and posture
- Caused by non-progressive disturbances occurring in the developing fetal or infant brain
- Often accompanied by secondary musculoskeletal problems and comorbidities (epilepsy, cognitive impairment)

Etiology & Risk Factors

- **Prenatal (70-80%):** Congenital malformations, TORCH infections, multiple gestations, genetic/metabolic disorders
- **Perinatal:** Prematurity (highest risk), Hypoxic-Ischemic Encephalopathy (HIE), kernicterus, neonatal sepsis, hypoglycemia
- **Postnatal (up to 2 yrs):** Meningoencephalitis, head trauma, near-drowning, status epilepticus

Pathophysiology & Neuroanatomy

- **Periventricular Leukomalacia (PVL):** Typically causes spastic diplegia (classic in premature infants)
- **Basal Ganglia/Thalamus injury:** Causes dyskinetic/athetoid CP (classic in severe HIE or kernicterus)
- **Multicystic encephalomalacia:** Causes spastic quadriplegia (severe diffuse injury)

Classification (Crucial Exam Focus)

- **1. Physiological (Motor Type):**
    - **Spastic (70-80%):** Pyramidal tract lesion; hypertonia, hyperreflexia, clonus, positive Babinski.
    - **Dyskinetic (10-15%):** Extrapyramidal lesion; fluctuating tone, involuntary movements (choreoathetoid or dystonic).
    - **Ataxic (<5%):** Cerebellar lesion; wide-based gait, intention tremor, dysmetria.
    - **Mixed:** Features of >1 type (most commonly spastic + dyskinetic).
- **2. Topographical (Mainly for Spastic CP):**
    - **Diplegia:** Legs involved more than arms.
    - **Hemiplegia:** One side of body involved (arm usually worse than leg).
    - **Quadriplegia:** All four limbs involved (often with bulbar involvement and severe cognitive deficit).
- **3. Functional Classification (Standard of Care):**
    - **GMFCS (Gross Motor Function Classification System):**
        - *Level I:* Walks without limitations.
        - *Level II:* Walks with limitations (no assistive devices needed outdoors).
        - *Level III:* Walks using hand-held mobility device.
        - *Level IV:* Self-mobility with limitations; may use powered mobility.
        - *Level V:* Transported in manual wheelchair (severe limitation).
    - *Note:* Similar scales exist for hand use (**MACS**), communication (**CFCS**), and eating/drinking (**EDACS**).

Clinical Features

- **Early clues:** Head lag >3 months, rolling over <2 months (extensor hypertonia), early hand preference <1 year (suggests hemiplegia)

- **Tone/Posture:** Spasticity, opisthotonos, scissoring of legs
- **Reflexes:** Delayed disappearance of primitive reflexes (Moro, ATNR), delayed appearance of postural/protective reflexes
- **Comorbidities:** Intellectual disability (50%), epilepsy (30-45%), visual/hearing deficits, feeding difficulties, drooling, sleep disorders

Diagnosis

- **Clinical criteria:** Primarily a clinical diagnosis based on history and serial neurological exams.
- **Neuroimaging: MRI Brain** is the modality of choice (abnormal in >85%). Look for PVL, malformations, or basal ganglia lesions.
- **Metabolic/Genetic testing:** Indicated if MRI is normal, features are atypical, or if there is regression of milestones (to rule out neurodegenerative disorders).
- **Screening:** Vision and hearing assessment, EEG (only if seizures present).

Management (Multidisciplinary Approach)

- **1. Medical Management (Spasticity):**
    - *Oral:* Baclofen (first-line), Diazepam, Tizanidine, Dantrolene.
    - *Focal:* **Botulinum toxin A** injections (target specific muscles e.g., gastrocnemius to delay contractures; effects last 3-6 months).
    - *Intrathecal:* Baclofen pump (for severe, refractory generalized spasticity).
- **2. Medical Management (Dyskinesia):**
    - Trihexyphenidyl, Levodopa, or Tetrabenazine.
- **3. Surgical Interventions:**
    - **Selective Dorsal Rhizotomy (SDR):** Cuts sensory nerve rootlets to permanently reduce spasticity (best for spastic diplegia, GMFCS II-III, good cognition).
    - **Orthopedic surgery:** Tendon lengthening (e.g., Achilles), muscle release, osteotomies for hip subluxation, spinal fusion for severe scoliosis.
- **4. Rehabilitation & Therapies:**
    - **Physiotherapy (PT):** Stretching, strengthening, constraint-induced movement therapy (CIMT) for hemiplegia.
    - **Occupational Therapy (OT):** ADL training, adaptive equipment.
    - **Orthotics:** Ankle-foot orthoses (AFOs) to prevent equinus deformity.
    - **Speech Therapy:** Swallowing assessment, augmentative and alternative communication (AAC) devices.
- **5. Comorbidity Management:**
    - *Seizures:* Standard antiepileptic drugs (e.g., Levetiracetam, Valproate).
    - *Feeding/Nutrition:* High-calorie diet, thickeners for aspiration risk, Gastrostomy tube (PEG) if severe dysphagia.

- *Drooling:* Anticholinergics (Glycopyrrolate), Botox to salivary glands.

Complications

- Joint contractures, hip subluxation/dislocation
- Scoliosis, osteopenia/fractures
- Aspiration pneumonia, severe malnutrition

Prognosis

- Depends heavily on GMFCS level and cognitive status.
- Independent sitting by age 2 years is a strong positive predictor for eventual ambulation.
- Normal life expectancy for mild forms; reduced in severe quadriplegia with recurrent respiratory infections.

Prevention

- **Antenatal: Magnesium sulfate** given to mothers at risk of preterm delivery (<32 weeks) for fetal neuroprotection.
- **Perinatal:** Therapeutic hypothermia for neonates (≥36 weeks) with moderate-to-severe HIE; delayed cord clamping.

Exam Summary: Must-Write Points

- **Definition:** Non-progressive motor disorder of the developing brain; but clinical manifestations *change* over time.
- **Classification:** Always mention **Topographical** (Diplegia, Hemiplegia, Quadriplegia), **Physiological** (Spastic, Dyskinetic, Ataxic), and **GMFCS** (Levels I-V).
- **Prematurity association:** Prematurity → PVL → Spastic Diplegia.
- **Kernicterus association:** Bilirubin toxicity → Basal ganglia damage → Dyskinetic/Athetoid CP.
- **Management triad:** Multidisciplinary rehab (PT/OT) + Medical (Botox/Baclofen for spasticity) + Surgical (Orthopedic tendon release/SDR).
- **Prevention:** Antenatal MgSO4 for premature neuroprotection is a highly tested update.

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20. Mechanism of seizures and choice of antiepileptic drugs

Subject: Neurology / CNS

Terminology Update (ILAE 2017): The term "Anti-Seizure Medication (ASM)" is now preferred over "Antiepileptic Drug (AED)".

Definitions

- **Seizure:** Transient occurrence of signs/symptoms due to abnormal excessive or synchronous neuronal activity in the brain.
- **Epilepsy:** ≥2 unprovoked seizures >24 hours apart, OR 1 unprovoked seizure with a >60% probability of recurrence over 10 years, OR diagnosis of an epilepsy syndrome.

Etiology (ILAE 2017 Classification)

- **Structural:** Cortical dysplasia, hypoxic-ischemic encephalopathy (HIE), tumors, trauma.
- **Genetic:** Dravet syndrome (*SCN1A*), Childhood Absence Epilepsy.
- **Infectious:** Neurocysticercosis (most common in India/developing nations), meningitis, encephalitis.
- **Metabolic:** Hypoglycemia, hypocalcemia, pyridoxine dependency.
- **Immune:** Anti-NMDA receptor encephalitis.
- **Unknown:** Cryptogenic.

Mechanism of Seizures (Pathophysiology)

- **Core Defect:** Imbalance favoring excitation over inhibition at the cellular and network levels.
- **Cellular Hallmark:** Paroxysmal Depolarizing Shift (PDS) – a prolonged depolarization of the neuronal membrane mediated by calcium influx, followed by a train of sodium-mediated action potentials.
- **Excitatory Excess:**
  - Overactivation of **Glutamate** receptors (NMDA and AMPA).
  - Excessive inward currents of **Na^+** and **Ca^{2+}**.
- **Inhibitory Failure:**
  - Dysfunction of **GABA** (Gamma-aminobutyric acid) receptors.
  - Impaired inward **Cl^-** currents or outward **K^+** currents.
- **Network Level:** Loss of "surround inhibition" allows the local discharge to become hypersynchronous and propagate via anatomical pathways (e.g., corpus callosum, thalamocortical tracts).

Clinical Evaluation & Diagnosis

- **History:** Aura, focality, motor vs. non-motor onset, level of awareness, post-ictal state.
- **Video EEG:** Gold standard for classifying seizure type and syndrome.
- **Neuroimaging:** MRI Brain (Epilepsy Protocol) is the modality of choice; CT only for emergencies (bleed, large mass).
- **Labs:** Glucose, calcium, magnesium, electrolytes, inborn errors of metabolism (IEM) workup if indicated.

Choice of Anti-Seizure Medications (ASMs)

Choice is dictated by seizure type, epilepsy syndrome, age, and comorbidity profile.

- **Focal Seizures:**
  - *First-line:* Oxcarbazepine, Carbamazepine, Levetiracetam.
  - *Alternatives:* Lamotrigine, Lacosamide, Topiramate.
- **Generalized Tonic-Clonic Seizures (GTCS):**

- *First-line:* Sodium Valproate, Levetiracetam, Lamotrigine.
- *Note:* **Avoid Valproate** in adolescent females of childbearing potential due to teratogenicity and PCOS risk; prefer Levetiracetam or Lamotrigine.

- **Absence Seizures:**
  - *First-line:* Ethosuximide (pure absence), Sodium Valproate (if combined with GTCS).
  - *Contraindicated:* Carbamazepine, Phenytoin, Oxcarbazepine (can worsen absence).
- **Myoclonic Seizures (e.g., JME):**
  - *First-line:* Sodium Valproate, Levetiracetam, Clonazepam.
  - *Contraindicated:* Carbamazepine, Phenytoin (aggravates myoclonus).
- **Neonatal Seizures:**
  - *First-line:* Phenobarbital.
  - *Second-line:* Levetiracetam, Phenytoin.
- **Syndrome-Specific Choices:**
  - *Infantile Spasms (West Syndrome):* ACTH or high-dose oral Prednisolone. **Vigabatrin** is 1st line if associated with Tuberous Sclerosis.
  - *Lennox-Gastaut Syndrome:* Valproate, Rufinamide, Clobazam, Lamotrigine.
  - *Dravet Syndrome:* Valproate, Clobazam, Stiripentol, Cannabidiol. (Strictly avoid Na-channel blockers like Phenytoin/Carbamazepine).

Mechanism of Action of Key ASMs

- **Na^+ Channel Blockers:** Phenytoin, Carbamazepine, Oxcarbazepine, Lamotrigine (prolongs inactive state of the channel).
- **Ca^{2+} Channel Blockers (T-type):** Ethosuximide (thalamic T-type channels - specific for absence).
- **GABA Enhancers:** Benzodiazepines, Barbiturates (allosteric modulators), Vigabatrin (inhibits GABA transaminase).
- **SV2A Vesicle Binding:** Levetiracetam, Brivaracetam (modulates neurotransmitter release).
- **Multiple Mechanisms:** Sodium Valproate (Na^+ block, T-type Ca^{2+} block, GABA increase), Topiramate.

Complications & Red Flags

- **Status Epilepticus (SE):** Seizure lasting >5 mins, or ≥2 seizures without returning to baseline. Requires immediate protocolized management (Benzodiazepines → IV Phenytoin/Levetiracetam/Valproate).
- **SUDEP:** Sudden Unexpected Death in Epilepsy (highest risk with uncontrolled nocturnal GTCS).
- **Neurocognitive Decline:** Due to epileptic encephalopathy (e.g., West syndrome, Lennox-Gastaut).

- **Drug Toxicity:** Stevens-Johnson Syndrome (Lamotrigine, Carbamazepine, Phenytoin), Hepatotoxicity/Pancreatitis (Valproate), Aplastic anemia (Felbamate).

Prognosis & Prevention

- **Remission:** ~70% of childhood epilepsies achieve remission.
- **Drug Withdrawal:** Consider weaning after 2 years of seizure freedom, provided EEG is normal and etiology is not high-risk (e.g., structural lesion, JME).
- **Prevention:** Antenatal care to prevent HIE, timely neurocysticercosis prevention (hygiene/sanitation), vaccination (preventing infectious etiologies).

Exam Summary

- **Mechanism:** Paroxysmal Depolarizing Shift (PDS) driven by excess Glutamate/Na^+/Ca^{2+} and deficient GABA/Cl^-/K^+.
- **Focal 1st line:** Oxcarbazepine / Levetiracetam.
- **Generalized 1st line:** Valproate / Levetiracetam.
- **Absence 1st line:** Ethosuximide (blocks T-type Ca^{2+} channels).
- **Trap:** Never use Carbamazepine/Phenytoin in Absence or Myoclonic seizures (worsens them).
- **Update:** Avoid Valproate in females of childbearing age; use Levetiracetam/Lamotrigine.

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21. Important epileptic syndromes in children

Subject: Neurology / CNS

Classification & Updates

- **ILAE 2022 Update:** Shift toward descriptive terminology (e.g., "Benign" replaced by "Self-limited"; "Mental retardation" replaced by "Developmental/Cognitive impairment").
- Categorized by age of onset: Neonatal/Infantile, Childhood, and Adolescent.

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1. West Syndrome (Infantile Spasms)

- **Age:** Peak onset 3–8 months.
- **Etiology:** Structural (HIE, malformations), Genetic (Tuberous Sclerosis Complex - most common identifiable), Metabolic, Unknown.
- **Classic Triad:**
    1. Epileptic spasms (flexor, extensor, or mixed; occur in clusters, especially upon awakening).
    2. Developmental arrest or regression.
    3. **EEG:** Hypsarrhythmia (chaotic, high-voltage, asynchronous slow waves and spikes).
- **Management:**
    - **First-line:** ACTH (intramuscular) or high-dose oral Prednisolone.

    - **First-line if Tuberous Sclerosis:** Vigabatrin (Risk: irreversible visual field constriction).
- **Prognosis:** Poor; 15-30% evolve into Lennox-Gastaut Syndrome.

2. Lennox-Gastaut Syndrome (LGS)

- **Age:** 3–5 years.
- **Pathophysiology:** Often the final common pathway of severe early-onset brain injury or evolution of West Syndrome.
- **Classic Triad:**
    1. Multiple seizure types (Tonic [nocturnal], Atonic [drop attacks], Atypical absence).
    2. Cognitive/Developmental impairment.
    3. **EEG:** Slow spike-and-wave complexes (<3 Hz) and fast paroxysmal activity in sleep.
- **Management:** Highly refractory.
    - **First-line:** Broad-spectrum ASMs (Sodium Valproate, Lamotrigine, Topiramate).
    - **Add-ons:** Rufinamide (specifically for drop attacks), Clobazam, Cannabidiol (CBD).
    - **Non-pharmacological:** Ketogenic diet, Vagus Nerve Stimulation (VNS), Corpus callosotomy (for drop attacks).

3. Childhood Absence Epilepsy (CAE)

- **Age:** 4–10 years (peak 5–7 years); female predominance.
- **Clinical:** Frequent, brief (5–15 seconds) staring spells with sudden onset/offset; unresponsiveness; *no post-ictal confusion*.
- **Provocation:** Easily triggered by hyperventilation (3 minutes) or photic stimulation.
- **EEG:** Classic **3-Hz generalized spike-and-wave** discharges on a normal background.
- **Management:**
    - **First-line:** Ethosuximide (DOC for isolated absence) or Sodium Valproate (if concurrent generalized tonic-clonic seizures [GTCS]).
- **Prognosis:** Excellent; usually remits by adolescence.

4. Self-Limited Epilepsy with Centrotemporal Spikes (SeLECTS)

- *Previously known as Benign Epilepsy with Centrotemporal Spikes (BECTS) / Rolandic Epilepsy.*
- **Age:** 3–13 years (peak 7–9 years).
- **Clinical:** Focal motor seizures typically involving the face, lips, and tongue (unilateral twitching, drooling, anarthria); usually occur during sleep or upon awakening; awareness often preserved.
- **EEG:** Biphasic, high-voltage spikes in centrotemporal regions, markedly activated by non-REM sleep.
- **Management:**
    - Often no treatment required if seizures are rare/exclusively nocturnal.

  - **First-line (if needed):** Oxcarbazepine, Carbamazepine, or Levetiracetam.
- **Prognosis:** Excellent; resolves universally by puberty (age 15–16).

5. Juvenile Myoclonic Epilepsy (JME / Janz Syndrome)

- **Age:** 12–18 years.
- **Clinical:**
  - Myoclonic jerks exclusively/predominantly in the morning (dropping toothbrush/cereal bowl).
  - Often accompanied by GTCS and sometimes absence seizures.
- **Triggers:** Sleep deprivation, alcohol, stress, photic stimulation.
- **EEG: 4–6 Hz generalized polyspike-and-wave** discharges.
- **Management:**
  - **First-line:** Sodium Valproate (Caution: highly teratogenic; avoid in females of childbearing age).
  - **Alternative (females):** Levetiracetam, Lamotrigine.
  - **Contraindicated:** Carbamazepine, Phenytoin (can worsen myoclonus).
- **Prognosis:** Excellent response to treatment, but requires **lifelong** ASM therapy (high relapse rate if stopped).

6. Dravet Syndrome (Severe Myoclonic Epilepsy in Infancy)

- **Genetics:** >80% have **SCN1A** gene mutation (voltage-gated sodium channel).
- **Clinical Evolution:**
  - *Year 1:* Prolonged, recurrent febrile/afebrile hemi-clonic seizures.
  - *Year 2 onward:* Multiple seizure types (myoclonic, atypical absence), developmental stagnation/regression.
- **Management:**
  - **First-line:** Valproate + Clobazam.
  - **Targeted Add-ons:** Stiripentol, Fenfluramine, Cannabidiol.
  - **Absolute Contraindication:** Sodium channel blockers (Phenytoin, Carbamazepine, Lamotrigine) strictly avoided as they exacerbate seizures.

General Diagnostic Approach to Pediatric Syndromes

- **History:** Exact semiology, age of onset, diurnal variation, triggers, developmental milestones.
- **Neuroimaging:** MRI Brain (Epilepsy protocol) indicated for all *except* classic CAE, SeLECTS, and JME with typical EEG/clinical picture.
- **Genetics:** Microarray or Epilepsy gene panels (e.g., SCN1A, CDKL5, PRRT2) for early-onset epileptic encephalopathies.

Exam Summary: Must-Write Points

- **West Syndrome:** 3-8 months, Infantile spasms + Regression + Hypsarrhythmia. Treat with ACTH/Steroids (Vigabatrin if Tuberous Sclerosis).
- **LGS:** 3-5 years, Multiple seizure types + Cognitive decline + Slow spike-wave (<3Hz). Highly refractory.
- **CAE:** 4-10 years, Hyperventilation-triggered staring + 3-Hz spike-wave. Treat with Ethosuximide.
- **SeLECTS (Rolandic):** 3-13 years, Nocturnal oro-facial twitching + Centrotemporal spikes. Resolves by puberty.
- **JME:** 12-18 years, Morning myoclonus (dropping objects) + 4-6 Hz polyspike-wave. Requires lifelong treatment (Valproate/Levetiracetam).
- **Dravet Syndrome:** SCN1A mutation. Avoid Na-channel blockers (Phenytoin/Carbamazepine).

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22. Developmental and epileptic encephalopathies

Subject: Neurology / CNS

Definition & Concept (ILAE 2017 Update)

- **Epileptic Encephalopathy (EE):** Epileptic activity itself (frequent seizures/interictal discharges) causes severe cognitive and behavioral impairment, which may improve if seizures are controlled.
- **Developmental Encephalopathy (DE):** The underlying etiology (e.g., genetic mutation) causes developmental delay independent of seizures.
- **DEE:** Coexistence of both; the underlying cause impairs development directly, and the frequent epileptic activity worsens the cognitive trajectory.

Etiology

- **Genetic (Most Common):**
    - *SCN1A* (Dravet syndrome)
    - *KCNQ2* (Benign familial neonatal epilepsy/DEE)
    - *STXBP1*, *ARX* (Ohtahara syndrome, Early Myoclonic Encephalopathy)
    - *CDKL5* (Early-onset DEE in females)
    - *SLC2A1* (GLUT1 deficiency syndrome)
- **Structural:** Malformations of cortical development (lissencephaly, focal cortical dysplasia), hypoxic-ischemic encephalopathy (HIE).
- **Metabolic:** Pyridoxine dependency, biotinidase deficiency, mitochondrial disorders.
- **Infectious/Immune:** Post-encephalitic (HSV), Rasmussen encephalitis.

Classic Syndromes (Age-Dependent Expression)

- **Neonatal (<1 month):**

- *Ohtahara Syndrome:* Tonic spasms, burst-suppression (awake & sleep), structural/genetic (*ARX*, *STXBP1*).
- *Early Myoclonic Encephalopathy (EME):* Erratic myoclonus, burst-suppression (mainly sleep), mostly metabolic.

- **Infantile (1–12 months):**
  - *West Syndrome:* Infantile spasms, hypsarrhythmia, developmental arrest/regression.
  - *Dravet Syndrome:* Prolonged febrile/afebrile hemiclonic seizures triggered by fever/vaccination → later multiple seizure types (*SCN1A* mutation).
- **Childhood (1–10 years):**
  - *Lennox-Gastaut Syndrome (LGS):* Multiple seizure types (tonic, atypical absence, drop attacks), slow spike-wave (<2.5 Hz) on EEG, cognitive decline.
  - *Epileptic Encephalopathy with Continuous Spikes and Waves during Sleep (CSWS):* Electrical status epilepticus in sleep (ESES), profound neurocognitive regression.
  - *Landau-Kleffner Syndrome (LKS):* Acquired epileptic aphasia (auditory agnosia), ESES pattern.

Pathophysiology

- **"Dual-Hit" Mechanism:** Primary genetic/structural defect impairs synaptogenesis/myelination + continuous epileptiform discharges disrupt normal neural network formation.
- **Channelopathies:** Altered ion flow (Na+, K+) leads to chronic neuronal hyperexcitability.
- **Synaptic vesicle dysfunction:** Defects in neurotransmitter release (e.g., *STXBP1*).

Clinical Features

- **Seizures:** Polymorphic (multiple types in one patient), high frequency, highly refractory to standard anti-seizure medications (ASMs).
- **Neurological:** Severe global developmental delay (GDD) or regression, hypotonia, spasticity, microcephaly.
- **Neurobehavioral:** Autism spectrum traits, hyperactivity, severe intellectual disability.
- **Motor:** "Drop attacks" (astatic seizures), ataxia, leading to frequent trauma.

Diagnosis

- **EEG (Mandatory):** Defines the syndrome (e.g., hypsarrhythmia, burst suppression, slow spike-wave, ESES).
- **Neuroimaging:** MRI Brain (Epilepsy protocol, 3 Tesla preferred) to rule out structural/surgical targets.
- **Genetics (High Yield):** Next-Generation Sequencing (NGS) epilepsy gene panel or Whole Exome Sequencing (WES) – now standard of care for unexplained DEE.
- **Metabolic Screen:** CSF glucose (GLUT1), CSF neurotransmitters, serum amino acids, urine organic acids, pyridoxine trial (in neonatal/infantile refractory seizures).

Management

- **Precision Medicine (Gene-Specific):**
    - *GLUT1 Deficiency:* Ketogenic diet (first-line).
    - *SCN1A (Dravet):* Avoid sodium channel blockers (Phenytoin, Carbamazepine, Lamotrigine). Use Valproate, Clobazam, Stiripentol.
    - *Pyridoxine-dependent epilepsy:* Lifelong Pyridoxine/Pyridoxal-5-phosphate.
- **Syndrome-Specific ASMs:**
    - *West Syndrome:* ACTH, High-dose oral Prednisolone, or Vigabatrin (drug of choice if Tuberous Sclerosis).
    - *LGS:* Valproate, Lamotrigine, Rufinamide, Clobazam.
- **Newer Approved Therapies (FDA/EMA):**
    - *Cannabidiol (Epidiolex):* Approved for Dravet, LGS, Tuberous Sclerosis.
    - *Fenfluramine:* Approved for Dravet and LGS (monitor for valvular heart disease).
- **Non-Pharmacological:**
    - *Ketogenic Diet:* Highly effective in refractory DEE.
    - *Surgical:* Vagal Nerve Stimulation (VNS), Corpus callosotomy (for drop attacks in LGS), resective surgery for focal structural lesions.
- **Supportive:** Aggressive PT/OT, speech therapy, helmet for drop attacks, individualized education plan (IEP).

Complications & Prognosis

- **Prognosis:** Generally poor; lifelong polytherapy, severe intellectual disability, complete dependency.
- **Complications:** Status epilepticus, aspiration pneumonia, orthopedic injuries (from falls/drop attacks).
- **SUDEP Risk:** Sudden Unexpected Death in Epilepsy is significantly elevated, especially in Dravet syndrome.

Exam Summary: Must-Write Points

- DEE represents a dual-pathology: underlying etiology causes delay (Developmental), while frequent seizures worsen it (Epileptic).
- Classic age-dependent progression: Ohtahara (neonate) → West (infant) → LGS (child).
- *SCN1A* mutation = Dravet syndrome; strictly avoid sodium channel blockers.
- EEG patterns define the syndrome: Burst suppression (Ohtahara/EME), Hypsarrhythmia (West), Slow spike-wave <2.5 Hz (LGS).
- Management requires polytherapy, Ketogenic diet, VNS, and newer agents like Cannabidiol and Fenfluramine.

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23. Risk factors for recurrence of febrile seizures

Subject: Neurology / CNS

Definition & Basics

- **Age:** 6 months to 60 months (peak at 18 months).
- **Criteria:** Seizure associated with temperature ≥38°C (100.4°F), absence of CNS infection/inflammation, no acute systemic metabolic abnormality, no history of prior afebrile seizures.
- **Overall Recurrence:** ~30–33% of children will have a second febrile seizure.
- **Age-dependent Recurrence:** 50% if 1st episode occurs <1 year of age; 20% if >1 year of age.

Risk Factors for Recurrence *Examiners look for these 4 major, classic predictors (Nelson/AAP):*

- **Early Age:** Onset <12–15 months of age.
- **Family History:** First-degree relative with a history of *febrile* seizures.
- **Fever Duration:** Short duration of fever (<1 hour) before the onset of the seizure.
- **Fever Peak:** Lower peak temperature at the time of the seizure onset.
- **Cumulative Risk Score:**
    - 0 factors: ~10–15% recurrence risk.
    - 1 factor: ~20–25% recurrence risk.
    - 2 factors: ~30–32% recurrence risk.
    - 3–4 factors: 50–70% recurrence risk.
- *Minor factors:* Frequent febrile illnesses, day-care attendance.

Risk Factors for Subsequent Epilepsy (Classic Trap) *Do not confuse recurrence of febrile seizures with the risk of developing epilepsy (afebrile seizures). Risk factors for epilepsy include:*

- **Complex Febrile Seizure:** Prolonged (>15 min), focal onset, or multiple episodes in 24 hours.
- **Neurodevelopment:** Pre-existing neurological or developmental abnormality.
- **Family History:** First-degree relative with *epilepsy* (afebrile seizures).
- **Fever Duration:** Brief duration of fever prior to seizure.
- *Epilepsy Risk:* Baseline (1%) → 1 risk factor (2%) → 2+ risk factors (~10%).

Etiology & Genetics

- **Inheritance:** Polygenic or autosomal dominant with incomplete penetrance.
- **Loci:** FEB1 to FEB11.
- **Genes:** *SCN1A*, *SCN1B*, *GABRG2* (Mutations overlap with GEFS+ [Generalized Epilepsy with Febrile Seizures Plus] and Dravet syndrome).

Clinical & Diagnosis

- **Simple vs. Complex:** Differentiating is key for prognosis and workup.
    - *Simple:* Generalized, <15 mins, once in 24 hours.

  - *Complex:* Focal, >15 mins, or recurs within 24 hours.

- **Lumbar Puncture (AAP Guidelines):**
  - *Recommended:* If signs of meningitis/CNS infection.
  - *Consider:* In infants 6–12 months if immunization status for *Hib* or *S. pneumoniae* is deficient/unknown, or if pre-treated with antibiotics (can mask meningeal signs).
- **EEG/Neuroimaging:** Not routinely indicated for simple febrile seizures.

Management & Prevention

- **Acute Management:** Airway, Breathing, Circulation. IV Lorazepam or Midazolam (buccal/IM/IN) if seizure >5 minutes.
- **Antipyretics (AAP 2024):** Paracetamol/Ibuprofen relieve child's discomfort but **do not** prevent the recurrence of febrile seizures.
- **Continuous Prophylaxis:** Daily AEDs (Valproate, Phenobarbital) are **not recommended** due to adverse effect profiles outweighing benefits.
- **Intermittent Prophylaxis:** Oral Clobazam or Diazepam at the onset of fever. *Indication:* Rarely used; reserved for cases with extreme parental anxiety or history of very prolonged/status febrile seizures.

Exam Summary

- **Must-Write Recurrence Factors:** Age <1 yr, FHx of febrile seizures, short fever duration, low peak temperature.
- **Must-Write Epilepsy Factors:** Complex seizure, abnormal neurodevelopment, FHx of epilepsy.
- **Trap:** Antipyretics do *not* prevent febrile seizure recurrence.
- **Prophylaxis:** Daily AEDs are contraindicated for simple febrile seizures; intermittent clobazam/diazepam is reserved for select, severe cases.

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24. Dravet syndrome

Subject: Neurology / CNS

Definition

- Rare, catastrophic developmental and epileptic encephalopathy (DEE) of infancy.
- Previously known as Severe Myoclonic Epilepsy in Infancy (SMEI).

Genetics & Pathophysiology

- **Gene:** *SCN1A* mutation in >80% of cases (encodes Nav1.1 voltage-gated sodium channel).
- **Inheritance:** >90% are *de novo* mutations.
- **Mechanism:** Loss-of-function mutation specifically affects GABAergic inhibitory interneurons → hyperexcitability and spontaneous seizures.

Clinical Features (Triphasic Evolution)

- **Febrile Stage (0–12 months):**
    - Onset in a previously normal, healthy infant (peak at 5–8 months).
    - Prolonged, recurrent febrile or afebrile seizures (often hemiclonic or generalized clonic).
    - Frequent progression to status epilepticus.
- **Worsening Stage (1–5 years):**
    - Emergence of multiple seizure types: myoclonic, atypical absence, focal impaired awareness.
    - Developmental stagnation or regression begins.
    - Appearance of ataxia, crouch gait, and pyramidal signs.
- **Stabilization Stage (>5 years to adulthood):**
    - Seizure frequency may decrease (myoclonic seizures often disappear).
    - Persistent moderate-to-severe intellectual disability.
    - Autistic features and behavioral issues predominate.

Classic Triggers

- Fever / Infections.
- Hyperthermia (e.g., hot baths, exertion).
- Vaccinations (triggers the onset, but vaccination is *not* the cause).
- Photic stimulation or visual patterns.

Diagnosis

- **Clinical:** Highly suspected in an infant with prolonged/hemiclonic febrile seizures.
- **Genetics:** *SCN1A* gene sequencing or epilepsy gene panel (confirmatory).
- **EEG:**
    - Early (first year): Usually normal (background and sleep).
    - Later (>1 year): Generalized spike-wave or polyspike-wave discharges, focal abnormalities, background slowing.
- **Neuroimaging (MRI):** Usually normal initially; mild generalized atrophy may appear later.

Management

- **ABSOLUTE CONTRAINDICATION (Exam Trap):** Avoid Sodium Channel Blockers (Phenytoin, Carbamazepine, Oxcarbazepine, Lamotrigine, Rufinamide) → they selectively further depress inhibitory interneurons, dramatically worsening seizures.
- **First-line maintenance:** Valproate (VPA) + Clobazam (CLB).
- **Second-line / Add-on therapy (ILAE / Recent Updates):**
    - **Stiripentol (STP):** Classic add-on to VPA + CLB.
    - **Cannabidiol (CBD / Epidiolex):** FDA-approved for Dravet syndrome (≥1 year old).

    - **Fenfluramine (FFA):** FDA-approved (2020) for seizures associated with Dravet (highly effective, requires echocardiogram monitoring for valvular heart disease).
    - **Topiramate / Levetiracetam:** Alternative add-ons.
- **Non-pharmacological:** Ketogenic diet (highly effective), Vagus Nerve Stimulation (VNS).
- **Rescue therapy:** Readily available buccal midazolam or rectal diazepam for prolonged seizures/status epilepticus.
- **Trigger management:** Aggressive antipyretic use during illness; avoid hot baths.

Complications & Prognosis

- **Prognosis:** Poor for seizure freedom and cognitive outcome; 100% have some degree of intellectual disability.
- **Mortality:** High premature mortality rate (up to 15-20% by adulthood).
- **Leading cause of death:** SUDEP (Sudden Unexpected Death in Epilepsy), followed by status epilepticus.

Exam Summary

- **Classic presentation:** Healthy infant (<1 yr) with prolonged febrile hemiclonic seizure.
- **Gene:** *SCN1A* mutation (Nav1.1 sodium channel).
- **Progression:** Multiple seizure types emerge in year 2 + developmental regression.
- **Never give:** Phenytoin, Carbamazepine, Lamotrigine (worsens seizures).
- **Best drugs:** Valproate, Clobazam, Stiripentol, Cannabidiol, Fenfluramine.
- **Major risk:** High rate of SUDEP.

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25. Guillain Barre syndrome types, treatment and prognosis

Subject: Neurology / CNS

Basics

- Most common cause of acute flaccid paralysis (AFP) worldwide post-polio eradication
- Acute, immune-mediated polyradiculoneuropathy
- Characterized by progressive, symmetric, ascending weakness and areflexia

Triggers & Pathogenesis

- **Antecedent illness:** Occurs 2–4 weeks prior in 70% cases
- **Pathogens:** *Campylobacter jejuni* (most common, 30%), *Mycoplasma pneumoniae*, EBV, CMV, Zika virus
- **Mechanism:** Molecular mimicry between pathogen antigens and peripheral nerve myelin/axonal gangliosides (e.g., GM1, GD1a, GQ1b)
- **Vaccines:** Historically linked to 1976 influenza vaccine; current risk is exceedingly rare (~1 per million)

Types (Subtypes of GBS)

- **AIDP (Acute Inflammatory Demyelinating Polyradiculoneuropathy):**
  - Most common subtype in North America/Europe (up to 90%)
  - Primary target: Schwann cell membrane/myelin
  - Excellent recovery prognosis
- **AMAN (Acute Motor Axonal Neuropathy):**
  - Most common in Asia/Latin America; frequent in children
  - Strongly associated with *C. jejuni* enteritis
  - Antibodies: Anti-GM1, Anti-GD1a
  - Target: Axolemma (node of Ranvier); purely motor
- **AMSAN (Acute Motor-Sensory Axonal Neuropathy):**
  - Severe variant of AMAN involving sensory fibers
  - Marked axonal degeneration; delayed/incomplete recovery
- **Miller Fisher Syndrome (MFS):**
  - Classic triad: Ophthalmoplegia, Ataxia, Areflexia
  - Antibodies: Anti-GQ1b (90% cases)
  - Usually descends (cranial nerves first)
- **Bickerstaff Brainstem Encephalitis:**
  - CNS variant of MFS; features altered sensorium and hyperreflexia + MFS triad

Clinical Features

- **Motor:** Symmetrical, ascending flaccid paralysis (distal to proximal)
- **Reflexes:** Decreased or absent deep tendon reflexes (DTRs) early in disease
- **Sensory:** Radicular back/leg pain (common early symptom in children), distal paresthesias
- **Cranial Nerves:** Bulbar palsy (CN IX, X), facial weakness (CN VII - bilateral)
- **Autonomic (Red Flag):** Tachycardia/bradycardia, labile blood pressure, urinary retention, ileus

Diagnosis

- **Clinical:** Brighton Criteria (Level 1: flaccid weakness, areflexia, monophasic course <28 days, CSF/EMG support)
- **CSF Analysis:**
  - *Cytoalbuminologic dissociation:* High protein (>45 mg/dL) with normal WBC count (<10 cells/mm^3)
  - *Pitfall:* CSF protein may be normal in the first week (repeat at week 2 if high index of suspicion)
- **EMG / NCS (Nerve Conduction Studies):**

  - Differentiates demyelinating (slowed conduction velocity, prolonged distal latency/F-waves) vs. axonal (decreased amplitude)

- **MRI Spine:** Contrast enhancement of the cauda equina and lumbar nerve roots (supports early diagnosis)

Treatment

- **Airway & Respiratory (Highest Priority):**
  - Monitor vital capacity (VC) and negative inspiratory force (NIF) every 4–6 hours
  - *Intubation indications:* VC < 15–20 mL/kg, bulbar dysfunction (loss of gag/cough), severe dysautonomia
- **Immunomodulation (Specific Therapy):**
  - *IVIG:* 2 g/kg total (usually divided as 0.4 g/kg/day for 5 days). First-line in children due to safety and ease of use.
  - *Plasmapheresis (PLEX):* 4–5 volume exchanges over 7–10 days. Equal efficacy to IVIG.
  - *Rule:* Start within 2 weeks of onset for maximum benefit. Do **NOT** combine IVIG and PLEX.
  - *Contraindication:* Corticosteroids are **ineffective** and not recommended (Nelson/AAP consensus).
- **Supportive Care:**
  - Autonomic monitoring (ICU admission for severe cases)
  - Pain management: Gabapentin, carbamazepine, or NSAIDs
  - DVT prophylaxis (LMWH) and pressure ulcer prevention in bedbound patients
  - Aggressive physiotherapy and rehabilitation

Prognosis

- **Timeline:** Progression peaks by 2–4 weeks; plateau phase lasts days to weeks; recovery takes weeks to months
- **Pediatric vs. Adult:** Children have a significantly better prognosis than adults
- **Recovery:** 80–90% of children recover completely with no residual deficits
- **Mortality:** <5% (usually secondary to autonomic arrhythmias, respiratory failure, or VAP)
- **Poor Prognostic Factors:** Rapid progression to intubation, AMSAN subtype, unexcitable nerves on EMG, failure to improve after 3 weeks
- **Recurrence:** Rare (2–5%)

Exam Summary

- **Classic CSF:** Cytoalbuminologic dissociation (high protein, normal cells; may be normal in week 1).
- **Subtypes to know:** AIDP (most common overall), AMAN (Asia/children, *C. jejuni*), MFS (Ataxia, Areflexia, Ophthalmoplegia, Anti-GQ1b).

- **Treatment trap:** IVIG and PLEX are equally effective; steroids have NO role.
- **Intubation trigger:** Vital capacity < 15–20 mL/kg or bulbar failure.
- **Prognosis:** Excellent in pediatrics; >80% achieve full recovery.

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26. Neurocysticercosis management and recent developments

Subject: Neurology / CNS

Basics & Etiology

- **Definition:** CNS infection by larval stage (cysticerci) of the pork tapeworm *Taenia solium*.
- **Transmission:** Fecal-oral ingestion of *T. solium* eggs from human feces (not by eating undercooked pork; eating pork causes intestinal taeniasis, not NCC).
- **Most Common:** Leading cause of acquired epilepsy in children in developing nations.

Pathophysiology & Stages

- **Vesicular:** Viable parasite, minimal host inflammation.
- **Colloidal Vesicular:** Parasite dying, intense inflammatory response, severe edema (highly epileptogenic).
- **Granular Nodular:** Cyst shrinks, early mineralization.
- **Calcified:** Dead parasite, dense calcification (can still act as an epileptogenic focus).

Clinical Features

- **Seizures:** Most common presentation (70-90%); typically focal with or without secondary generalization.
- **Raised ICP:** Headache, vomiting, papilledema (common in parenchymal encephalitis or intraventricular cysts).
- **Focal Deficits:** Hemiparesis, cranial nerve palsies.
- **Ocular/Spinal:** Visual loss, radiculopathy (requires urgent attention).

Diagnosis

- **Diagnostic Criteria:** Del Brutto Criteria (Absolute, Major, Minor, Epidemiologic).
- **MRI Brain (Investigation of Choice):** Best for vesicular/colloidal stages and extraparenchymal cysts.
    - *Buzzword:* "Hole-with-dot" sign (cystic lesion with invaginated scolex) = Absolute diagnostic criterion.
    - *Recent Development:* 3D volumetric sequences (FIESTA/CISS) highly sensitive for intraventricular cysts and scolex identification.
- **CT Brain:** Best for identifying calcified cysts ("starry sky" appearance in multiple calcific NCC).
- **Serology:** Enzyme-linked Immunoelectrotransfer Blot (EITB) is the test of choice (highly specific); ELISA is less reliable.
- **Fundoscopy:** Mandatory before starting treatment to rule out ocular NCC.

Management Algorithm

- **Step 1: Resuscitation & Symptomatic**
    - Airway, Breathing, Circulation.
    - Manage acute seizures: IV Lorazepam → IV Levetiracetam, Fosphenytoin, or Valproate.
- **Step 2: Anti-inflammatory (Crucial)**
    - Must start Corticosteroids (Dexamethasone 0.1 mg/kg/day OR Prednisolone 1 mg/kg/day) 1–2 days *before* cysticidal drugs.
    - *Rationale:* Prevents severe inflammatory response and brain edema caused by dying parasites.
- **Step 3: Cysticidal Therapy (Targeted)**
    - *Single viable/enhancing cyst:* Albendazole (15 mg/kg/day in 2 divided doses for 10–14 days).
    - *Multiple viable cysts (≥3):* **Recent Update (IDSA/ASTMH Guidelines):** Dual therapy with Albendazole + Praziquantel (50 mg/kg/day) for 10–14 days.
- **Absolute Contraindications to Cysticidal Therapy:**
    - Ocular NCC (risk of blindness from inflammation).
    - Spinal NCC (risk of irreversible cord damage).
    - Cysticercotic encephalitis (diffuse cerebral edema).
    - Calcified cysts (parasite is already dead; cysticidal drugs offer no benefit).

Surgical Management

- **Intraventricular cysts:** Endoscopic excision.
- **Hydrocephalus:** Ventriculoperitoneal (VP) shunt placement.
- **Ocular cysts:** Surgical extraction.

Recent Developments & Updates

- **IDSA/ASTMH 2018 & Recent IAP Consensus:** Shifted from monotherapy to **Dual Therapy** (Albendazole + Praziquantel) for >2 viable parenchymal cysts (faster resolution, fewer residual calcifications).
- **AED Duration:** Previously treated for standard 2 years. *Now:* AEDs can be tapered and stopped 6 months after complete resolution of the cystic lesion on imaging, *unless* a calcified focus remains (requires prolonged AEDs due to high relapse risk).
- **Cimetidine/Grapefruit juice:** Sometimes co-administered to increase bioavailability of Praziquantel.

Complications & Prognosis

- Refractory epilepsy (associated with residual calcifications).
- Obstructive hydrocephalus.

- Prognosis is generally excellent for single parenchymal cysts (spontaneous resolution common).

Prevention

- Strict hand hygiene and improved sanitation.
- Proper cooking of pork (breaks the transmission cycle by preventing human intestinal taeniasis).
- Mass drug administration (Praziquantel) for taeniasis in endemic areas.

Exam Summary

- **Etiology:** Fecal-oral ingestion of *T. solium* eggs (NOT eating pork).
- **Classic MRI:** "Hole-with-dot" (cystic lesion with scolex).
- **Mandatory Pre-requisite:** Fundoscopy to rule out ocular NCC before starting cysticidal drugs.
- **Treatment Sequence:** AEDs → Steroids → Cysticidal drugs.
- **Update:** Dual therapy (Albendazole + Praziquantel) is now standard for ≥3 viable cysts. Do not treat purely calcified cysts with antiparasitics.

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27. Tuberculoma

Subject: Neurology / CNS

Definition & Basics

- Focal, tumor-like granulomatous mass caused by *Mycobacterium tuberculosis*.
- Most common cause of space-occupying lesion (SOL) in children in TB-endemic regions.
- Most common location in children: Infratentorial (cerebellum/brainstem); in adults: Supratentorial.

Pathophysiology

- Hematogenous dissemination from primary focus (lungs, lymph nodes).
- Seeding in brain parenchyma forms subpial or subependymal microgranulomas (Rich foci).
- Coalescence of microgranulomas → central caseating necrosis → fibrous capsule formation → Tuberculoma.

Clinical Features

- **Supratentorial lesions:** Focal seizures (most common presentation), hemiparesis, visual field defects.
- **Infratentorial lesions:** Cerebellar ataxia, cranial nerve palsies, brainstem syndromes.
- **Raised Intracranial Pressure (ICP):** Headache, early morning vomiting, papilledema (due to mass effect or obstructive hydrocephalus).
- **Systemic signs:** Fever, weight loss, and night sweats are often *absent* in isolated tuberculomas (unlike TB meningitis).

Diagnosis

- **MRI Brain with Contrast (Gold Standard):**
  - *Non-caseating:* T1 isointense, T2 hyperintense, homogeneous nodular enhancement.
  - *Caseating (solid center):* T1 isointense/hypointense, T2 hypointense, ring enhancement.
  - *Caseating (liquid center):* T1 hypointense, T2 hyperintense, ring enhancement.
  - **"Target Sign" (Pathognomonic):** Central calcification/enhancement surrounded by a hypointense rim and perilesional edema.
- **MR Spectroscopy (MRS):** Prominent **Lipid/Lactate peak** (differentiates from Neurocysticercosis [amino acid peak] and neoplasms [choline peak]).
- **Supportive Workup:**
  - Search for primary focus: CXR, Gastric aspirate/induced sputum for CBNAAT (GeneXpert MTB/RIF).
  - Immunological: Mantoux test (TST) or IGRA (positive in 50-70%).
  - CSF analysis: Often normal; defer if significant mass effect/raised ICP exists (risk of herniation).

Management

- **Medical Therapy (First-line):** Anti-Tubercular Therapy (ATT)
  - *Intensive Phase:* 2 months of HRZE (Isoniazid, Rifampicin, Pyrazinamide, Ethambutol).
  - *Continuation Phase:* 10–16 months of HRE (Total duration 12–18 months depending on radiological resolution).
- **Corticosteroids:**
  - Indications: Significant perilesional edema, severe mass effect, raised ICP.
  - Drug: Oral Prednisolone (1–2 mg/kg/day) or IV Dexamethasone for 4–8 weeks, followed by a slow taper.
- **Antiseizure Medications (ASMs):**
  - Initiate if the child presents with seizures.
  - *Trap:* Routine ASM prophylaxis for asymptomatic tuberculomas is generally not recommended unless cortical involvement poses high risk.
- **Paradoxical Upgrading Reaction (PUR):**
  - *Definition:* Clinical/radiological worsening (enlargement of lesion or appearance of new lesions) 2–12 weeks after starting ATT, due to restored immune response.
  - *Management:* **Do not stop ATT**. Add or increase the dose of systemic corticosteroids.
- **Surgical Indications (Rare):**
  - Impending brain herniation / severe midline shift.
  - Obstructive hydrocephalus requiring Ventriculoperitoneal (VP) shunt or External Ventricular Drain (EVD).

- Diagnostic dilemma (stereotactic biopsy to rule out malignancy/fungal mass).
- Failure of medical therapy.

Complications & Prognosis

- Intractable epilepsy (calcified residual lesions act as seizure foci).
- Permanent focal neurological deficits (hemiparesis, ataxia).
- Optic atrophy and vision loss (secondary to prolonged raised ICP).
- *Prognosis:* Generally excellent with timely medical management; complete radiological resolution may take up to 2 years.

Exam Summary: Must-Write Points

- Most common pediatric CNS SOL in endemic areas; infratentorial > supratentorial in kids.
- Presents classically with new-onset focal seizures and raised ICP without overt systemic TB signs.
- MRI classic finding: "Target sign" with perilesional edema and ring enhancement.
- MRS classic finding: Elevated Lipid/Lactate peak.
- Treatment is medical: 12–18 months of ATT + steroids for edema; surgery is reserved for complications (hydrocephalus/herniation).
- Paradoxical upgrading reaction requires steroids, NOT cessation of ATT.

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28. Movement disorders in children

Subject: Neurology / CNS

Definition

- Neurologic syndromes characterized by either excess movement (hyperkinesia) or paucity of voluntary movement (hypokinesia) without primary weakness or spasticity.
- Primarily arise from basal ganglia or cerebellar dysfunction.

Classification & Clinical Features

- **Tics:** Sudden, rapid, recurrent, non-rhythmic motor movements or vocalizations. Suppressible, preceded by a premonitory urge, exacerbate with stress, disappear in sleep.
  - *Tourette Syndrome:* Multiple motor + ≥1 vocal tic for >1 year.
- **Chorea:** Brief, irregular, flowing, "dance-like" movements moving randomly from one body part to another. Motor impersistence (milkmaid grip, darting tongue).
- **Athetosis:** Slow, continuous, writhing movements, predominantly distal (fingers/toes). Often coexists with chorea (choreoathetosis).
- **Dystonia:** Sustained or intermittent muscle contractions causing twisting, repetitive movements, or abnormal postures. Worsens with voluntary action (action dystonia); relieved by sensory tricks (*geste antagoniste*).

- **Myoclonus:** Sudden, brief, shock-like muscle jerks. Can be positive (contraction) or negative (asterixis/loss of tone). Not suppressible.
- **Tremor:** Rhythmic, oscillatory movement around a joint.
    - *Resting:* Parkinsonism.
    - *Postural/Action:* Essential tremor, physiologic.
    - *Intention:* Cerebellar lesion.
- **Parkinsonism (Hypokinetic):** Bradykinesia, rigidity (lead-pipe/cogwheel), resting tremor, postural instability. (Rare in children; suspect drug-induced, Wilson disease, or juvenile Huntington).

Etiology

- **Acquired / Acute:**
    - *Post-infectious/Autoimmune:* Sydenham chorea (Group A Strep), PANDAS/PANS, Anti-NMDAR encephalitis, SLE.
    - *Drug-induced:* Dopamine antagonists (metoclopramide, haloperidol) causing acute dystonia or tardive dyskinesia.
    - *Vascular/Ischemic:* Basal ganglia stroke, Moyamoya.
- **Static / Non-progressive:**
    - *Dyskinetic Cerebral Palsy:* Kernicterus (bilirubin encephalopathy), severe hypoxic-ischemic encephalopathy (HIE).
- **Genetic / Metabolic (Progressive):**
    - *Metabolic:* Wilson disease, Glutaric aciduria type 1, Lesch-Nyhan syndrome.
    - *Neurodegeneration with Brain Iron Accumulation (NBIA):* Pantothenate kinase-associated neurodegeneration (PKAN).
    - *Genetic:* Dopa-responsive dystonia (GCH1 mutation), Huntington disease (CAG repeats), Spinocerebellar ataxias.

Pathophysiology

- **Hyperkinetic:** Underactivity of the indirect pathway or overactivity of the direct basal ganglia pathway → excessive thalamocortical drive.
- **Hypokinetic:** Overactivity of the indirect pathway or underactivity of the direct pathway → reduced thalamocortical drive.

Diagnostic Approach

- **History:** Age of onset, family history, drug exposure, perinatal history (jaundice/asphyxia), effect of sleep (most movement disorders disappear in sleep except severe myoclonus/palatal tremor).
- **Clinical Clues:** Kayser-Fleischer rings (Wilson), self-mutilation (Lesch-Nyhan), psychiatric/behavioral changes (Huntington, PANDAS, Wilson).
- **Laboratory Evaluation:**

- *First-line:* CBC, electrolytes, LFTs, thyroid profile.
- *Specific:* ASO titer, Anti-DNase B, throat swab (Sydenham); Serum ceruloplasmin, 24-hr urinary copper, slit-lamp exam (Wilson); Autoimmune encephalitis panel (CSF/Serum).

- **Neuroimaging (MRI Brain):**
  - *PKAN:* "Eye of the tiger" sign (globus pallidus).
  - *Wilson:* "Face of the giant panda" sign (midbrain).
  - *Glutaric aciduria:* Bat-wing appearance of Sylvian fissures, basal ganglia hyperintensities.
  - *Kernicterus:* Bilateral globus pallidus hyperintensity.
- **Electrophysiology:** EEG with surface EMG to differentiate epileptic vs. non-epileptic myoclonus.
- **Genetics:** Targeted gene panels or Whole Exome Sequencing (WES) for undiagnosed progressive disorders.

Management

- **General Principles:** Treat the underlying cause (e.g., Penicillin for Sydenham, Chelators for Wilson, stop offending drugs).
- **Symptomatic Pharmacotherapy:**
  - *Tics:* Comprehensive Behavioral Intervention for Tics (CBIT) is first-line. Drugs: Alpha-2 agonists (Clonidine, Guanfacine); Atypical antipsychotics (Aripiprazole, Risperidone) for severe cases.
  - *Chorea:* Valproate, Carbamazepine. For severe/refractory: VMAT2 inhibitors (Tetrabenazine), Haloperidol.
  - *Dystonia:*
    - **Rule/Standard of Care:** *Every* child with unexplained dystonia must receive a trial of Levodopa/Carbidopa (to rule out highly treatable Dopa-responsive dystonia).
    - *Medications:* Anticholinergics (Trihexyphenidyl), Baclofen, Clonazepam.
    - *Focal dystonia:* Botulinum toxin injections.
  - *Tremor:* Propranolol, Primidone (for essential tremor).
  - *Myoclonus:* Clonazepam, Levetiracetam, Valproate.
- **Surgical / Advanced:**
  - Deep Brain Stimulation (DBS) of Globus Pallidus internus (GPi) for medically refractory primary dystonia.
  - Intrathecal baclofen pump for severe generalized dystonia/spasticity.

Complications & Prognosis

- *Complications:* Joint contractures, orthopedic deformities (scoliosis), chronic pain, severe weight loss (due to constant movement), social isolation, depression.

- *Prognosis:* Excellent for transient tics, Sydenham chorea, and Dopa-responsive dystonia. Poor for neurodegenerative disorders (NBIA, Huntington).

Exam Summary: Must-Write Points

- **Tics vs. Chorea:** Tics are suppressible with a premonitory urge; chorea is unsuppressible, random, and flowing.
- **Sydenham Chorea:** Post-streptococcal, auto-immune, features motor impersistence (milkmaid grip); treat with penicillin prophylaxis.
- **Dopa-Responsive Dystonia:** Diurnal variation (worse in evening); absolute indication for a Levodopa trial in all pediatric dystonias.
- **Wilson Disease:** Suspect in any child >3 years with unexplained movement disorder + hepatic dysfunction; check ceruloplasmin and KF rings.
- **Acute Dystonic Reaction:** Often secondary to antiemetics (metoclopramide); immediately treat with IV Diphenhydramine or Promethazine.

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29. Cerebral palsy and role of botulinum toxin

Subject: Neurology / CNS

Definition

- Group of permanent, non-progressive disorders of movement and posture causing activity limitation.
- Attributed to non-progressive disturbances occurring in the developing fetal or infant brain.
- Often accompanied by sensory, cognitive, communication, and behavioral disturbances, or epilepsy.

Etiology & Pathophysiology

- **Prenatal (70-80%):** TORCH infections, placental insufficiency, brain malformations, genetic disorders.
- **Perinatal:** Prematurity (highest risk factor), Hypoxic-Ischemic Encephalopathy (HIE), kernicterus, hypoglycemia.
- **Postnatal (<2 yrs):** Meningitis, encephalitis, head trauma, near-drowning.
- **Classic MRI Correlates:**
    - *Prematurity* + *Spastic Diplegia:* Periventricular Leukomalacia (PVL).
    - *Term* + *Spastic Quadriplegia:* Parasagittal cerebral injury / Multicystic encephalomalacia.
    - *Term* + *Dyskinetic CP:* Basal ganglia and thalamic lesions (status marmoratus).

Classification

- **Topographic:** Diplegia (legs > arms), Hemiplegia (one side), Quadriplegia (all four limbs + trunk).

- **Physiologic:** Spastic (70-80%, pyramidal tract), Dyskinetic (10-15%, extrapyramidal/choreoathetoid/dystonic), Ataxic (<5%, cerebellar), Mixed.
- **Functional (GMFCS - Gross Motor Function Classification System):**
    - Level I: Walks without limitations.
    - Level V: Transported in a manual wheelchair; severely limited head/trunk control.

Clinical Features

- **Motor Red Flags:** Early handedness (<18 months; indicates contralateral weakness), delayed motor milestones.
- **Tone/Posture:** Early hypotonia evolving into hypertonia/spasticity by 6–18 months.
- **Reflexes:** Persistence of primitive reflexes (e.g., Moro >6 months, asymmetric tonic neck reflex), brisk deep tendon reflexes, clonus, positive Babinski.
- **Specific Gaits:** Scissoring gait (adductor spasticity), Equinus gait (toe-walking due to calf spasticity).

Diagnosis

- **Clinical:** Based on serial developmental assessments and neurologic exams.
- **Imaging: MRI Brain** is the modality of choice (preferably done >2 years of age for complete myelination, though often done earlier if clinically indicated).
- **Metabolic/Genetic Testing:** Indicated if MRI is normal, features are atypical, or if there is a progressive loss of milestones (rule out neurodegenerative disorders).

General Management

- **Multidisciplinary Approach:** Physiotherapy (PT), Occupational Therapy (OT), Speech therapy.
- **Medical (Systemic Spasticity):** Oral Baclofen, Diazepam, Tizanidine, Dantrolene.
- **Medical (Dystonia):** Trihexyphenidyl, Levodopa trial, Gabapentin.
- **Surgical:** Selective Dorsal Rhizotomy (SDR) for pure spastic diplegia, orthopedic tendon lengthening, hip surveillance/reconstruction.

Role of Botulinum Toxin (BoNT) in CP

Mechanism of Action

- Cleaves SNARE proteins (SNAP-25 for BoNT-A) at the neuromuscular junction.
- Irreversibly inhibits presynaptic release of Acetylcholine (ACh).
- Produces localized, reversible chemical denervation and flaccid paralysis of the injected overactive muscle.

Indications in CP

- **Focal/Regional Spasticity:** Best for dynamic contractures (e.g., equinus gait, hamstring tightness, adductor scissoring).
- **Focal Dystonia:** To improve positioning and reduce pain.

- **Sialorrhea (Drooling):** Injection into submandibular/parotid glands.
- **Pain Management:** To relieve painful muscle spasms.

Administration & Timing

- **Optimal Age:** 2 to 6 years (the "window of opportunity" before dynamic spasticity becomes a fixed, bony contracture).
- **Preparation:** BoNT-A (OnabotulinumtoxinA or AbobotulinumtoxinA) is most commonly used.
- **Technique:** Intramuscular injection, ideally under **Ultrasound (USG) or Electromyography (EMG) guidance** for precise localization.
- **Dosing:** Max dose depends on the formulation (e.g., OnabotulinumtoxinA max is typically 15–20 Units/kg total body dose per session).

Clinical Effects & Strategy

- **Onset:** 24–72 hours; peak effect at 2–4 weeks.
- **Duration:** Reversible; lasts 3 to 6 months (as nerve terminals sprout new endings).
- **Synergistic Therapy:** BoNT is *never* a standalone treatment. It must be immediately followed by intensive PT, orthotics (AFOs), and serial casting to stretch the muscle while it is relaxed.

Contraindications & Cautions

- **Absolute:** Fixed, structural (bony) contractures (BoNT only works on dynamic muscle tone), known hypersensitivity, concurrent neuromuscular junction disorders (e.g., Myasthenia Gravis).
- **Drug Interactions:** Avoid concurrent use with Aminoglycosides (potentiates neuromuscular blockade).

Complications of BoNT

- **Local:** Pain at injection site, hematoma, excessive localized weakness.
- **Systemic (Rare but severe):** Unintended spread causing botulism-like toxicity (dysphagia, aspiration, generalized weakness, respiratory depression).

Complications of CP

- **Neurological:** Epilepsy (highest in spastic quadriplegia; ~50%), intellectual disability (50%), cortical visual impairment, sensorineural hearing loss.
- **Gastrointestinal:** GERD, aspiration pneumonia, malnutrition, constipation.
- **Orthopedic:** Hip subluxation/dislocation (requires routine radiographic surveillance), scoliosis, osteopenia/fractures.

Prognosis

- Independent sitting by age 2 years is the strongest predictor of future ambulation.
- Failure to achieve head control by 9 months or independent sitting by 3 years indicates a very poor prognosis for walking.

Prevention

- **Antenatal: MgSO4** given to mothers at <32 weeks gestation for fetal neuroprotection.
- **Perinatal:** Delayed cord clamping, therapeutic hypothermia for moderate-to-severe HIE in term infants (reduces death/disability by 25%).

Exam Summary

- **Definition:** Non-progressive motor disorder of developing brain; PVL is the classic MRI finding for premature spastic diplegia.
- **Red Flags:** Handedness <18 months, persistent primitive reflexes.
- **BoNT Mechanism:** Presynaptic ACh release blockade via SNARE protein cleavage.
- **BoNT Indication:** Dynamic focal spasticity (not fixed contractures); optimal age 2-6 years.
- **BoNT Strategy:** Must be combined with intensive PT and serial casting; effects last 3-6 months.
- **Prevention:** Antenatal MgSO4 (<32 weeks) and therapeutic hypothermia for HIE.

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30. Pediatric stroke etiologies investigations and management

Subject: Neurology / CNS

Basics

- **Definition:** Sudden onset focal neurological deficit lasting >24 hours, or <24 hours with neuroimaging evidence of cerebral infarction or hemorrhage.
- **Classification:** Arterial Ischemic Stroke (AIS), Hemorrhagic Stroke (HS), Cerebral Sinus Venous Thrombosis (CSVT).
- **Key Difference:** Unlike adults, pediatric stroke is rarely atherosclerotic; requires exhaustive search for congenital/acquired anomalies.

Etiology

- **Arteriopathies (Most common cause of AIS):**
    - Focal Cerebral Arteriopathy (FCA) / Transient Cerebral Arteriopathy (TCA).
    - Post-varicella arteriopathy (typically basal ganglia infarcts 1–12 months post-infection).
    - Moyamoya disease/syndrome (progressive stenosis of internal carotid arteries; "puff of smoke" collaterals).
    - Arterial dissection (cervical trauma, connective tissue disorders like Marfan/Ehlers-Danlos).
    - Vasculitis (SLE, Takayasu arteritis, Kawasaki disease).
- **Cardiac Disorders:**
    - Congenital heart disease (especially cyanotic CHD with right-to-left shunt).
    - Rheumatic heart disease, infective endocarditis, arrhythmias, cardiac surgery/ECMO.
- **Hematologic & Prothrombotic:**
    - **Sickle Cell Disease (SCD):** Highest risk group (causes large vessel vasculopathy).

    - Thrombophilias: Factor V Leiden, Prothrombin G20210A, Protein C/S deficiency, Antithrombin deficiency, Antiphospholipid syndrome.
    - Iron deficiency anemia (especially associated with CSVT).
- **Infections:** Meningitis, encephalitis, HIV, COVID-19.
- **Hemorrhagic Stroke specific:** Arteriovenous malformations (AVMs), aneurysms, cavernous angiomas, bleeding diathesis (Hemophilia, severe thrombocytopenia).

Clinical Features

- **Infants/Toddlers:** Seizures (most common presentation), altered mental status, poor feeding, delayed motor milestones (handedness before 1 year is a red flag for contralateral stroke).
- **Older Children:** Acute hemiparesis, hemifacial weakness, aphasia, visual field defects, ataxia.
- **Hemorrhagic/CSVT:** Severe headache, vomiting, lethargy, signs of raised intracranial pressure (ICP).

Investigations

- **Neuroimaging (Urgent):**
    - **Non-contrast CT Head:** First line to rapidly rule out hemorrhage.
    - **MRI Brain with DWI/ADC:** *Gold standard*. DWI shows restricted diffusion (bright) within minutes of ischemic stroke.
    - **MRA (Arteriography) / MRV (Venography):** To evaluate vascular anatomy, occlusions, Moyamoya, or CSVT.
- **Cardiac Workup:**
    - Echocardiogram (rule out thrombus, structural defects, PFO).
    - ECG / Holter monitor (rule out arrhythmias).
- **Laboratory Workup:**
    - *First tier:* CBC, reticulocyte count, iron profile (ferritin), PT/APTT, ESR/CRP, comprehensive metabolic panel.
    - *SCD Screen:* Sickle solubility test / Hb electrophoresis (mandatory in endemic populations/African descent).
    - *Thrombophilia panel:* (Best done pre-anticoagulation or 3 months post-stroke) Lupus anticoagulant, anticardiolipin, Factor VIII, homocysteine, Protein C/S, Antithrombin, Factor V Leiden.
    - *Autoimmune:* ANA, dsDNA, ANCA (if vasculitis suspected).

Management

- **Acute Supportive Care (Neuroprotection):**
    - Maintain ABCs. Keep head in midline, elevated 15–30°.
    - **Rule of Norms:** Maintain normoxia, normoglycemia, normothermia, normotension (avoid sudden lowering of BP as it decreases cerebral perfusion).
    - Treat clinical seizures aggressively (prophylactic AEDs not routinely recommended).

- **Hyperacute Therapy (AIS):**
    - *IV tPA (Alteplase):* **AHA/ASA Update:** May be considered in carefully selected children ≥2 years with AIS within 4.5 hours of symptom onset (requires strict exclusion criteria and pediatric stroke expert consultation).
    - *Mechanical Thrombectomy:* Standard of care for Large Vessel Occlusion (LVO) in older children/adolescents up to 24 hours (extrapolated from adult guidelines).
- **Disease-Specific Acute Management:**
    - *Sickle Cell Disease:* Urgent exchange transfusion (target HbS <30% and total Hb ~10 g/dL).
    - *Hemorrhagic:* Neurosurgical consultation (EVD for hydrocephalus, hematoma evacuation), reverse coagulopathy.
- **Secondary Prevention (AIS):**
    - *Non-cardioembolic / FCA:* Aspirin (3–5 mg/kg/day).
    - *Cardioembolic / Arterial Dissection / Severe Thrombophilia:* Anticoagulation (LMWH or Warfarin) for 3–6 months.
    - *Moyamoya:* Surgical revascularization (EDAS - encephaloduroarteriosynangiosis).
    - *SCD:* Chronic regular blood transfusions; Hydroxyurea.

Complications & Prognosis

- **Complications:** Post-stroke epilepsy, spasticity/contractures, cognitive and behavioral deficits, malignant cerebral edema.
- **Prognosis:** Better neuroplasticity than adults, but >50% have long-term motor or cognitive morbidity. Recurrence risk is highest in untreated SCD and Moyamoya.

Exam Summary

- **SCD** is the most critical risk factor for pediatric stroke; requires urgent exchange transfusion, not tPA.
- **MRI with DWI** is the gold standard diagnostic modality for acute ischemic stroke.
- Always investigate for **arteriopathies** (Moyamoya, post-varicella) and **cardiac** causes.
- **AHA/ASA update:** IV tPA (within 4.5h) and mechanical thrombectomy are now considered in eligible pediatric LVOs.
- Secondary prophylaxis: **Aspirin** for most AIS; **Anticoagulation** for cardioembolic/dissection/CSVT.

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31. Conditions mimicking seizures

Subject: Neurology / CNS

Definition

- **Paroxysmal Non-Epileptic Events (PNEEs):** Episodic behavioral, motor, or sensory events mimicking epileptic seizures but lacking hypersynchronous abnormal cortical EEG discharges.

Classification by Age

- **Neonates:** Jitteriness, benign neonatal sleep myoclonus, apnea/ALTE/BRUE.
- **Infants & Toddlers:** Breath-holding spells (BHS), Sandifer syndrome, shuddering attacks, gratification disorder (infantile masturbation), benign myoclonus of early infancy.
- **School-age & Adolescents:** Syncope, psychogenic non-epileptic seizures (PNES), tics, parasomnias (night terrors), migraine variants, narcolepsy/cataplexy.

Key Mimics & Clinical Clues

- **Jitteriness (Neonates):**
  - Triggered by stimulus (noise/touch).
  - Consists of tremors, *not* clonic jerks.
  - *Key differentiator:* Stops with passive flexion or gentle holding of the limb; no abnormal eye movements.
- **Benign Neonatal Sleep Myoclonus:**
  - Bilateral, synchronous jerks occurring *only* during quiet sleep.
  - *Key differentiator:* Stops immediately upon waking; normal EEG.
- **Breath-Holding Spells (6 mos – 5 yrs):**
  - *Cyanotic:* Provoked by anger/frustration → intense crying → apnea (expiration) → cyanosis → loss of consciousness (LOC) → limpness (or brief clonic jerks).
  - *Pallid:* Provoked by sudden pain/fright → vagal bradycardia → pallor → LOC.
  - *Key differentiator:* Clear provoking factor preceding the event; normal EEG.
- **Sandifer Syndrome (Infants):**
  - Severe gastroesophageal reflux (GERD) causing dystonic posturing, back arching, and torticollis.
  - *Key differentiator:* Occurs during or shortly after feeding; normal EEG. (Frequently misdiagnosed as infantile spasms).
- **Syncope (Older children):**
  - Vasovagal: Prodrome of dizziness, visual blurring, diaphoresis, nausea.
  - Convulsive syncope: Brief myoclonic/clonic jerks *after* LOC due to global cerebral hypoperfusion.
  - *Red flag:* Exertional syncope (requires ECG to rule out Long QT/HOCM).
- **Psychogenic Non-Epileptic Seizures (PNES):**
  - Often associated with stress, trauma, or psychiatric comorbidities.
  - Features: Asynchronous thrashing, pelvic thrusting, side-to-side head shaking, crying during the event.
  - *Key differentiator:* Eyes firmly **closed** (true seizures usually eyes open); resists eye opening; no post-ictal confusion; normal EEG during the event.

- **Gratification Disorder (Infantile Masturbation):**
    - Dystonic posturing, rocking, facial flushing, diaphoresis, staring.
    - *Key differentiator:* Occurs when bored/alone; stops with distraction.
- **Tics:**
    - Sudden, rapid, recurrent, non-rhythmic motor movements.
    - *Key differentiator:* Preceded by a premonitory urge; partially suppressible; no LOC.

Diagnosis

- **History & Examination:** Detailed sequence of events (aura, provocation, post-ictal state).
- **Home Video Recording:** First-line diagnostic tool; highly sensitive for distinguishing PNEEs from true seizures.
- **Video-EEG (vEEG):** Gold standard. Confirms absence of epileptiform discharges during the clinical event.
- **ECG:** Mandatory in all children presenting with unexplained LOC/convulsive syncope (rule out prolonged QTc, arrhythmias).
- **Labs:** Targeted only (e.g., Ferritin for BHS; electrolytes/glucose if clinically indicated).

Management

- **General:** Reassurance and education (most PNEEs are benign and self-limiting).
- **BHS:** Check serum ferritin; treat with Iron therapy (3-6 mg/kg/day) even if not anemic (reduces frequency of spells).
- **Sandifer Syndrome:** Anti-reflux measures, PPIs.
- **Syncope:** Hydration, increased salt intake, avoidance of triggers, counter-pressure maneuvers.
- **PNES:** Multidisciplinary approach; Cognitive Behavioral Therapy (CBT); avoid unnecessary anti-seizure medications (ASMs).

Complications & Prognosis

- **Misdiagnosis:** Up to 20-30% of patients diagnosed with intractable epilepsy actually have PNES.
- **Iatrogenic Harm:** Unnecessary administration of ASMs (leading to side effects) or intubation for "status epilepticus" in PNES.
- **Prognosis:** Excellent for infantile mimics (BHS, sleep myoclonus resolve with age). PNES requires dedicated psychiatric intervention.

Exam Summary

- **Jitteriness vs. Seizure:** Jitteriness stops with passive holding and lacks abnormal eye movements.
- **Sandifer Syndrome:** Arching/posturing linked to feeds + GERD; mimics infantile spasms.

- **PNES Buzzwords:** Eyes closed, asynchronous thrashing, pelvic thrusting, normal vEEG during the event, no post-ictal state.
- **Convulsive Syncope:** Jerks occur *after* the patient falls/loses consciousness (due to hypoxia), preceded by a prodrome.
- **Investigation of Choice:** Video-EEG is the gold standard; smartphone home videos are the most practical initial step. Always do an ECG for syncope mimics.

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32. Neurodegenerative disorders in children

Subject: Neurology / CNS

Definition

- Progressive loss or regression of previously acquired developmental milestones (cognitive, motor, sensory, or language).
- Results from progressive neuronal death, defective myelination, or accumulation of toxic metabolites.

Classification (Clinical Topographic Approach)

- **Grey Matter Diseases:** Primarily affect the cortex.
    - *Features:* Early cognitive decline (dementia), refractory seizures, visual loss (retinal/macular), myoclonus; late motor involvement.
    - *Examples:* Tay-Sachs disease, Neuronal Ceroid Lipofuscinosis (NCL/Batten disease), Rett syndrome, Alpers disease.
- **White Matter Diseases (Leukodystrophies):** Primarily affect myelin.
    - *Features:* Early motor decline, prominent UMN signs (spasticity, hyperreflexia), optic atrophy; late cognitive loss.
    - *Examples:* Metachromatic Leukodystrophy (MLD), Krabbe disease, X-linked Adrenoleukodystrophy (X-ALD), Canavan disease.
- **Basal Ganglia Diseases:** Primarily affect the extrapyramidal system.
    - *Features:* Dystonia, choreoathetosis, rigidity, tremor.
    - *Examples:* Wilson disease, Pantothenate Kinase-Associated Neurodegeneration (PKAN/NBIA), Huntington disease, Leigh syndrome.
- **Spinocerebellar Diseases:**
    - *Features:* Progressive ataxia, neuropathy.
    - *Examples:* Friedreich ataxia, Ataxia-Telangiectasia.

Pathophysiology

- **Lysosomal Storage:** Defective lysosomal enzymes cause accumulation of macromolecules (e.g., sphingolipids in Tay-Sachs/Gaucher).
- **Peroxisomal Dysfunction:** Defective very-long-chain fatty acid (VLCFA) metabolism leads to myelin destruction (e.g., X-ALD).

- **Mitochondrial Failure:** Impaired oxidative phosphorylation causes energy deficit in high-demand neural tissues (e.g., Leigh syndrome).
- **Metal Toxicity:** Abnormal copper/iron deposition causes oxidative stress and apoptosis (e.g., Wilson disease, PKAN).

Clinical Clues & Buzzwords

- **Cherry-red spot (Macula):** Tay-Sachs, Niemann-Pick (Type A), Sandhoff disease.
- **Macrocephaly:** Alexander disease, Canavan disease, Tay-Sachs (late), Mucopolysaccharidoses (MPS).
- **Hepatosplenomegaly:** Gaucher, Niemann-Pick, MPS (Hurler/Hunter).
- **Eye-of-the-tiger sign (MRI):** PKAN.
- **Alopecia + Skin rash + Ataxia:** Biotinidase deficiency (highly treatable).
- **Startle response to sound (Hyperacusis):** Tay-Sachs, Krabbe disease.

Diagnosis

- **Neuroimaging (First-line):** MRI Brain with spectroscopy. Differentiates white vs. grey matter disease and identifies specific patterns (e.g., frontal predominance in Alexander, parieto-occipital in X-ALD).
- **Metabolic Screening:**
    - Blood: Lactate, pyruvate, ammonia, VLCFA (X-ALD), biotinidase level.
    - Urine: Organic acids, glycosaminoglycans (MPS).
    - Tandem Mass Spectrometry (TMS) for acylcarnitines and amino acids.
- **Enzyme Assays:** Confirmatory for lysosomal storage disorders (using leukocytes or cultured skin fibroblasts).
- **Genetic Testing (Current Gold Standard):**
    - Targeted Gene Panels or Whole Exome Sequencing (WES).
    - *Update:* WES has largely replaced sequential single-gene testing and invasive muscle/nerve biopsies.
- **Ophthalmologic Exam:** Fundoscopy (optic atrophy, retinitis pigmentosa, cherry-red spot), Slit-lamp (Kayser-Fleischer rings in Wilson).
- **Electrophysiology:** EEG (seizures), VEP/BAER (sensory pathway integrity), NCV (demyelinating neuropathy in MLD/Krabbe).

Management

- **Specific / Disease-Modifying Therapies:**
    - *Hematopoietic Stem Cell Transplant (HSCT):* Arrests progression if done early (presymptomatic/early symptomatic) in X-ALD, Krabbe, MLD, and Hurler syndrome.
    - *Enzyme Replacement Therapy (ERT):* Intravenous recombinant enzymes for Gaucher, Pompe, and specific MPS (I, II, IVA, VI). *Note:* IV ERT does not cross the blood-brain barrier effectively; intraventricular trials are ongoing.

- *Substrate Reduction Therapy:* Miglustat for Gaucher and Niemann-Pick type C.
- *Dietary/Medical:* Copper restriction + Penicillamine/Trientine (Wilson); Lorenzo's oil + Lorenzo diet (X-ALD); Biotin (Biotinidase deficiency).

- **Supportive & Palliative Care (Multidisciplinary):**
  - *Seizure control:* Antiseizure medications (avoid valproate in mitochondrial disorders due to hepatotoxicity/POLG mutations).
  - *Spasticity/Dystonia:* Baclofen, trihexyphenidyl, botulinum toxin injections.
  - *Nutrition:* Nasogastric or PEG tube feeding for severe dysphagia to prevent aspiration.
  - *Respiratory:* Chest physiotherapy, suctioning, BiPAP for central hypoventilation.

Complications & Prognosis

- **Complications:** Recurrent aspiration pneumonia, severe contractures, status epilepticus, decubitus ulcers, malnutrition.
- **Prognosis:** Generally poor and universally fatal for most untreatable forms. Rate of decline depends on the specific mutation and age of onset (infantile forms usually progress faster than juvenile/adult forms).

Prevention

- **Genetic Counseling:** Autosomal recessive (most common), X-linked (X-ALD, Hunter, Pelizaeus-Merzbacher), or Mitochondrial (maternal inheritance).
- **Prenatal Diagnosis:** Chorionic villus sampling (CVS) at 10–12 weeks or amniocentesis at 15–18 weeks for enzyme assay or targeted mutation analysis in at-risk pregnancies.
- **Newborn Screening (NBS):** Expanded NBS now includes Pompe, MPS I, X-ALD, and Biotinidase deficiency in many regions.

Exam Summary

- **Hallmark:** Loss of acquired milestones; never normal development followed by a plateau (which suggests static encephalopathy/CP).
- **Grey vs. White:** Grey matter = Seizures/Dementia/Vision loss early; White matter = Spasticity/Motor signs early.
- **Key Triad for Treatable Mimic:** Alopecia, rash, and seizures = Biotinidase deficiency (treat with oral biotin).
- **Diagnosis:** MRI Brain + Whole Exome Sequencing (WES) is the modern diagnostic pathway of choice.
- **Treatment:** Early HSCT is life-saving for X-ALD, Krabbe, and MLD before significant neurological damage occurs.

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33. Sleep myoclonus EEG findings diagnosis and treatment

Subject: Neurology / CNS

Definition & Basics

- **Entity:** Benign Neonatal Sleep Myoclonus (BNSM) is the classic exam prototype.
- **Nature:** Non-epileptic, paroxysmal movement disorder.
- **Onset:** Typically first week of life (days 1–7).
- **Duration:** Spontaneously resolves by 2–6 months of age.

Etiology & Pathophysiology

- **Cause:** Idiopathic; physiological maturation delay.
- **Mechanism:** Immaturity of the reticular activating system and descending inhibitory spinal pathways.
- **Triggers:** Gentle rocking, loud noises, or tactile stimulation during sleep.

Clinical Features

- **Character:** Sudden, brief, shock-like muscle jerks.
- **Distribution:** Distal limbs > proximal; can be focal, multifocal, or generalized (massive myoclonus).
- **State-dependent:** Occurs **exclusively** during sleep (predominantly quiet/NREM sleep).
- **Arrest:** Jerking stops *immediately* upon abrupt awakening.
- **Neurological Exam:** Completely normal between episodes.

Diagnosis & EEG Findings

- **Primary Approach:** Clinical diagnosis based on state-dependency (sleep only).
- **Video-EEG (Gold Standard):**
    - **Background:** Normal for gestational age.
    - **During Event: No epileptiform discharges** corresponding to the clinical jerks.
    - **Artifacts:** Only muscle/movement artifacts are seen on the trace during the jerk.
- **Polysomnography (Optional):** Confirms occurrence during quiet (NREM) sleep.
- **Rule Out:** Neonatal seizures, hyperekplexia (stiff baby syndrome), jitteriness, drug withdrawal (NAS).

Management (Treatment)

- **First-line:** Reassurance and parental education.
- **Intervention:** Stop rocking the baby if it triggers episodes.
- **Medications: None indicated.**
- **Exam Trap / Contraindication:** Avoid Anti-Epileptic Drugs (AEDs). Benzodiazepines (e.g., clonazepam) and phenobarbital can paradoxically **worsen** or prolong the myoclonus.

Prognosis & Complications

- **Outcome:** Excellent; universally benign.
- **Development:** Normal neurodevelopmental trajectory.

- **Epilepsy Risk:** No increased risk of future epilepsy.

Exam Summary: Must-Write Points

- **Classic Triad:** Occurs only in sleep + stops on waking + normal EEG.
- **EEG Finding:** Strictly normal background with no ictal correlates (muscle artifact only).
- **Management:** Reassurance only; strictly avoid AEDs (especially benzodiazepines) as they exacerbate the condition.
- **Prognosis:** Self-limiting, resolves by 6 months with zero risk of subsequent epilepsy.

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34. Periventricular calcification CT findings and treatment

Subject: Neurology / CNS

Etiology & Basics

- **Classic Cause:** Congenital Cytomegalovirus (cCMV) infection.
- **Differential Diagnosis:** Toxoplasmosis (causes *diffuse/scattered* intraparenchymal calcifications), congenital Rubella (basal ganglia calcifications), Zika virus (subcortical calcifications).
- **Exam Mnemonic: C**MV = **C**ircumventricular/Central calcification; **T**oxoplasmosis = **T**hroughout the parenchyma.

Pathophysiology

- Maternal primary infection (highest risk) or reactivation → transplacental transmission.
- Fetal viremia targets the rapidly dividing cells of the germinal matrix.
- Viral replication causes cellular necrosis, triggering dystrophic calcification in the subependymal/periventricular zones.

Clinical Features

- **Asymptomatic (90%):** Normal at birth but at high risk for delayed/progressive sensorineural hearing loss (SNHL).
- **Symptomatic (10%):**
    - Neurological: Microcephaly, seizures, hypotonia.
    - Systemic: Petechiae ("blueberry muffin" rash), hepatosplenomegaly, jaundice, direct hyperbilirubinemia.
    - Ocular: Chorioretinitis.

CT Findings (Core Question)

- **Primary Finding:** Bilateral, symmetric, high-density calcium deposits lining the margins of the lateral ventricles (subependymal).
- **Associated Anomalies:** Ventriculomegaly / hydrocephalus (ex vacuo due to brain atrophy).
- **Neuronal Migration Defects:** Polymicrogyria, pachygyria, lissencephaly, or schizencephaly.

- **White Matter:** Diffuse hypodensity (leukoencephalopathy) or delayed myelination.
- *Note:* Cranial USG is the initial screening modality (shows hyperechoic periventricular flares/calcifications), but Non-Contrast CT (NCCT) is the most sensitive imaging for detecting calcification.

Diagnosis

- **Gold Standard:** Detection of CMV DNA by PCR in saliva or urine.
- **Timing:** Must be done within the **first 21 days of life** (distinguishes congenital from postnatal/breast milk acquired infection).
- **Supportive Labs:** Thrombocytopenia, elevated transaminases, conjugated hyperbilirubinemia.

Treatment (Core Question)

- **Indications:** Symptomatic cCMV with moderate-to-severe disease (e.g., CNS involvement, microcephaly, chorioretinitis, severe end-organ disease).
- **First-line Drug:** Oral **Valganciclovir** (16 mg/kg/dose twice daily).
- **Alternative/Severe cases:** IV **Ganciclovir** (6 mg/kg/dose twice daily) if the infant has life-threatening disease or cannot tolerate oral feeds.
- **Duration: 6 months** total therapy (per AAP and CASG trials) to maximize audiologic and neurodevelopmental outcomes.
- **Monitoring during therapy:** Absolute Neutrophil Count (ANC) weekly for 6 weeks, then monthly (high risk of bone marrow suppression/neutropenia); LFTs, RFTs.

Complications & Prognosis

- **SNHL:** cCMV is the leading cause of non-genetic SNHL in children. Can be unilateral/bilateral, and is often progressive or late-onset.
- **Neurological:** Cerebral palsy, severe intellectual disability, intractable epilepsy.
- **Prognosis:** Presence of periventricular calcifications and microcephaly correlates strongly with poor neurodevelopmental outcomes.

Prevention

- No licensed vaccine currently available.
- Maternal behavioral interventions: Strict hand hygiene, avoiding sharing food/utensils, and avoiding contact with saliva/urine of toddlers (primary reservoir for CMV).

Exam Summary: Must-Write Points

- **CMV = Periventricular** calcification; **Toxo = Diffuse** parenchymal calcification.
- Pathogenesis involves viral tropism for the periventricular germinal matrix leading to necrosis.
- Diagnostic confirmation requires urine/saliva CMV PCR at **<21 days of life**.
- Treatment for symptomatic cases is **Oral Valganciclovir for 6 months**.
- Major adverse effect of treatment to monitor: **Neutropenia**.

- Leading complication: Progressive **Sensorineural Hearing Loss (SNHL)**.

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35. Coma in children diagnosis and management

Subject: Neurology / CNS

Definition

- State of unarousable unresponsiveness with complete absence of wakefulness and awareness
- Clinically defined as a Pediatric Glasgow Coma Scale (pGCS) score $\le$ 8

Pathophysiology

- Requires bilateral cerebral hemisphere dysfunction OR
- Depression/lesion of the Ascending Reticular Activating System (ARAS) in the brainstem (pons to thalamus)
- Mechanisms: Hypoxia-ischemia, metabolic derangement, toxic suppression, or mechanical compression (herniation)

Etiology (Mnemonic: AEIOU TIPS)

- **A**lcohol / Abuse (Non-accidental trauma)
- **E**pilepsy (Non-convulsive status epilepticus - NCSE) / Encephalopathy
- **I**nfection (Meningitis, encephalitis, cerebral malaria)
- **O**verdose / Oxygen deficiency (Hypoxic-ischemic encephalopathy)
- **U**remia / metabolic (Hepatic failure, Inborn Errors of Metabolism - IEMs)
- **T**rauma / Tumor
- **I**nsulin (Hypoglycemia / DKA)
- **P**oisoning
- **S**troke / Shock

Clinical Features & Localizing Signs

- **Breathing Patterns:**
    - *Cheyne-Stokes:* Bilateral cortical/diencephalic lesion
    - *Central neurogenic hyperventilation:* Midbrain/upper pontine lesion
    - *Ataxic/Biot:* Lower medullary lesion (impending arrest)
- **Pupillary Changes:**
    - *Pinpoint & reactive:* Pontine lesion, opioid/organophosphate toxicity
    - *Unilateral dilated & fixed:* Uncal herniation (CN III compression)
    - *Bilateral dilated & fixed:* Severe anoxia, brain death, anticholinergic toxicity
- **Motor Posturing:**

- *Decorticate (Flexor):* Lesion above the red nucleus (cerebral white matter, internal capsule)
- *Decerebrate (Extensor):* Lesion below the red nucleus (midbrain/pons) – worse prognosis

- **Brainstem Reflexes:**
  - *Oculocephalic (Doll's eye):* Normal = eyes move opposite to head turn; Absent = brainstem injury (Contraindicated in cervical spine injury)
  - *Oculovestibular (Cold caloric):* Cold water in ear ⇒eyes deviate toward stimulus (COWS mnemonic for nystagmus fast phase, but in coma only slow deviation occurs)

Diagnosis & Investigations

- **Tier 1 (Immediate Bedside):**
  - Capillary blood glucose (CBG) – rule out hypoglycemia immediately
  - ABG/VBG, electrolytes, Ca, Mg
  - Ammonia, LFTs, BUN/Creatinine
  - Blood cultures, Toxicology screen (blood/urine)
- **Tier 2 (Neuroimaging & Specifics):**
  - *NCCT Head:* First-line imaging; rapid, identifies bleeds, tumors, midline shift, hydrocephalus
  - *MRI Brain:* Superior for hypoxic-ischemic injury, encephalitis, demyelination (done once stable)
  - *Lumbar Puncture:* For suspected CNS infection (Absolute contraindication: Signs of raised ICP, focal neurology, coagulopathy, unstable vitals)
  - *Continuous EEG:* Mandatory for unexplained coma to rule out NCSE (accounts for up to 20% of unexplained pediatric comas)

Management

- **Step 1: Stabilization (ABCDE)**
  - *Airway:* Intubate if GCS $\le$ 8 or absent gag reflex
  - *Breathing:* Maintain SpO_2 > 94%, target normocapnia (pCO_2 35-40 mmHg)
  - *Circulation:* Isotonic fluid bolus (Normal Saline) for shock; avoid hypotonic fluids
  - *C-Spine:* Immobilize if trauma suspected
- **Step 2: Empiric "Coma Cocktail"**
  - *Dextrose:* 2-5 mL/kg of 10% Dextrose (if CBG < 60 mg/dL)
  - *Naloxone:* 0.1 mg/kg IV (if opioid toxidrome suspected)
  - *Antimicrobials:* Empiric Ceftriaxone + Vancomycin + IV Acyclovir (if infectious etiology suspected)

    - *Flumazenil:* Use with extreme caution (risk of intractable seizures in chronic benzo users or TCA overdose)

- **Step 3: Raised ICP Management**
    - Head elevation to 30°, keep neck midline (optimizes venous drainage)
    - *Hyperosmolar therapy:* 3% Hypertonic Saline (3-5 mL/kg IV over 10-20 mins) OR Mannitol 20% (0.25-1 g/kg IV)
    - *Update (Brain Trauma Foundation/AAP):* Routine prophylactic hyperventilation is strictly contraindicated (causes cerebral ischemia). Use brief hyperventilation (pCO_2 30-35 mmHg) ONLY as a bridge for acute herniation.
    - Maintain normothermia (treat fever aggressively to reduce cerebral metabolic demand)
- **Step 4: Definitive/Specific Therapy**
    - Antiseizure medications (Levetiracetam/Fosphenytoin) for clinical/EEG seizures
    - Neurosurgical consultation for hematoma evacuation, EVD (Extraventricular Drain) for hydrocephalus
    - Specific antidotes (e.g., Fomepizole for toxic alcohols)

Complications

- Cerebral herniation and brain death
- Aspiration pneumonia, pressure ulcers, DVT (immobility)
- Diabetes Insipidus (DI) or SIADH (pituitary/hypothalamic axis dysfunction)

Prognosis

- Depends heavily on etiology: Toxic/metabolic comas have best prognosis; anoxic/hypoxic injuries have the worst
- Absence of pupillary and corneal reflexes at 72 hours post-cardiac arrest predicts poor neurological outcome
- Possible outcomes: Full recovery, mild/severe neuro-disability, persistent vegetative state, brain death

Exam Summary

- **Must-Write Rule:** "GCS $\le$ 8, intubate."
- **First step:** Always check CBG (Hypoglycemia is the most rapidly reversible cause of coma).
- **Herniation Clue:** Unilateral dilated pupil + contralateral hemiparesis = Uncal herniation.
- **ICP Update:** Avoid routine hyperventilation; target pCO_2 35-40 mmHg. 3% Saline is preferred over Mannitol in trauma/hypovolemia.
- **Hidden Cause:** Always order an EEG in unexplained coma to rule out Non-Convulsive Status Epilepticus (NCSE).

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36. Movement disorders in children

Subject: Neurology / CNS

Definition

- Neurological syndromes causing excess (hyperkinetic) or paucity (hypokinetic) of movement without primary weakness or sensory loss.
- Arise primarily from basal ganglia/extrapyramidal system dysfunction.

Classification & Clinical Features

- **Tics:** Sudden, rapid, recurrent, non-rhythmic motor or vocal acts. Suppressible, preceded by an urge, disappear in sleep.
- **Chorea:** Brief, irregular, flowing, "dance-like" movements flitting from one body part to another. Unpredictable.
- **Dystonia:** Sustained or intermittent muscle contractions causing abnormal, often repetitive, twisting postures (e.g., retrocollis). Triggered by voluntary action (overflow).
- **Myoclonus:** Lightning-fast, shock-like muscle jerks. Can be positive (muscle contraction) or negative (loss of tone, e.g., asterixis).
- **Tremor:** Rhythmic, oscillatory movement around a joint axis. (Resting, postural, or kinetic/action).
- **Athetosis:** Slow, continuous, writhing movements, predominantly distal (often coexists with chorea as choreoathetosis).
- **Stereotypies:** Repetitive, fixed, rhythmic, purposeless movements (e.g., hand flapping). Stop with distraction; common in autism but also in normal neurodevelopment.

Etiology

- **Acquired (Most Common):**
    - Dyskinetic Cerebral Palsy (kernicterus, hypoxic-ischemic encephalopathy).
    - Post-infectious/Immune: Sydenham chorea (Group A Strep), PANDAS, Anti-NMDAR encephalitis.
    - Drug-induced: Acute dystonia (metoclopramide, typical antipsychotics), tardive dyskinesia.
- **Metabolic:**
    - Wilson disease (must rule out in any child >3 years with a movement disorder).
    - Glutaric aciduria type 1 (acute striatal necrosis).
    - Lesch-Nyhan syndrome (choreoathetosis + self-mutilation).
- **Genetic/Neurodegenerative:**
    - Dopa-responsive dystonia (GCH1 mutation).
    - Primary torsion dystonia (DYT1).
    - Huntington disease (Juvenile form: presents with rigidity/Parkinsonism, Westphal variant).
    - Pantothenate kinase-associated neurodegeneration (PKAN).

Pathophysiology

- Disruption of the cortico-basal ganglia-thalamo-cortical loops.
- Imbalance between the **direct pathway** (facilitates movement via D1 receptors) and **indirect pathway** (inhibits movement via D2 receptors).
- Neurotransmitter mismatch: Dopamine vs. Acetylcholine/GABA.

Diagnosis & Evaluation

- **Clinical Phenotyping:** Differentiate hyperkinetic vs. hypokinetic, suppressible vs. non-suppressible, state of consciousness.
- **Neuroimaging (MRI Brain):**
    - "Eye of the tiger" sign: PKAN.
    - "Face of giant panda" sign: Wilson disease.
    - Basal ganglia hyperintensities: Glutaric aciduria, mitochondrial disorders.
- **Metabolic Screen:** Serum ceruloplasmin, 24-hour urine copper, urine organic acids, plasma amino acids, serum lactate.
- **Infectious/Immune Panel:** ASOT, Anti-DNAse B, throat swab, Autoimmune encephalitis panel (CSF and serum).
- **Electrophysiology:** EEG (to differentiate myoclonus from myoclonic epilepsy), EMG.
- **Genetics:** Targeted Next-Generation Sequencing (NGS) panels for dystonia/chorea.

Management

- **General:** Treat underlying cause. Physical/occupational therapy for joint contractures.
- **Tics / Tourette Syndrome:**
    - *First-line:* Comprehensive Behavioral Intervention for Tics (CBIT) / Habit Reversal Therapy.
    - *Pharmacotherapy:* Alpha-2 agonists (Clonidine, Guanfacine).
    - *Severe/Refractory:* Atypical antipsychotics (Aripiprazole, Risperidone) or VMAT2 inhibitors (Valbenazine).
- **Chorea:**
    - Sydenham: Penicillin prophylaxis (mandatory). For movements: Valproic acid or Carbamazepine. Severe/refractory: Corticosteroids/IVIG.
    - Symptomatic control: Tetrabenazine (dopamine depleter).
- **Dystonia:**
    - *Levodopa trial:* Mandatory for all unexplained childhood-onset dystonia (to rule out highly treatable Dopa-Responsive Dystonia).
    - *Systemic:* High-dose anticholinergics (Trihexyphenidyl - children tolerate massive doses compared to adults), Baclofen.
    - *Focal:* Botulinum toxin injections.

- *Refractory:* Deep Brain Stimulation (DBS) of Globus Pallidus internus (GPi).

- **Acute Drug-Induced Dystonia:**
  - IV/IM Diphenhydramine or Promethazine.

Red Flags (Indications for Extensive Workup)

- Regression of developmental milestones.
- Unexplained cognitive decline or psychiatric symptoms.
- Presence of Kayser-Fleischer (KF) rings on slit-lamp exam.
- Focal neurological deficits or spasticity.

Exam Summary

- **Tourette Syndrome:** >1 year duration, multiple motor + at least one vocal tic, <18 years onset. CBIT is 1st line.
- **Wilson Disease:** Always suspect in a child >3 years with unexplained liver disease + movement disorder (chorea/tremor/dystonia).
- **Dopa-Responsive Dystonia (Segawa Syndrome):** Diurnal variation (worse in evening), dramatically cured by low-dose Levodopa.
- **Sydenham Chorea:** Latency of 1-6 months post-Strep infection; requires secondary rheumatic fever prophylaxis.
- **Acute Dystonia:** Post-antiemetic (metoclopramide); treat instantly with IV Diphenhydramine.

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37. Neurocutaneous syndromes in children

Subject: Neurology / CNS

Basics & Definition

- **Definition:** Congenital, hereditary disorders characterized by hamartomas and tumors involving tissues of neuroectodermal origin (CNS, skin, eyes) and occasionally mesoderm/endoderm.
- **Synonym:** Phakomatoses.
- **Core Pathophysiology:** Defective tumor suppressor genes leading to uninhibited cell proliferation (often via Ras or mTOR pathways).

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1. Neurofibromatosis Type 1 (Von Recklinghausen Disease)

Etiology & Pathophysiology

- **Genetics:** Autosomal Dominant (AD); 50% *de novo* mutations.
- **Gene:** *NF1* gene on Chromosome 17q11.2.
- **Protein:** Neurofibromin (tumor suppressor, downregulates Ras-MAPK pathway).

Clinical Features & Diagnosis

- **Diagnostic Criteria (Revised 2021 - *Update*):** Requires ≥2 of the following:
    - ≥6 Café-au-lait macules (CALMs): >5 mm prepubertal, >15 mm postpubertal.
    - Freckling in axillary or inguinal regions (Crowe sign).
    - ≥2 Neurofibromas of any type OR 1 plexiform neurofibroma.
    - Optic pathway glioma (OPG).
    - ≥2 Lisch nodules (iris hamartomas) OR ≥2 choroidal abnormalities (new).
    - Distinctive osseous lesion: Sphenoid dysplasia, anterolateral bowing of tibia, or pseudarthrosis.
    - Heterozygous pathogenic *NF1* variant (new inclusion in 2021).
    - First-degree relative with NF1.
- **Other features:** Macrocephaly, learning disabilities, ADHD, short stature, renal artery stenosis (hypertension).

Management & Surveillance

- **Routine:** Annual BP check, ophthalmology exam, spine evaluation (scoliosis), developmental screening.
- **Medical Therapy (*Update*):** Selumetinib (MEK inhibitor) approved for symptomatic, inoperable plexiform neurofibromas in children ≥2 years.

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2. Neurofibromatosis Type 2 (Central NF)

Etiology & Pathophysiology

- **Genetics:** AD.
- **Gene:** *NF2* gene on Chromosome 22q12.2.
- **Protein:** Merlin (Schwannomin).

Clinical Features & Diagnosis

- **Classic Triad (MISME): M**ultiple **I**nherited **S**chwannomas, **M**eningiomas, **E**pendymomas.
- **Hallmark:** Bilateral vestibular schwannomas (acoustic neuromas) leading to deafness, tinnitus, ataxia.
- **Eyes:** Posterior subcapsular lenticular opacities (juvenile cataracts).
- **Skin:** CALMs present but much fewer than NF1; plexiform neurofibromas are rare.

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3. Tuberous Sclerosis Complex (Bourneville Disease)

Etiology & Pathophysiology

- **Genetics:** AD; highly variable penetrance.
- **Genes:** *TSC1* (Chromosome 9, Hamartin) or *TSC2* (Chromosome 16, Tuberin).
- **Mechanism:** Loss of inhibition of mTOR pathway → unchecked cell growth.

Clinical Features

- **Skin:**
  - Ash-leaf spots (hypomelanotic macules, enhanced by Wood's lamp).
  - Facial angiofibromas (previously "sebaceous adenomas" - malar butterfly distribution).
  - Shagreen patch (leathery connective tissue nevus, usually lumbosacral).
  - Periungual fibromas (Koenen tumors).
- **CNS:** Cortical tubers, Subependymal nodules (SENs), Subependymal giant cell astrocytomas (SEGAs).
- **Neurology:** Seizures (classic: **Infantile spasms**), Autism spectrum disorder, intellectual disability.
- **Visceral:**
  - Heart: Rhabdomyomas (often present prenatally, spontaneously regress).
  - Kidneys: Angiomyolipomas (AMLs), renal cysts.
  - Lungs: Lymphangioleiomyomatosis (LAM - mostly adult females).

Management

- **Seizures: Vigabatrin** is the 1st-line drug of choice for infantile spasms in TSC.
- **Tumors:** mTOR inhibitors (Everolimus, Sirolimus) for growing SEGAs and symptomatic renal AMLs.

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4. Sturge-Weber Syndrome (Encephalotrigeminal Angiomatosis)

Etiology & Pathophysiology

- **Genetics:** Somatic mosaic mutation in the *GNAQ* gene. **Not inherited** (sporadic).
- **Pathology:** Failure of fetal cortical veins to regress → venous stasis and ischemia.

Clinical Features

- **Skin:** Port-wine stain (Nevus flammeus) in the ophthalmic (V1) ± maxillary (V2) trigeminal nerve distribution.
- **CNS:** Ipsilateral leptomeningeal angiomatosis, focal motor seizures (often contralateral), hemiparesis, intellectual disability.
- **Eyes:** Ipsilateral glaucoma, buphthalmos.

Diagnosis & Management

- **Imaging:** Skull X-ray/CT shows classic **"tram-track" calcifications** (gyral calcifications). MRI with contrast is the modality of choice for leptomeningeal angioma.
- **Treatment:**
  - Aggressive seizure control.
  - Low-dose aspirin (to prevent stroke-like episodes from venous stasis).

- Laser therapy (pulsed dye) for port-wine stain.
- Ophthalmology referral for glaucoma surgery/drops.

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5. Von Hippel-Lindau Disease (Brief)

- **Genetics:** AD, *VHL* gene (Chromosome 3p25).
- **Key Features:** Retinal and cerebellar hemangioblastomas, renal cell carcinoma (clear cell), pheochromocytoma, pancreatic cysts.

Exam Summary: Must-Write Buzzwords & Traps

- **NF1 vs NF2 Trap:** NF1 = Ch 17, Neurofibromin, Lisch nodules, Sphenoid dysplasia. NF2 = Ch 22, Merlin, Bilateral vestibular schwannomas, Juvenile cataracts.
- **TSC Triad:** Seizures, mental retardation, facial angiofibromas.
- **TSC Specifics:** Infantile spasms → Give Vigabatrin (monitor for visual field defects). Rhabdomyomas regress. mTOR inhibitors (Everolimus) shrink SEGAs.
- **SWS Trap:** It is **sporadic** (somatic *GNAQ*), NOT inherited. Port-wine stain must involve V1 to have high risk of CNS involvement.
- **Wood's Lamp:** Essential early screening tool in neonates with suspected TSC to identify ash-leaf spots.

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37. Approach to a floppy child

Subject: Important Questions

Approach to a Floppy Child

Definition & Basics

- **Hypotonia:** Decreased resistance to passive stretch of a joint.
- **Weakness:** Decreased maximum muscle power (strength).
- **Key Rule:** Central causes typically present with hypotonia but preserved power; peripheral causes present with both hypotonia and severe weakness.

Clinical Assessment (Signs of Hypotonia)

- **Resting Posture:** "Frog-leg" posture (abducted/externally rotated hips, partially flexed knees), marked head lag.
- **Traction Response (Pull-to-sit):** Head completely falls back; no active flexion.
- **Ventral Suspension:** "Inverted U" posture (head and limbs hang limply down).
- **Vertical Suspension:** Infant slips through the examiner's hands due to shoulder girdle weakness.

Differentiating Central vs. Peripheral

- **Central (80% of cases):**
  - *Sensorium:* Depressed, abnormal sleep-wake cycle, or encephalopathic.
  - *Reflexes (DTRs):* Normal or brisk (hyperreflexia).

- *Power:* Relatively preserved.
- *Associated features:* Seizures, dysmorphism, microcephaly, fisting of hands, crossed adductor reflex.

- **Peripheral (20% of cases):**
  - *Sensorium:* Alert, tracks objects with eyes (bright-eyed floppy baby).
  - *Reflexes (DTRs):* Decreased or absent (areflexia).
  - *Power:* Markedly decreased (profound weakness).
  - *Associated features:* Fasciculations (especially tongue), absent antigravity movements, muscle atrophy, bell-shaped chest.

Top Etiologies by Location

- **Central (Brain/Spinal Cord):**
  - *Acquired:* Hypoxic-Ischemic Encephalopathy (HIE) (most common), intracranial hemorrhage, sepsis/meningitis.
  - *Genetic/Syndromic:* Down syndrome, Prader-Willi syndrome, Zellweger syndrome.
  - *Metabolic:* Hypothyroidism, aminoacidopathies, mitochondrial disorders.
- **Peripheral (Motor Unit):**
  - *Anterior Horn Cell (AHC):* Spinal Muscular Atrophy (SMA) Type 1 (Werdnig-Hoffmann disease).
  - *Peripheral Nerve:* Congenital hypomyelinating neuropathy.
  - *Neuromuscular Junction (NMJ):* Infant botulism, transient neonatal myasthenia gravis, congenital myasthenic syndromes.
  - *Muscle:* Congenital muscular dystrophies, congenital myopathies (Nemaline, Central core), Pompe disease (Glycogen storage disease Type II).

Stepwise Diagnostic Approach

- **Step 1: History & Physical Examination**
  - *Prenatal:* Polyhydramnios (swallowing defect), reduced fetal movements.
  - *Natal:* Apgar scores, birth trauma, perinatal asphyxia.
  - *Localize:* Determine if Central or Peripheral based on DTRs and sensorium.
- **Step 2: Investigating Central Hypotonia**
  - **Neuroimaging:** MRI Brain (modality of choice) for structural anomalies/HIE.
  - **Genetics:** Karyotype/Chromosomal Microarray (CMA) for dysmorphism; Methylation studies for Prader-Willi.
  - **Metabolic:** TFTs (rule out hypothyroidism), serum ammonia, lactate, tandem mass spectrometry (TMS).
- **Step 3: Investigating Peripheral Hypotonia**
  - **Serum CPK:** Markedly elevated in muscular dystrophies; normal/mildly elevated in neurogenic causes.
  - **Genetics (First-line for LMN signs):** *SMN1* gene deletion testing for SMA.

- **EMG/NCS:** Differentiates neuropathy, myopathy, and NMJ defects (decremental response in myasthenia).
- **Enzyme assay:** Alpha-glucosidase (GAA) for Pompe disease.
- **Update (Nelson 21st Ed):** Rapid Whole Exome Sequencing (rWES) is now increasingly preferred as a first-line diagnostic tool for unexplained severe neonatal hypotonia over invasive muscle biopsies.

Management

- **Supportive Care (Crucial):**
  - *Airway/Breathing:* Non-invasive ventilation (BiPAP), cough assist devices, tracheostomy if prolonged ventilation needed.
  - *Nutrition:* NG tube or gastrostomy (PEG) for bulbar dysfunction/aspiration risk.
  - *Rehabilitation:* PT/OT to prevent contractures, orthopedic monitoring for scoliosis.
- **Specific Disease-Modifying Therapies:**
  - *SMA (Update - AAP/IAP):* Nusinersen (intrathecal antisense oligonucleotide), Onasemnogene abeparvovec (Zolgensma - IV gene therapy for <2 years), Risdiplam (oral).
  - *Pompe Disease:* Enzyme Replacement Therapy (Alglucosidase alfa).
  - *Infant Botulism:* Botulism Immune Globulin Intravenous (BIG-IV).
  - *Myasthenia:* Pyridostigmine, Neostigmine.
  - *Hypothyroidism:* Levothyroxine.

Exam Summary: Must-Write Points

- Always distinguish hypotonia (low tone) from weakness (low power).
- Central hypotonia = depressed sensorium, brisk reflexes, preserved power, seizures.
- Peripheral hypotonia = alert baby, absent reflexes, severe weakness, fasciculations.
- Tongue fasciculations + bell-shaped chest + bright eyes = SMA Type 1.
- HIE is the most common cause of central hypotonia; Down syndrome is the most common genetic cause.
- *SMN1* gene testing is the gold standard for SMA; rWES is largely replacing muscle biopsy for undiagnosed peripheral hypotonia.

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37. SMA syndrome, types, recent advances in management

Subject: Important Questions

*Note: In pediatric exams, "SMA" with "types and recent advances" refers to **Spinal Muscular Atrophy**. (Superior Mesenteric Artery syndrome is a rare GI obstruction lacking these specific types and recent gene therapies).*

Definition

- Autosomal recessive neurodegenerative disorder.
- Characterized by progressive degeneration of **anterior horn cells** in the spinal cord and motor nuclei in the lower brainstem.

Genetics & Pathophysiology

- **Locus:** Chromosome 5q13.
- **Primary Defect:** Homozygous deletion or mutation in the ***SMN1*** **(Survival Motor Neuron 1)** gene.
- **Modifier Gene:** ***SMN2*** gene produces a truncated, mostly unstable protein (only 10% functional).
- **Mechanism:** Loss of *SMN1* → apoptosis of lower motor neurons. Disease severity is inversely proportional to the number of *SMN2* gene copies.

Types of SMA (Clinical Classification)

- **Type 0 (Prenatal):**
  - Onset: In utero (decreased fetal movements).
  - Features: Severe joint contractures, facial diplegia, respiratory failure at birth.
  - Lifespan: <6 months (usually 1 copy of *SMN2*).
- **Type 1 (Werdnig-Hoffmann Disease):**
  - Onset: <6 months.
  - Milestones: **Never sit** unsupported.
  - Features: Severe hypotonia ("floppy infant"), paradoxical breathing (bell-shaped chest), tongue fasciculations, absent deep tendon reflexes (DTRs).
  - Lifespan: <2 years without respiratory support/treatment (usually 2 copies of *SMN2*).
- **Type 2 (Dubowitz Disease):**
  - Onset: 6–18 months.
  - Milestones: **Sit independently**, but **never stand/walk** independently.
  - Features: Postural tremor of fingers, progressive scoliosis, restrictive lung disease.
  - Lifespan: 3rd to 4th decade (usually 3 copies of *SMN2*).
- **Type 3 (Kugelberg-Welander Disease):**
  - Onset: >18 months.
  - Milestones: **Stand and walk** independently (may lose ability later).
  - Features: Proximal weakness (legs > arms), falls, waddling gait.
  - Lifespan: Normal (usually 3–4 copies of *SMN2*).
- **Type 4 (Adult-Onset):**
  - Onset: >21 years (usually 2nd/3rd decade).
  - Features: Mild proximal weakness. Normal lifespan (4–8 copies of *SMN2*).

Clinical Clues (All Types)

- **Intact:** Intellect, sensation, and extraocular movements are universally spared.
- **Weakness:** Symmetrical, proximal > distal, lower limbs > upper limbs.
- **Hallmarks:** Areflexia/hyporeflexia, tongue fasciculations, bell-shaped chest (diaphragm spared, intercostals weak).

Diagnosis

- **First-line:** Targeted molecular genetic testing (PCR/MLPA).

    - Confirms homozygous deletion of exon 7 in *SMN1* (95% cases).
- **Second-line:** *SMN2* copy number analysis (mandatory for guiding prognosis and therapy).
- **Creatine Kinase (CK):** Normal or mildly elevated (unlike Duchenne Muscular Dystrophy).
- **EMG/Muscle Biopsy:** *Historical.* Shows large motor unit potentials / grouped atrophy. Only done if genetic test is negative but clinical suspicion is high.

Management: Recent Advances (Disease-Modifying Therapies)

These FDA/EMA-approved breakthroughs have transformed SMA from a fatal disease to a treatable condition.

- **1. Onasemnogene abeparvovec (Zolgensma):**
    - *Class:* Gene replacement therapy.
    - *Mechanism:* Uses Adeno-Associated Virus 9 (AAV9) vector to deliver a fully functional human *SMN* gene to motor neurons.
    - *Route/Dose:* Single, one-time intravenous infusion.
    - *Indication:* Children <2 years of age with biallelic *SMN1* mutations.
    - *Adverse Effects:* Hepatotoxicity (requires prophylactic prednisolone), thrombocytopenia, elevated troponin.
- **2. Nusinersen (Spinraza):**
    - *Class:* Antisense Oligonucleotide (ASO).
    - *Mechanism:* Binds to *SMN2* pre-mRNA → alters splicing to include exon 7 → produces full-length, functional SMN protein.
    - *Route:* Intrathecal injection (does not cross blood-brain barrier).
    - *Dosing:* 4 loading doses, then maintenance every 4 months **lifelong**.
- **3. Risdiplam (Evrysdi):**
    - *Class:* Small-molecule *SMN2* splicing modifier.
    - *Mechanism:* Similar to Nusinersen (promotes inclusion of exon 7 in *SMN2*), but systemic.
    - *Route/Dose:* **Oral** daily liquid.
    - *Indication:* Patients >2 months of age.

Management: Multidisciplinary Supportive Care

- **Respiratory:** Non-invasive ventilation (BiPAP) during sleep, mechanical in-exsufflator (cough assist), pneumococcal/influenza/RSV immunizations.
- **Nutritional:** Early gastrostomy tube (G-tube) for bulbar dysfunction/failure to thrive, reflux management.
- **Orthopedic:** Bracing/spinal fusion for progressive scoliosis, physical therapy to prevent contractures.

Prevention

- **Carrier Screening:** Recommended for all couples planning pregnancy (ACOG/ACMG guidelines).
- **Newborn Screening (NBS):** Now implemented in many countries. Allows pre-symptomatic initiation of gene therapy (highest efficacy).

Exam Summary: Must-Write Points

- **Genetics:** *SMN1* deletion (5q13); severity depends inversely on *SMN2* copy number.
- **Types Trap:** Type 1 (never sit), Type 2 (never walk), Type 3 (walks).
- **Clinical buzzwords:** Tongue fasciculations, bell-shaped chest, spared intellect/EOMs, areflexia.
- **Gold Standard Diagnosis:** Molecular genetics for *SMN1* exon 7 deletion (do NOT write muscle biopsy as first-line).
- **Recent Advances (High-Yield):** Zolgensma (AAV9 gene replacement, single IV dose <2 yrs), Nusinersen (ASO, intrathecal lifelong), Risdiplam (oral splicing modifier).

Nephrology

38. Chronic kidney disease in children

Subject: Nephrology

Definition

- **KDIGO Criteria:** Kidney damage (structural/functional abnormalities) OR Estimated Glomerular Filtration Rate (eGFR) <60 mL/min/1.73 m^2 present for **>3 months**, with implications for health.
- **Staging (eGFR based):** G1 (≥90 with damage), G2 (60–89), G3a (45–59), G3b (30–44), G4 (15–29), G5 (<15 or dialysis).

Etiology

- **<5 years (Congenital/Structural):** CAKUT (Congenital Anomalies of Kidney and Urinary Tract) is the most common overall (e.g., Posterior Urethral Valves, renal hypoplasia/dysplasia).
- **>5 years (Acquired/Glomerular):** Glomerulonephritis (FSGS, Lupus nephritis, IgA nephropathy), Hemolytic Uremic Syndrome (HUS).
- **Hereditary/Cystic:** ARPKD, Alport syndrome, Nephronophthisis, Cystinosis.

Pathophysiology

- Initial insult reduces functional nephron mass.
- Remaining nephrons undergo adaptive hyperfiltration (mediated by RAAS activation).
- Intraglomerular hypertension leads to proteinuria and direct podocyte injury.
- Proteinuria triggers tubular inflammation, resulting in progressive tubulointerstitial fibrosis and glomerulosclerosis.

Clinical Features

- **Early:** Often asymptomatic; polyuria, polydipsia, secondary enuresis (due to loss of concentrating ability in CAKUT), anorexia, unexplained fatigue.
- **Growth:** Severe growth failure (stunting), delayed puberty (hallmarks of pediatric CKD).
- **Fluid/Electrolytes:** Edema, hypertension, volume overload.
- **Hematologic:** Pallor, fatigue (normocytic normochromic anemia).

- **Bone (CKD-MBD):** Deformities, genu valgum/varum, slipped capital femoral epiphysis (SCFE), bone pain.
- **Uremic (Late):** Nausea, vomiting, pruritus, uremic frost, encephalopathy, pericarditis.

Diagnosis

- **eGFR Calculation:** Updated Bedside Schwartz Equation: 0.413 × Height (cm) / Serum Creatinine (mg/dL)
- **Blood:** Elevated urea/creatinine, hyperkalemia, metabolic acidosis (low bicarbonate), hypocalcemia, hyperphosphatemia, elevated intact PTH (iPTH), low Vitamin D.
- **Urine:** Urinalysis (active sediments, casts), Urine Protein-to-Creatinine Ratio (UPCR) or Albumin-to-Creatinine Ratio (UACR).
- **Imaging:** USG KUB (small contracted kidneys with loss of corticomedullary differentiation; or large cystic kidneys), VCUG/DMSA (to evaluate CAKUT scars).
- **Biopsy:** Indicated for unexplained glomerular disease; contraindicated in small, end-stage echogenic kidneys.

Management

- **Delay Progression:**
    - **ACE inhibitors/ARBs:** First-line for proteinuric CKD (monitor for hyperkalemia and acute creatinine bump).
    - **Blood Pressure:** KDIGO 2024 target is 24-hour MAP <50th percentile for age/sex/height (measured via ABPM).
- **Nutrition & Growth:**
    - Calories: 100% of RDA for chronological age.
    - Protein: 100–140% of RDA for *ideal* body weight (avoid protein loading).
    - **rhGH (Recombinant Human Growth Hormone):** Indicated if height <3rd percentile or growth velocity <25th percentile despite optimal nutrition and metabolic control.
- **Anemia Management:**
    - Target Hb: 11–12 g/dL (Avoid >13 g/dL due to cardiovascular risk).
    - Ensure iron repletion (ferritin >100 ng/mL, TSAT >20%) before starting Erythropoiesis-Stimulating Agents (ESAs).
- **CKD-MBD (Mineral Bone Disorder):**
    - Dietary phosphate restriction.
    - Phosphate binders (Calcium carbonate, Sevelamer) taken *with* meals.
    - Active Vitamin D (Calcitriol or Alfacalcidol) for secondary hyperparathyroidism.
- **Acid-Base & Electrolytes:**
    - Oral Sodium Bicarbonate (target serum bicarbonate >22 mEq/L).
    - Dietary potassium restriction if hyperkalemic.

- **Renal Replacement Therapy (RRT):**
    - **Pre-emptive Kidney Transplant:** Treatment of choice for pediatric ESRD (maximizes growth and neurodevelopment).
    - **Peritoneal Dialysis (PD):** Preferred modality for infants and young children.
    - **Hemodialysis (HD):** Used in older children or if PD fails/contraindicated.

Complications

- **Cardiovascular:** LVH, hypertension, accelerated atherosclerosis (leading cause of mortality in pediatric CKD).
- **Neurocognitive:** Impaired executive function, lower IQ, poor school performance.
- **Infections:** Increased susceptibility due to uremic immunosuppression and dialysis access devices.

Prognosis & Prevention

- **Prognosis:** Irreversible and progressive; 10-year survival post-transplant is >80%.
- **Prevention:** Antenatal USG screening for CAKUT, prompt treatment of pediatric UTIs, early surgical correction of PUV.

Exam Summary: High-Yield Must-Write Points

- **Definition:** eGFR <60 or structural damage for >3 months.
- **Formula:** Always write the updated Schwartz formula ($0.413 \times Ht / SCr$).
- **Etiology Rule:** CAKUT dominates in early childhood; Glomerulopathies in older children.
- **Growth:** Stunting is classic. Treat with max nutrition, correct acidosis, and use rhGH if unresponsive.
- **Transplant:** Pre-emptive living-donor renal transplant is the ultimate goal in pediatrics.

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39. Management of chronic renal failure

Subject: Nephrology

Definition & Staging

- **Definition:** Structural/functional kidney damage OR GFR < 60 mL/min/1.73m^2 for > 3 months.
- **eGFR Calculation:** Updated Bedside Schwartz Equation = $0.413 \times \text{Height (cm)} / \text{Serum Creatinine (mg/dL)}$.
- **KDIGO Staging:** G1 (≥90), G2 (60–89), G3a (45–59), G3b (30–44), G4 (15–29), G5 (<15 or Dialysis).

Etiology

- **< 5 years:** CAKUT (Congenital Anomalies of Kidney and Urinary Tract) – Renal hypoplasia/dysplasia, Posterior Urethral Valves (PUV).

- **> 5 years:** Glomerulopathies (FSGS, SLE nephritis), Hereditary (Alport syndrome, Polycystic Kidney Disease), HUS.

Clinical Features

- **Early:** Asymptomatic, polyuria/polydipsia (tubular concentrating defect in CAKUT), enuresis, failure to thrive (FTT).
- **Late:** Oliguria, volume overload, severe pallor, refractory rickets (genu valgum/varum), hypertension, uremic fetor, encephalopathy.

Diagnosis & Evaluation

- **Blood:** CBC, Urea, Creatinine, Electrolytes (Na, K, Cl, HCO3), Ca, PO4, ALP, PTH, 25-OH Vit D, Iron profile (Ferritin, TSAT).
- **Urine:** Urinalysis, Urine Protein/Creatinine Ratio (UPCR) or Albumin/Creatinine Ratio (UACR).
- **Imaging:** USG KUB (small, echogenic kidneys with loss of corticomedullary differentiation; or structural anomalies), VCUG/DMSA if CAKUT suspected.

Management: Conservative / Medical

- **Goals:** Delay progression, prevent complications, optimize growth, prepare for Renal Replacement Therapy (RRT).

1. Nutrition & Growth

- **Calories:** 100% of Recommended Dietary Allowance (RDA) for chronological age.
- **Protein:** 100–140% of RDA for *ideal* body weight (Do NOT severely restrict protein in children; risks malnutrition and poor growth).
- **Feeding:** Early use of nasogastric tube or gastrostomy (PEG) if oral intake < 80% of needs.
- **Growth Hormone:** Recombinant human Growth Hormone (rhGH) indicated if height < 3rd percentile and growth velocity < 25th percentile *after* correcting nutrition, acidosis, and CKD-MBD.

2. Fluid & Electrolytes

- **Fluid:** Unrestricted in polyuric CAKUT; strictly restricted in oliguric/anuric glomerular disease.
- **Acidosis:** Oral Sodium Bicarbonate (1–3 mEq/kg/day); Target serum HCO3 > 22 mEq/L.
- **Potassium:** Dietary restriction, loop diuretics; use potassium-binding resins (e.g., Calcium polystyrene sulfonate) for chronic hyperkalemia.

3. Hypertension & Proteinuria

- **KDIGO 2021 Update:** Target 24-hour MAP < 50th percentile for age/sex/height.
- **First-line:** ACE inhibitors (Enalapril) or ARBs (Losartan) – both anti-hypertensive and antiproteinuric.
- **Monitoring:** Check K+ and Creatinine 1–2 weeks after initiating ACEi/ARB.

4. Anemia of CKD

- **Target:** Hb 11–12 g/dL (Avoid >13 g/dL due to cardiovascular risk).
- **Iron Repletion First:** Maintain Ferritin > 100 ng/mL and TSAT > 20% (Oral or IV iron).

- **ESA (Erythropoiesis-Stimulating Agents):** Start Erythropoietin (50–100 U/kg/dose SC 1–3x/week) or Darbepoetin alfa *only after* iron stores are replete.

5. CKD-Mineral Bone Disease (CKD-MBD)

- **Pathophysiology:** ↓ GFR → PO4 retention → ↓ 1-alpha-hydroxylase → ↓ active Vit D → ↓ Ca absorption → Secondary Hyperparathyroidism.
- **Step 1 (Phosphate):** Dietary restriction. Add phosphate binders with meals (Calcium carbonate/acetate). *Update:* Use non-calcium binders (Sevelamer) if hypercalcemic.
- **Step 2 (Native Vit D):** Supplement Cholecalciferol if 25-OH Vit D < 30 ng/mL.
- **Step 3 (Active Vit D):** Add Calcitriol or Alfacalcidol to suppress elevated PTH *only after* controlling serum phosphorus (to prevent metastatic calcification).

6. Immunization

- **Schedule:** Routine + High-risk vaccines.
- **Specifics:** Double-dose Hepatitis B (0, 1, 2, 6 months), Pneumococcal (PCV15/20 + PPSV23), Annual Influenza.
- **Live vaccines:** Administer well before transplantation; contraindicated post-transplant.

Management: Renal Replacement Therapy (RRT)

- **Indications:** GFR < 10–15 mL/min/1.73m^2, refractory hyperkalemia, fluid overload, uremic encephalopathy/pericarditis, severe FTT.
- **Preparation:** "Vein preservation" (avoid venipunctures in non-dominant arm for future AV fistula).
- **Pre-emptive Renal Transplant:** Treatment of choice in pediatrics; yields best growth and survival outcomes.
- **Peritoneal Dialysis (PD):** Modality of choice for infants and young children (Continuous Cycling PD - CCPD).
- **Hemodialysis (HD):** Used in older children or if PD fails/contraindicated.

Complications

- **Cardiovascular:** Left ventricular hypertrophy, hypertension (leading cause of mortality).
- **Neurological:** Uremic encephalopathy, seizures, developmental delay.
- **Skeletal:** Renal osteodystrophy (osteitis fibrosa cystica, adynamic bone disease).

Exam Summary

- **Formula:** Always use the Updated Bedside Schwartz formula
- **Etiology trap:** CAKUT is the most common cause in young children, NOT glomerulonephritis.
- **BP Target:** KDIGO 2021 mandates targeting MAP < 50th percentile, with ACEi/ARB as first-line.
- **Anemia rule:** Never start Erythropoietin without first checking and repleting iron stores (TSAT > 20%).
- **Ultimate Goal:** Pre-emptive living-donor renal transplantation is the gold standard for pediatric ESRD.

40. CAPD in pediatric CKD

Subject: Nephrology

Definition & Basics

- **CAPD:** Continuous Ambulatory Peritoneal Dialysis; a manual, home-based renal replacement therapy (RRT) utilizing the peritoneal membrane as a semi-permeable filter.
- **Pediatric Context:** PD is the preferred chronic dialysis modality for infants and young children (<5 years) due to difficulty with vascular access and better preservation of residual renal function compared to hemodialysis.
- *Note:* While Automated PD (APD/CCPD) using a cycler machine at night is now most common in pediatrics, CAPD remains essential for daytime dwells, non-compliant patients, or resource-limited settings.

Indications in Pediatric CKD

- **eGFR < 15 mL/min/1.73m^2** (CKD Stage 5) with:
- Refractory fluid overload / hypertension.
- Intractable electrolyte imbalances (hyperkalemia, severe acidosis).
- Uremic symptoms (pericarditis, encephalopathy, bleeding).
- Growth failure or severe malnutrition refractory to medical therapy.

Contraindications

- **Absolute:** Omphalocele, gastroschisis, diaphragmatic hernia, obliterated peritoneal cavity (severe adhesions), active necrotizing enterocolitis (NEC).
- **Relative:** Ventriculoperitoneal (VP) shunt (risk of ascending meningitis), ostomies, severe inflammatory bowel disease, poor psychosocial support/caregiver non-compliance.

Mechanism & Physiology

- **Diffusion:** Clearance of uremic solutes (urea, creatinine) down a concentration gradient.
- **Osmosis:** Ultrafiltration (fluid removal) driven by an osmotic gradient, typically created by glucose (dextrose) or Icodextrin in the dialysate.
- **Membrane:** Pediatric peritoneal surface area relative to weight is roughly twice that of adults, leading to faster equilibration of solutes and rapid absorption of glucose.

Prescription & Technique

- **Access:** Double-cuff Tenckhoff catheter (surgically placed, directed into the true pelvis).
- **Fill Volume:** 800–1200 mL/m^2 body surface area (or 30–40 mL/kg in infants). Start at 10–20 mL/kg and gradually increase to prevent leaks/hernias.
- **Exchanges:** Typically 4–5 manual exchanges per day in CAPD.
- **Dwell Time:** 4–6 hours during the day; 8 hours overnight.
- **Dialysate Strength:** Dextrose concentrations (1.5%, 2.5%, 4.25%). Higher dextrose = higher ultrafiltration (but higher risk of peritoneal membrane degradation over time).

- **Biocompatible Fluids:** Neutral pH, low GDP (glucose degradation products) fluids are currently preferred to preserve membrane function.

Adequacy & Monitoring

- **Target Kt/V:** Total weekly Kt/V urea > 1.8 (KDIGO/IPNA guidelines).
- **PET (Peritoneal Equilibration Test):** Classifies membrane transport status (High, High-Average, Low-Average, Low).
    - *High Transporters (common in young children):* Rapid solute clearance but rapid loss of osmotic gradient; do better with short, frequent dwells (APD).
    - *Low Transporters:* Better for CAPD (long dwells).

Complications

- **Infectious:**
    - *Peritonitis:* Most common complication. Organisms: *Staphylococcus epidermidis* (most common), *S. aureus*, Gram-negatives (Pseudomonas), Fungal (Candida).
    - *Exit-site / Tunnel infections.*
- **Mechanical:** Inguinal/umbilical hernias, dialysate leaks, hydrothorax (pleuroperitoneal leak).
- **Metabolic:** Hypoproteinemia (protein loss in dialysate), hyperglycemia, obesity, hypertriglyceridemia.
- **Long-term:** Encapsulating Peritoneal Sclerosis (EPS) – a rare, life-threatening fibrotic bowel obstruction secondary to long-term PD and bio-incompatible fluids.

Management of PD Peritonitis (ISPD 2022 Updates)

- **Diagnosis (requires 2 of 3):**
    1. Clinical signs (abdominal pain, cloudy effluent, fever).
    2. Dialysate WBC > 100/µL with > 50% polymorphonuclear cells (PMNs).
    3. Positive dialysate culture.
- **Empiric Therapy:** Intraperitoneal (IP) antibiotics covering Gram-positive and Gram-negative organisms.
    - *First-line:* IP Cefazolin (or Vancomycin if high MRSA prevalence) + IP Ceftazidime (or Aminoglycoside).
- **Fungal Prophylaxis:** Oral nystatin or fluconazole whenever the child receives broad-spectrum antibiotics for any reason, to prevent fungal peritonitis.
- **Catheter Removal Indications:** Refractory peritonitis (>5 days of appropriate ABX without clearing), fungal peritonitis, or concurrent severe tunnel infection.

Exam Summary

- PD is the RRT of choice for infants/toddlers due to vascular access challenges.
- Pediatric fill volumes are calculated by BSA (800–1200 mL/m^2).
- Infants are naturally "high transporters" on PET; they absorb glucose rapidly, making shorter dwells (APD) physiologically better, though CAPD is used.

- *Must-know diagnostic criteria for Peritonitis:* Cloudy fluid, WBC > 100/µL, >50% PMNs.
- *ISPD 2022 Update:* Emphasizes IP empiric therapy (Vancomycin/Cefazolin + Ceftazidime) and strict fungal prophylaxis during systemic antibiotic use.

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41. Rapidly progressive glomerulonephritis

Subject: Nephrology

Definition

- **Clinical:** Syndrome characterized by a rapid decline in glomerular filtration rate (GFR) over days to weeks (typically >50% decline in ≤3 months) with nephritic urinary sediment.
- **Pathological:** Crescentic glomerulonephritis (crescents present in >50% of glomeruli).

Classification & Etiology Classified by immunofluorescence (IF) patterns on renal biopsy:

- **Type 1: Anti-GBM Disease (Linear IF):** Rare in children. Anti-GBM antibodies targeting Type IV collagen. ± Pulmonary hemorrhage (Goodpasture syndrome).
- **Type 2: Immune-Complex Mediated (Granular IF):** *Most common in pediatrics.* Includes severe Post-Streptococcal GN (PSGN), Lupus Nephritis, IgA Vasculitis (HSP), IgA Nephropathy, and Membranoproliferative GN (MPGN).
- **Type 3: Pauci-Immune (Negative/Scanty IF):** ANCA-associated vasculitis (AAV). Includes Granulomatosis with Polyangiitis (GPA/PR3-ANCA) and Microscopic Polyangiitis (MPA/MPO-ANCA).

Pathophysiology

- Severe glomerular capillary injury → Rupture of glomerular basement membrane (GBM).
- Leakage of fibrinogen, macrophages, and T-cells into Bowman space.
- Proliferation of parietal epithelial cells → **Crescent formation**.
- Cellular crescents compress capillary tufts → Ischemia and rapid GFR loss.
- Progression to fibrocellular, then fibrous crescents → Irreversible scarring (ESRD).

Clinical Features

- **Renal:** Rapid onset of oliguria/anuria, gross hematuria (tea/cola-colored urine), worsening edema, new-onset severe hypertension.
- **Systemic (Etiology-specific):**
    - *AAV/Goodpasture:* Hemoptysis, pulmonary infiltrates (pulmonary-renal syndrome).
    - *SLE:* Malar rash, arthritis, cytopenias.
    - *IgA Vasculitis:* Purpura, abdominal pain, arthralgia.

Diagnosis

- **Urinalysis:** Dysmorphic RBCs, **RBC casts** (hallmark of active GN), sub-nephrotic to nephrotic range proteinuria.
- **Blood Chemistry:** Rapidly rising BUN and serum creatinine, hyperkalemia, metabolic acidosis.

- **Serology (The "RPGN Panel"):**
    - ANA, anti-dsDNA (SLE).
    - C3, C4 (Low in PSGN, SLE, MPGN; Normal in IgA, AAV, Anti-GBM).
    - ANCA (p-ANCA/MPO, c-ANCA/PR3).
    - Anti-GBM antibodies.
    - ASOT / Anti-DNase B (PSGN).
- **Renal Biopsy (Gold Standard):** Essential for diagnosis and prognosis. Determines percentage of cellular (reversible) vs. fibrous (irreversible) crescents.

Management *Current KDIGO & Nelson Guidelines approach:*

- **Supportive/Emergent:** Treat fluid overload, hypertension, and hyperkalemia. Initiate hemodialysis if refractory.
- **Induction Immunosuppression (Immediate):**
    - **IV Methylprednisolone pulses:** 10–30 mg/kg/day (max 1g) for 3–5 days, followed by oral Prednisolone (1 mg/kg/day).
    - **Plus Cytotoxic/Biologic Agent:** IV Cyclophosphamide OR Rituximab.
    - *Update (KDIGO 2024):* Rituximab is increasingly favored as first-line for pediatric ANCA-associated RPGN due to lower gonadal toxicity compared to cyclophosphamide.
- **Plasmapheresis (Therapeutic Plasma Exchange):**
    - *Indications:* All Anti-GBM disease, ANCA vasculitis with severe renal failure (serum Cr >5.7 mg/dL or requiring dialysis), or concurrent severe pulmonary hemorrhage.
- **Maintenance Therapy:** Azathioprine, Mycophenolate Mofetil (MMF), or Rituximab infusions, combined with tapering low-dose oral steroids.

Complications

- End-Stage Renal Disease (ESRD) requiring chronic dialysis or transplant.
- Life-threatening pulmonary hemorrhage.
- Immunosuppression toxicity: Opportunistic infections (PCP, fungal), cytopenias, secondary malignancies.

Prognosis

- Depends heavily on the underlying etiology and timing of intervention.
- Type 2 (Immune-complex, e.g., PSGN) generally has the best prognosis in children.
- High percentage of fibrous crescents or frank anuria at presentation predicts poor renal survival.

Exam Summary: Must-Write Points

- **Definition:** Rapid GFR decline over days/weeks + >50% glomerular crescents on biopsy.
- **Triad of IF patterns:** Linear (Anti-GBM), Granular (Immune-complex - *most common in kids*), Pauci-immune (ANCA).

- **Urine hallmark:** Dysmorphic RBCs and RBC casts.
- **Core Treatment:** IV Methylprednisolone pulses + Cyclophosphamide/Rituximab.
- **Plasmapheresis rule:** Mandatory for Anti-GBM and severe pulmonary-renal syndromes.

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42. Hemolytic uremic syndrome, typical and atypical

Subject: Nephrology

Definition

- **Classic Triad:** Microangiopathic hemolytic anemia (MAHA), Thrombocytopenia, Acute Kidney Injury (AKI).
- **Thrombotic Microangiopathy (TMA):** Pathological hallmark characterized by endothelial injury and microthrombi.

Classification & Etiology

- **Typical HUS (STEC-HUS / D+ HUS):**
  - Accounts for 90% of pediatric cases.
  - Caused by Shiga toxin-producing *Escherichia coli* (STEC) – classically **O157:H7** (also O104:H4).
  - Other pathogens: *Shigella dysenteriae* type 1, *Campylobacter*.
- **Atypical HUS (aHUS / D- HUS):**
  - **Complement Dysregulation:** Mutations in alternative pathway proteins (Factor H [most common], Factor I, MCP, C3, Factor B, Thrombomodulin).
  - **Autoimmune:** Anti-Factor H autoantibodies (associated with CFHR1/CFHR3 deletion).
  - **Infection-associated:** Invasive *Streptococcus pneumoniae* (neuraminidase exposes Thomsen-Friedenreich [T] antigen).
  - **Metabolic:** Intracellular Cobalamin C (cblC) defect.
  - **Genetic non-complement:** DGKE mutations (infantile onset).

Pathophysiology

- **Typical HUS:** Ingestion of contaminated food/water → Gut colonization → Release of Shiga toxin (Stx) → Toxin enters circulation → Binds to **globotriaosylceramide (Gb3)** receptors on renal/brain endothelium → Endothelial swelling, apoptosis → Platelet aggregation → Microthrombi → RBC shearing (schistocytes).
- **Atypical HUS:** Defective complement regulation → Unchecked Alternative Pathway activation → Uncontrolled Membrane Attack Complex (MAC / C5b-9) formation on host endothelial cells → Diffuse TMA.

Clinical Features

- **Typical HUS:**
  - Prodrome (3–8 days): Abdominal pain, vomiting, bloody diarrhea.

- Sudden onset pallor, petechiae, jaundice, and oliguria/anuria.
- Neurological: Seizures, encephalopathy (severe cases).

- **Atypical HUS:**
  - No diarrheal prodrome (usually); insidious or trigger-induced (e.g., URTI, pregnancy) onset.
  - Severe, difficult-to-control hypertension.
  - Higher incidence of extrarenal manifestations (neuro, cardiac, GI ischemia).
  - *Pneumococcal HUS:* Severe pneumonia/empyema + HUS triad + positive direct Coombs test.

Diagnosis

1. Core Triad Labs:

- **MAHA:** Hb <8 g/dL, ↑ Reticulocytes, ↑ LDH, ↓ Haptoglobin, peripheral smear showing **schistocytes** (helmet cells).
- **Thrombocytopenia:** Platelets typically <100,000/mm^3 (no active bleeding usually).
- **AKI:** ↑ Urea/Creatinine, hyperkalemia, metabolic acidosis, hematuria, proteinuria.
- **Coombs Test:** Negative (Except in Pneumococcal HUS where it is positive).

2. Etiology-Specific Labs:

- **Typical HUS:** Stool culture on **Sorbitol-MacConkey agar** (O157:H7 does not ferment sorbitol); PCR for *stx1* and *stx2* genes; Stx enzyme immunoassay.
- **Atypical HUS:**
  - Low C3, normal C4 (Alternative pathway activation).
  - Quantitative levels: Factor H, Factor I.
  - Anti-Factor H antibodies.
  - Genetic panel for complement mutations.
  - Homocysteine and methylmalonic acid (for cblC defect).

Management

1. Typical HUS (Supportive Care):

- **Fluids/Electrolytes:** Meticulous fluid balance; restrict fluids if oliguric; manage hyperkalemia.
- **Transfusions:** Packed RBCs for Hb <6 g/dL or symptomatic anemia. *Avoid platelet transfusions* (fuels microthrombi) unless active severe bleeding or prior to invasive procedures.
- **Renal Replacement Therapy (RRT):** Dialysis (peritoneal or hemo) required in ~50% of cases for anuria, refractory hyperkalemia, or volume overload.
- **Contraindications: Antibiotics** (increase Stx release by lysing bacteria) and **anti-motility agents** (delay toxin clearance) are strictly contraindicated in STEC-HUS.

2. Atypical HUS (Targeted Therapy):

- **First-line: Eculizumab** or **Ravulizumab** (monoclonal antibodies blocking cleavage of C5 to C5a/C5b, halting MAC formation).
    - *Mandatory:* Meningococcal vaccination/prophylaxis before starting anti-C5 therapy.
- **Plasma Exchange (PLEX):** Used if anti-C5 therapy is unavailable or while awaiting diagnostic confirmation; removes autoantibodies/mutant proteins, replaces functional complement regulators.
- **Anti-Factor H Ab HUS:** PLEX + Immunosuppression (Corticosteroids, Rituximab, Cyclophosphamide).
- **Pneumococcal HUS:** Avoid unwashed blood products (plasma contains anti-T antibodies which worsen hemolysis); use washed RBCs.

Complications

- Acute: Seizures, stroke, bowel necrosis, cardiomyopathy, hyperkalemic arrhythmias.
- Chronic: Chronic Kidney Disease (CKD), End-Stage Renal Disease (ESRD), chronic hypertension, diabetes mellitus (pancreatic microthrombi).

Prognosis

- **Typical HUS:** Excellent acute survival (>95%); ~5-10% long-term risk of ESRD.
- **Atypical HUS:** Poor without targeted therapy (up to 50% progress to ESRD or death in acute phase). High recurrence rate post-renal transplant (especially with Factor H mutations) unless treated with Eculizumab/liver-kidney transplant.

Exam Summary

- **Triad:** MAHA (schistocytes), Thrombocytopenia, AKI.
- **Typical HUS Trap:** Do NOT give antibiotics or loperamide for STEC bloody diarrhea.
- **Pathology Buzzwords:** STEC binds Gb3 receptor; aHUS involves Alternative Complement MAC (C5b-9) dysregulation.
- **Atypical HUS Drug:** Eculizumab/Ravulizumab (anti-C5); must give meningococcal prophylaxis.
- **Pneumococcal HUS Trap:** T-antigen exposure; direct Coombs positive; must use *washed* RBCs, avoid plasma.

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43. Nephrotic syndrome recent advances

Subject: Nephrology

Definition & Diagnostic Criteria (Current)

- **Nephrotic Range Proteinuria:** Urine Protein:Creatinine Ratio (UPCR) >2 mg/mg (>200 mg/mmol) or >40 mg/m^2/hr
- **Hypoalbuminemia:** Serum albumin <2.5 g/dL (IAP/IPNA) or <3.0 g/dL (KDIGO)
- **Remission:** Trace/negative dipstick OR UPCR <0.2 mg/mg for 3 consecutive days

Pathogenesis & Biomarker Advances

- **Anti-Nephrin Antibodies:** Recently discovered in Minimal Change Disease (MCD); confirms MCD as an autoimmune podocytopathy
- **suPAR (Soluble Urokinase Receptor):** Implicated in primary Focal Segmental Glomerulosclerosis (FSGS) pathogenesis
- **CD80 (B7-1):** Upregulated on podocytes in MCD; targeted by novel therapies
- **Anti-PLA2R & Anti-THSD7A:** Revolutionized diagnosis of Membranous Nephropathy (non-invasive diagnosis, biopsy often bypassed)

Genetics: The Paradigm Shift

- **Next-Generation Sequencing (NGS):** Now standard of care for specific indications
- **Indications for Genetic Testing (IPNA 2020/2022):** Congenital/infantile onset (<1 year), Steroid-Resistant Nephrotic Syndrome (SRNS), familial history, syndromic features
- **Common Mutations:** *NPHS1* (Finnish type), *NPHS2* (Podocin - most common childhood SRNS), *WT1* (Denys-Drash/Frasier)
- **Clinical Impact:** If monogenic SRNS is confirmed → immunosuppression is futile (stop steroids/CNIs) → avoid renal biopsy → prepare for transplant (low recurrence risk)

Management Updates: First Episode (KDIGO 2021 / IPNA 2022 / IAP 2021)

- **Previously:** Prolonged steroid courses (up to 6 months) were thought to reduce relapses
- **Now (PREDNOS Trial/KDIGO 2021):** Shorter courses are equally effective. Maximum duration is 8 to 12 weeks
- **IAP 2021 Regimen:** 6 weeks daily (2 mg/kg/day, max 60 mg) followed by 6 weeks alternate day (1.5 mg/kg, max 40 mg)
- **Genetic testing:** Not recommended for first-episode typical SSNS (Steroid-Sensitive Nephrotic Syndrome)

Management Updates: FRNS & SDNS

- **URTI Prophylaxis:** Transitioning to daily low-dose prednisolone (0.5 mg/kg/day) for 5–7 days at the onset of URTI in FRNS/SDNS significantly reduces relapse rates
- **First-line Steroid-Sparing Agents:** Mycophenolate Mofetil (MMF) or Levamisole (less toxic than cyclophosphamide)
- **Rituximab (Anti-CD20):**
    - *Advance:* Now a mainstream, highly effective therapy for complicated FRNS/SDNS and CNI-dependent cases
    - *Prerequisite:* Must be given when the child is in remission
    - *Monitoring:* CD19 cell counts to guide re-dosing

Management Updates: SRNS

- **First-line Therapy:** Calcineurin Inhibitors (CNIs)
- *Advance:* **Tacrolimus** is now preferred over Cyclosporine due to a better cosmetic side-effect profile (less hirsutism/gum hypertrophy), improving adherence

- **ACEi/ARBs:** Universal recommendation for all SRNS patients for anti-proteinuric and renoprotective effects
- **SGLT2 Inhibitors (Dapagliflozin):** Emerging use in pediatric proteinuric kidney diseases (DAPA-CKD trial extrapolation) to slow progression

Novel & Emerging Therapies

- **Sparsentan:** Dual Endothelin (ETA) and Angiotensin II (AT1) receptor antagonist; recently FDA-approved for primary IgA Nephropathy and undergoing trials for FSGS (DUPLEX study)
- **Ofatumumab / Obinutuzumab:** Fully humanized anti-CD20 monoclonal antibodies used for Rituximab-resistant or allergic cases
- **Abatacept:** CD80 (B7-1) co-stimulation blocker; utilized in refractory primary FSGS and post-transplant recurrence
- **Finerenone:** Non-steroidal mineralocorticoid receptor antagonist; emerging for chronic proteinuria management

Exam Summary

- **Duration of initial steroids:** 8–12 weeks max (prolonged courses are obsolete).
- **Genetics in SRNS:** Mandatory prior to escalating immunosuppression; positive mutation = stop steroids/CNIs.
- **Biomarker of the decade:** Anti-nephrin antibodies for MCD; Anti-PLA2R for Membranous Nephropathy.
- **URTI management:** 5-7 days of daily low-dose steroids during URTI prevents relapses in FRNS.
- **Biologics:** Rituximab is the gold standard for difficult FRNS/SDNS; Tacrolimus is the CNI of choice for SRNS.

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44. Steroid resistant nephrotic syndrome

Subject: Nephrology

Definition

- **IPNA 2020 & KDIGO 2021 Update:** Failure to achieve complete remission after **4 weeks** of daily standard-dose oral corticosteroid (Prednisolone 60 mg/m^2/day or 2 mg/kg/day; max 60 mg/day).
- *Previously:* Defined as 8 weeks of therapy; updated to 4 weeks to minimize steroid toxicity and expedite alternative treatments.
- **Late-responder:** Achieves remission between 4 and 6 weeks (often treated as steroid-dependent/frequently relapsing rather than true SRNS).
- **Secondary SRNS:** Initial steroid response followed by development of resistance during a subsequent relapse.

Etiology & Histology

- **Histopathology:** Focal Segmental Glomerulosclerosis (FSGS) is most common (~70%), followed by Minimal Change Disease (MCD) and Mesangial Proliferative Glomerulonephritis.

- **Genetic (Podocytopathies):** Accounts for ~30% of pediatric SRNS (higher in infants).
    - *NPHS1* (Nephrin): Congenital nephrotic syndrome (Finnish type).
    - *NPHS2* (Podocin): Most common autosomal recessive SRNS in childhood.
    - *WT1*: Denys-Drash syndrome, Frasier syndrome.
    - *LAMB2*: Pierson syndrome.
    - *INF2, TRPC6*: Autosomal dominant (often adolescent/adult onset).
- **Secondary Causes:** Viral (HIV, Parvovirus B19, CMV), Drugs (Pamidronate, NSAIDs, Calcineurin inhibitor toxicity), Autoimmune (SLE, IgA vasculitis), Obesity/Hyperfiltration.

Pathophysiology

- **Podocyte injury:** Disruption of the slit diaphragm, actin cytoskeleton, or glomerular basement membrane (GBM).
- Leads to foot process effacement, massive protein leak, and eventual glomerulosclerosis (FSGS).
- Lacks the typical T-cell mediated cytokine response seen in steroid-sensitive nephrotic syndrome (SSNS), hence steroid unresponsiveness.

Clinical Features

- Persistent, refractory edema and massive proteinuria.
- *Red Flags (vs. SSNS):* Higher incidence of hypertension, gross hematuria, and impaired estimated Glomerular Filtration Rate (eGFR) at presentation.
- *Syndromic Clues:*
    - Ambiguous genitalia / Wilms tumor → *WT1* mutation.
    - Microcoria / Neurological deficits → *LAMB2* (Pierson).
    - Sensorineural deafness / Lenticonus → *COL4A* variants (Alport spectrum).

Diagnosis & Evaluation

- **Confirm Resistance:** Ensure medication compliance and rule out concurrent infections (which can cause transient resistance).
- **Kidney Biopsy: Mandatory** in all SRNS patients before initiating second-line immunosuppression (to determine histology and rule out secondary glomerulonephritis).
- **Genetic Testing:** Indicated for:
    - Congenital/infantile onset (<1 year of age).
    - Family history of SRNS or consanguinity.
    - Presence of extrarenal syndromic features.
    - Failure to respond to Calcineurin Inhibitors (CNIs).
- **Laboratory Workup:** eGFR, electrolytes, C3/C4 (normal in primary SRNS), ANA/dsDNA, viral serology (HIV, HBV, HCV).

Management

- **1. Renoprotective & Supportive (All patients):**
    - **ACE inhibitors or ARBs:** First-line for proteinuria reduction and hypertension control (Target BP < 50th percentile).
    - **Diuretics:** Loop diuretics ± thiazides for edema; caution to avoid intravascular volume depletion.
    - **Statins:** For severe, persistent dyslipidemia.
    - **Anticoagulation:** Prophylactic LMWH if prior thrombosis or extremely high risk.
- **2. Immunosuppressive Therapy (Non-Genetic SRNS):**
    - *First-line:* **Calcineurin Inhibitors (CNIs)** — Oral Tacrolimus or Cyclosporine A.
    - Duration: Minimum 6 months to assess efficacy. If partial/complete remission achieved, continue for 12–24 months minimum.
    - *Second-line / Alternatives:* Mycophenolate Mofetil (MMF) ± high-dose Dexamethasone pulses; Cyclophosphamide.
    - *Rituximab:* Limited efficacy in pure SRNS compared to SDNS, but may be trialed in refractory cases.
- **3. Genetic SRNS Management:**
    - **Stop Immunosuppression:** Genetically mediated SRNS does *not* respond to immunosuppressants; continuing them only causes toxicity.
    - Focus entirely on renoprotection (ACEi/ARB), nutrition, and preparation for Renal Replacement Therapy (RRT).

Complications

- Progression to Chronic Kidney Disease (CKD) and End-Stage Renal Disease (ESRD).
- Severe infections (peritonitis, sepsis, cellulitis) due to prolonged hypogammaglobulinemia and heavy immunosuppression.
- Thromboembolism (Renal vein thrombosis, DVT, pulmonary embolism).
- CNI Toxicity: Acute nephrotoxicity (reversible AKI) or chronic toxicity (irreversible striped interstitial fibrosis/tubular atrophy).

Prognosis & Transplant Outcomes

- **Renal Survival:** ~50% of non-responders progress to ESRD within 10 years.
- **Post-Transplant Recurrence:**
    - *Idiopathic/Non-genetic FSGS:* High risk of recurrence in the allograft (~30–50%). Treated with plasmapheresis and rituximab.
    - *Genetic SRNS:* Extremely low risk of recurrence (<2%), making them excellent transplant candidates.

Exam Summary: Must-Write Points

- **Definition update:** Failure to achieve remission after **4 weeks** of daily steroids (IPNA 2020).
- **Histology:** FSGS is the most common underlying pathology.

- **Mandatory steps:** Kidney biopsy is compulsory for all SRNS; Genetic testing is crucial for infants, familial cases, or syndromic presentations.
- **First-line specific therapy:** Calcineurin inhibitors (Tacrolimus/Cyclosporine) for non-genetic SRNS.
- **Genetic SRNS rule:** Do not use immunosuppression; focus on ACEi/ARBs and prepare for transplant.
- **Transplant paradox:** Non-genetic FSGS has a high recurrence rate post-transplant (~30-50%); genetic SRNS rarely recurs.

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45. Approach to a child with proteinuria in a 5 year old

Subject: Nephrology

Definition & Quantification (KDIGO/IAP)

- **Normal:** Urine Protein Creatinine Ratio (UPCR) < 0.2 mg/mg; Excretion < 4 mg/m^2/hr
- **Abnormal:** Persistent UPCR > 0.2 mg/mg
- **Nephrotic Range:** UPCR > 2.0 mg/mg; Excretion > 40 mg/m^2/hr; Dipstick 3+ or 4+

Pathophysiology Classification

- **Glomerular:** Increased permeability to macromolecules (e.g., albumin); most common pathological cause in children
- **Tubular:** Defective reabsorption of low-molecular-weight proteins (e.g., β2-microglobulin)
- **Overflow:** Excess plasma proteins exceeding tubular reabsorption capacity (rare in pediatrics)
- **Secretory:** Overproduction of Tamm-Horsfall proteins

Etiology (in a 5-Year-Old)

- **Transient (Most Common):** Fever, exercise, stress, dehydration, seizures
- **Orthostatic:** Present when upright, absent while supine (more common in adolescents, but must rule out)
- **Persistent Nephrotic Range:** Minimal Change Disease (MCD) accounts for >80% at this age; Focal Segmental Glomerulosclerosis (FSGS)
- **Persistent Non-Nephrotic Range:** Glomerulonephritis (Post-infectious, IgA nephropathy), Reflux nephropathy, Tubulointerstitial nephritis

Clinical Evaluation

- **History:** Recent fever/infection (transient vs. PSGN), gross hematuria, frothy urine, periorbital/pedal edema, rash, joint pain
- **Physical Exam:**
    - **Vitals:** Blood pressure (mandatory to rule out nephritic/secondary causes)
    - **Anthropometry:** Weight (baseline for edema tracking), height
    - **Systemic:** Ascites, pleural effusion, skin lesions (HSP, SLE)

Diagnostic Algorithm (Stepwise Approach)

- **Step 1: Confirm & Rule Out Transient/Orthostatic**
    - Re-test with First Morning Void (FMV) urine dipstick
    - If FMV is negative: Diagnosis is Orthostatic or Transient proteinuria (no further workup needed, reassure)
    - If FMV is positive (≥1+): Proceed to Step 2
- **Step 2: Quantify**
    - Check UPCR on the FMV sample
    - If UPCR > 0.2 mg/mg: Confirms persistent proteinuria
- **Step 3: Differentiate (Nephrotic vs. Non-Nephrotic)**
    - UPCR 0.2 – 2.0: Sub-nephrotic (Evaluate for GN, reflux)
    - UPCR > 2.0: Nephrotic range
- **Step 4: Laboratory Workup (Persistent Proteinuria)**
    - **Baseline:** Complete blood count, Renal function tests (BUN, Creatinine), Serum electrolytes
    - **Nephrotic profile:** Serum albumin (<3 g/dL), Fasting lipid profile (hypercholesterolemia)
    - **Urine:** Microscopy (RBCs, casts, WBCs)
    - **Imaging:** USG KUB (kidney size, echogenicity, rule out structural anomalies)
- **Step 5: Extended Workup (If red flags present)**
    - Serum C3/C4 (low in PSGN, SLE, MPGN)
    - ANA, ASOT / Anti-DNAse B, Hepatitis B/C, HIV

Indications for Renal Biopsy

- *Note: A typical 5-year-old with pure nephrotic syndrome is treated empirically for MCD without biopsy.*
- **Pre-treatment indications:** Age < 1 yr or > 12 yrs, gross hematuria, persistent hypertension, low C3, renal failure (unexplained by hypovolemia)
- **Post-treatment indications:** Steroid resistance (failure to remit after 4 weeks of daily steroids)

Management

- **Transient/Orthostatic:** Reassurance; annual BP and urinalysis
- **Persistent Sub-nephrotic:**
    - Antiproteinuric agents: ACE inhibitors (Enalapril) or ARBs (Losartan)
    - Treat underlying cause (e.g., treat UTI, manage reflux)
- **Idiopathic Nephrotic Syndrome (Presumed MCD):**
    - **IAP/KDIGO Regimen:** Oral Prednisolone 2 mg/kg/day (max 60 mg) for 6 weeks, followed by 1.5 mg/kg on alternate days for 6 weeks, then stop.

- **Diet:** Salt restriction (1-2 g/day) during edema; normal protein intake (do not overfeed protein).
- **Fluid:** Restrict only if severe edema or hyponatremia is present.
- **Diuretics:** Oral Furosemide only if edema is symptomatic/distressing; use with caution to avoid thrombosis/hypovolemia.
- **Infection prophylaxis:** Update pneumococcal and influenza vaccines (give during remission).

Complications

- **Infections:** Spontaneous Bacterial Peritonitis (Streptococcus pneumoniae), cellulitis
- **Thrombosis:** Renal vein thrombosis, DVT, sagittal sinus thrombosis (due to loss of Antithrombin III and hemoconcentration)
- **Hypovolemia:** Shock, Acute Kidney Injury (AKI)
- **Drug toxicity:** Steroid toxicity (cushingoid, hypertension, cataracts, growth failure)

Prognosis

- **MCD:** >90% respond to steroids; excellent long-term renal survival, though relapses are common.
- **Orthostatic/Transient:** Benign, does not progress to Chronic Kidney Disease (CKD).
- **Proteinuria with Hypertension/Hematuria:** Higher risk of progression to CKD; requires close nephrology follow-up.

Exam Summary (Must-Write Points)

- Always check a **First Morning Void (FMV)** to rule out orthostatic proteinuria.
- Quantify using **UPCR** (Nephrotic > 2.0 mg/mg).
- In a 5-year-old, nephrotic-range proteinuria without hematuria/hypertension is **Minimal Change Disease** until proven otherwise.
- Do **NOT** biopsy a classic 5-year-old nephrotic presentation before empirical steroid trial.
- **Red flags** mandating biopsy/workup: Low C3, persistent hypertension, gross hematuria, renal failure.

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46. Pediatric urinary tract infection diagnosis and imaging protocol

Subject: Nephrology

Definitions

- **Atypical UTI:** Severe illness/septicemia, poor urine flow, abdominal/bladder mass, ↑creatinine, non-*E. coli* organism, or failure to respond to antibiotics within 48 hours.
- **Recurrent UTI:** ≥2 upper UTIs, OR 1 upper + ≥1 lower UTI, OR ≥3 lower UTIs.

Etiology

- **Most Common:** *Escherichia coli* (80–90%).

- **Others:** *Klebsiella*, *Proteus* (common in uncircumcised boys, alkaline urine), *Enterobacter*, *Enterococcus*.
- **Viral:** Adenovirus (classic cause of acute hemorrhagic cystitis).
- **Fungal:** *Candida* (immunosuppressed, prolonged broad-spectrum antibiotics, indwelling catheters).

Clinical Features

- **Neonates/Infants:** Fever without localizing signs (most common), prolonged jaundice, poor feeding, failure to thrive, vomiting, irritability.
- **Older Children:** Dysuria, frequency, urgency, suprapubic pain, flank pain, new-onset secondary enuresis.

Diagnosis

1. Urine Sample Collection

- **Toilet-trained:** Mid-stream clean catch (MSCC).
- **Non-toilet-trained:** Urethral catheterization or Suprapubic aspiration (SPA).
- **Exam Trap:** Perineal bag specimen has a high false-positive rate (85%); useful *only* to rule out UTI if the dipstick/culture is negative.

2. Urinalysis (Screening)

- **Leukocyte Esterase (LE):** Surrogate for pyuria; highly sensitive.
- **Nitrite:** Surrogate for Gram-negative bacteriuria; highly specific but poorly sensitive in infants (requires 4 hours of bladder incubation to convert nitrate to nitrite).
- **Microscopy:** >5 WBC/hpf (centrifuged) or >10 WBC/mm^3 (uncentrifuged).

3. Urine Culture (Gold Standard)

- *Requirement:* Both pyuria on urinalysis AND single-organism growth on culture.
- **Significant Colony Counts (AAP/IAP criteria):**
    - **SPA:** Any Gram-negative bacilli or >10^3 CFU/mL Gram-positive cocci.
    - **Catheterization:** ≥50,000 CFU/mL.
    - **MSCC:** ≥100,000 CFU/mL.

Imaging Protocol (AAP 2011/2016 & IAP 2021 Updates)

Goal: Identify structural anomalies and Vesicoureteral Reflux (VUR) while minimizing radiation.

1. USG KUB (Kidneys, Ureters, Bladder)

- **Indications:** All children <2 years with first febrile UTI; any child with atypical/recurrent UTI.
- **Timing:**
    - *Atypical/Severe UTI:* Within 48 hours (to rule out obstruction/abscess).
    - *Uncomplicated UTI:* Within 1–2 weeks after clinical improvement.

2. VCUG (Voiding Cystourethrogram)

- **IAP/AAP Update:** *Previously:* Done for all first febrile UTIs. *Now:* NOT routinely recommended after a first febrile UTI if USG is normal.
- **Indications:**
    - Abnormal USG (hydronephrosis, ureteric dilatation, scarring, small kidney).
    - Atypical UTI.
    - Recurrent UTI.
    - Pathogen is non-*E. coli* (relative indication per some guidelines, absolute if combined with other risks).
- **Timing:** Done after the urine is sterile (usually 1–2 weeks post-infection) to avoid disseminating infection; prophylactic antibiotics given until VCUG is completed.

3. DMSA Scan (Dimercaptosuccinic Acid)

- **Indications:** To detect permanent renal scarring.
- **Timing:** 4–6 months after the acute UTI episode (acute phase DMSA to diagnose pyelonephritis is no longer routinely recommended due to high cost and lack of management change).

Management

- **Indications for Hospitalization (IV Antibiotics):** Age <2 months, clinical sepsis, vomiting/inability to tolerate PO, immunocompromised, failure of outpatient therapy.
- **Empiric IV:** Ceftriaxone, Cefotaxime, or Ampicillin + Aminoglycoside (preferred in neonates).
- **Empiric PO:** Cefixime, Cephalexin, Amoxicillin-Clavulanate. (Avoid Amoxicillin alone due to high resistance).
- **Duration:**
    - Febrile/Upper UTI: 7–14 days.
    - Afebrile/Lower UTI: 3–5 days.

Prophylaxis (CAP - Continuous Antibiotic Prophylaxis)

- **Current Indications:** VUR Grade III–V, recurrent UTIs, or awaiting VCUG.
- **Drugs:**
    - <2 months: Cephalexin or Amoxicillin.
    - 2 months: Cotrimoxazole or Nitrofurantoin.
- **Contraindications:** Nitrofurantoin and Cotrimoxazole are contraindicated in infants <1 month and in G6PD deficiency.

Complications & Outcomes

- Renal scarring (Reflux Nephropathy).
- Secondary hypertension.
- Chronic Kidney Disease (CKD) / End-Stage Renal Disease (ESRD).
- *Prognosis:* Excellent with early detection; risk of scarring increases with recurrent pyelonephritis and delay in antibiotic initiation (>48 hrs).

Exam Summary

- **Diagnosis requires both:** Pyuria on urinalysis + ≥50,000 CFU/mL (catheter) or ≥100,000 CFU/mL (MSCC) of a single uropathogen.
- **Bag urine:** Never use for culture; only use to rule out UTI if dipstick is negative.
- **First febrile UTI (<2 yrs):** USG KUB is mandatory.
- **VCUG indication:** Do NOT do routinely for 1st UTI. Reserve for abnormal USG, atypical UTI, or recurrent UTI.
- **DMSA scan:** Done at 4–6 months post-infection to assess for permanent renal scarring.

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47. Vesicoureteral reflux

Subject: Nephrology

Definition & Types

- **Definition:** Abnormal retrograde flow of urine from the bladder into the upper urinary tract (ureter/kidney).
- **Primary VUR:** Congenital defect of the vesicoureteral junction (VUJ) due to a short submucosal/intramural ureter.
- **Secondary VUR:** Due to elevated intravesical pressure overcoming a normal VUJ (e.g., Posterior Urethral Valves [PUV], Neurogenic bladder, Bladder Bowel Dysfunction [BBD]).

Pathophysiology

- **Normal VUJ:** Ureter enters bladder obliquely; intramural tunnel length to ureter diameter ratio is **5:1**, creating a competent one-way "flap-valve".
- **VUR Mechanism:** Lateral ectopia of ureteric orifice → tunnel-to-diameter ratio falls **< 2:1** → flap-valve failure.
- **Intrarenal Reflux:** Infected urine reaches renal pelvis → enters collecting ducts at the **polar regions** (where papillae are compound/flat and lack anti-reflux slit-like openings) → parenchymal infection → inflammation → **Reflux Nephropathy** (scarring).

Grading (International Reflux Study Classification)

Must-know for exams; dictates management.

- **Grade I:** Reflux into non-dilated ureter only.
- **Grade II:** Reflux into pelvis and calyces without dilation.
- **Grade III:** Mild to moderate dilation of ureter, pelvis, and calyces; minimal blunting of fornices.
- **Grade IV:** Moderate dilation and tortuosity of ureter; obliteration of sharp angle of fornices.
- **Grade V:** Gross dilation and tortuosity of ureter; loss of papillary impressions in most calyces.

Clinical Features

- **Antenatal:** Often detected as isolated antenatal hydronephrosis (ANH).

- **Postnatal: Febrile UTI** (most common presentation in infants and children).
- **Associated Conditions:** BBD (constipation, daytime urgency/incontinence, withholding maneuvers).

Diagnosis & Evaluation

- **USG KUB (Screening):** First-line imaging. Assesses hydroureteronephrosis and gross scarring. Normal USG does *not* rule out VUR.
- **MCU / VCUG (Micturating Cystourethrogram): Gold Standard** for diagnosis and grading. Done after achieving sterile urine.
    - *AAP/IAP Update:* **Do not** perform routine MCU after the first febrile UTI in children 2–24 months.
    - *Indications for MCU:* Abnormal USG (scarring/hydronephrosis), atypical/complex UTI (non-E. coli, septicemia), or recurrence of febrile UTI.
- **DMSA Scan: Gold Standard** for detecting cortical scarring. Done 4–6 months post-UTI to differentiate permanent scar from acute pyelonephritis (photopenic defects).

Management

1. Medical Management (Conservative)

- **Goal:** Prevent febrile UTIs and subsequent renal scarring while awaiting spontaneous resolution.
- **Continuous Antibiotic Prophylaxis (CAP):**
    - *Previously:* Given to all children with VUR.
    - *Now (Targeted CAP):* Indicated for **Grade III–V**, infants <1 year with VUR, or children with VUR + BBD.
    - *Drugs:* <2 months: Cephalexin or Amoxicillin; >2 months: Cotrimoxazole or Nitrofurantoin (given at 1/3rd to 1/4th of therapeutic dose, once daily at bedtime).
- **BBD Treatment:** Aggressive management of constipation and voiding dysfunction (urotherapy, anticholinergics if indicated) is mandatory; untreated BBD prevents VUR resolution.

2. Surgical Management

- **Indications for Surgery:**
    - Breakthrough febrile UTIs despite compliant CAP.
    - New renal scars forming on follow-up DMSA.
    - High-grade VUR (Grade IV–V) persisting beyond 2–3 years of age.
    - Non-compliance with medical therapy.
- **Endoscopic Treatment:** Subureteric injection of bulking agents (Dextranomer/hyaluronic acid – **Deflux**). High success for lower grades, day-care procedure.
- **Open/Laparoscopic Reimplantation:** Creation of a new submucosal tunnel (e.g., Cohen cross-trigonal, Leadbetter-Politano). >95% success rate for high-grade VUR.

Complications & Outcomes

- **Reflux Nephropathy:** Can progress to secondary Focal Segmental Glomerulosclerosis (FSGS).
- **Hypertension:** Renin-mediated due to focal ischemia in scarred areas.
- **CKD/ESRD:** Bilateral severe scarring is a leading cause of pediatric ESRD.
- **Spontaneous Resolution:**
    - Grades I–II: ~80% resolve spontaneously by 5 years.
    - Grade III: ~50% resolve.
    - Grades IV–V: Rarely resolve spontaneously; early surgical planning favored.

💡 **Exam Summary**

- **Core Pathology:** Short intramural ureter → loss of 5:1 ratio → flap-valve failure. Polar compound papillae are highly susceptible to intrarenal reflux and scarring.
- **Grading:** Grade I (ureter only) to Grade V (gross tortuosity/loss of papillary impressions).
- **Guideline Trap:** Do *not* order MCU after the first simple febrile UTI in a 2-24 month old if USG is normal.
- **CAP Update:** Prophylaxis is now selective (Grade III-V, infants, BBD), not universal.
- **Gold Standards:** MCU for grading VUR; DMSA for detecting renal scars.

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48. Proteinuria evaluation in children

Subject: Nephrology

Definition & Quantification

- **Dipstick:** Detects primarily albumin; 1+ (30 mg/dL), 2+ (100 mg/dL), 3+ (300 mg/dL), 4+ (>1000 mg/dL)
- **False positives:** Highly concentrated urine (SG >1.025), highly alkaline urine (pH >8.0), gross hematuria, chlorhexidine contamination
- **Normal:** Spot Urine Protein/Creatinine Ratio (UPCR) < 0.2 mg/mg (< 0.5 in infants < 6 months) or 24-hr urine < 4 mg/m^2/hr
- **Abnormal (Non-nephrotic):** UPCR 0.2–2.0 mg/mg or 24-hr urine 4–40 mg/m^2/hr
- **Nephrotic range:** UPCR > 2.0 mg/mg or 24-hr urine > 40 mg/m^2/hr

Etiology & Classification

- **Transient (Functional):** Fever, vigorous exercise, stress, seizures, cold exposure (resolves when trigger removed)
- **Orthostatic (Postural):** Present when upright, absent while supine; peaks in adolescence; entirely benign
- **Persistent Glomerular:** Disrupted size/charge barrier (e.g., Minimal Change Disease, FSGS, PSGN, IgA Nephropathy, Lupus Nephritis)

- **Persistent Tubular:** Defective proximal tubule reabsorption of low-molecular-weight (LMW) proteins (e.g., Fanconi syndrome, Dent disease, Interstitial nephritis)
- **Overflow:** Excess LMW protein overwhelms normal tubules (rare in pediatrics; e.g., lysozyme in myelomonocytic leukemia)

Pathophysiology

- **Glomerular:** Podocyte effacement ⇒loss of polyanionic charge barrier ⇒albuminuria
- **Tubular:** Megalin-cubilin receptor dysfunction in proximal tubule ⇒failure to reabsorb filtered β2-microglobulin and retinol-binding protein (RBP)

Clinical Clues

- **History:** Recent sore throat/skin infection (PSGN), joint pain/rash (SLE, HSP), frothy urine, hearing loss (Alport), family history of renal failure
- **Physical:** Hypertension (mandatory check), periorbital/pedal edema, ascites, palpable purpura, abdominal mass, growth failure (tubular disorders)

Stepwise Diagnostic Algorithm

- **Step 1: Confirm & Rule Out Transient Causes**
    - Repeat dipstick on a healthy, afebrile day
    - Check urine microscopy: If RBCs/casts present ⇒evaluate for glomerulonephritis
- **Step 2: Differentiate Orthostatic vs. Persistent**
    - Obtain First Morning Void (FMV) UPCR (patient voids at bedtime, collects first urine immediately upon waking)
    - *FMV UPCR < 0.2:* Orthostatic proteinuria (No further workup; annual follow-up)
    - *FMV UPCR > 0.2:* Persistent proteinuria (Proceed to Step 3)
- **Step 3: Evaluate Persistent Proteinuria**
    - **Renal Function:** Serum urea, creatinine, eGFR, electrolytes, albumin, lipid profile
    - **Serology/Immunology:** C3/C4, ANA, Anti-dsDNA, ASOT/Anti-DNase B, Hepatitis B/C, HIV
    - **Imaging:** Renal ultrasound (size, echogenicity, structural anomalies)
    - **Tubular markers:** Urine β2-microglobulin, urine amino acids, glycosuria with normal blood sugar (Fanconi)

Indications for Renal Biopsy (Red Flags)

- Age < 1 year or > 12 years with nephrotic-range proteinuria
- Steroid-Resistant Nephrotic Syndrome (SRNS)
- Persistent proteinuria + macroscopic hematuria (or RBC casts)
- Low C3 persisting beyond 8–12 weeks (suggests MPGN or Lupus, rather than PSGN)
- Unexplained elevated creatinine / declining eGFR
- Positive systemic serology (ANA, Anti-dsDNA)

Management Principles

- **Transient/Orthostatic:** Reassurance; no activity restriction; annual BP and urinalysis
- **Persistent Non-Nephrotic:**
    - ACE inhibitors (e.g., Enalapril) or ARBs to reduce efferent arteriolar resistance and intraglomerular pressure
    - *KDIGO 2021 Update:* Target 24-hour MAP < 50th percentile for age/sex/height
- **Nephrotic Range:** Corticosteroids (if consistent with idiopathic nephrotic syndrome)
- **Tubular Proteinuria:** Treat underlying cause; supplement lost electrolytes/bicarbonate
- **Diet:** Avoid excessive protein loading; restrict sodium (1-2 mEq/kg/day) if edematous/hypertensive

Complications

- Progression to Chronic Kidney Disease (proteinuria is directly nephrotoxic to tubules)
- Hypoalbuminemia ⇒edema, hypercoagulability (loss of Antithrombin III), infections (loss of Factor B/IgG)

Exam Summary

- **First step for asymptomatic proteinuria:** First Morning Void (FMV) UPCR to rule out orthostatic proteinuria.
- **Orthostatic criteria:** Daytime UPCR elevated, FMV UPCR normal (<0.2). Benign, no biopsy needed.
- **Dipstick caveat:** Detects albumin, misses LMW tubular proteins (Bence-Jones, β2-microglobulin).
- **Biopsy triggers:** Age extremes (<1 or >12 yr), hematuria + proteinuria, low C3, hypertension, SRNS.
- **Renoprotection:** ACEi/ARB therapy is first-line for persistent, non-nephrotic glomerular proteinuria to reduce hyperfiltration.

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49. CAKUT anomalies and management

Subject: Nephrology

Definition

- **CAKUT:** Spectrum of structural malformations of the embryonic kidney and urinary tract.
- **Significance:** Most common cause of chronic kidney disease (CKD) and End-Stage Renal Disease (ESRD) in children (accounts for 40–50% of pediatric CKD).

Etiology & Genetics

- **Embryology:** Defective cross-talk between the ureteric bud and metanephric mesenchyme (normally occurs weeks 4–10).
- **Genetics:** Identified in 10–20% of cases.

- *HNF1B*: Renal cysts and diabetes syndrome (RCAD).
- *PAX2*: Papillorenal syndrome.
- *EYA1/SIX1*: Branchio-oto-renal (BOR) syndrome.
- *RET*: Hirschsprung-associated CAKUT.

- **Teratogens/Environmental:** Maternal diabetes, maternal use of ACE inhibitors/ARBs, cocaine, oligohydramnios.

Spectrum of Anomalies

- **Kidney (Parenchymal/Position):**
  - *Agenesis:* Bilateral (Potter sequence, fatal); Unilateral (compensatory hypertrophy).
  - *Hypoplasia:* Small kidneys, reduced nephron mass.
  - *Dysplasia:* Multicystic dysplastic kidney (MCDK) – non-functioning, involutes over time.
  - *Anomalies of position/fusion:* Ectopic kidney, Horseshoe kidney (arrested at inferior mesenteric artery, Turner syndrome association).
- **Pelvis & Ureter:**
  - *Ureteropelvic Junction Obstruction (UPJO):* Most common cause of antenatal hydronephrosis.
  - *Vesicoureteral Reflux (VUR):* Most common urologic anomaly in children.
  - *Others:* Primary megaureter, ectopic ureter, duplex collecting system, ureterocele.
- **Bladder & Urethra:**
  - *Posterior Urethral Valves (PUV):* Most severe obstructive uropathy; exclusively in males.
  - *Prune Belly Syndrome:* Deficient abdominal musculature, cryptorchidism, urinary tract dilation.

Pathophysiology

- Ureteric bud mis-induction ⇒abnormal nephrogenesis ⇒reduced nephron endowment.
- Structural obstruction/reflux ⇒elevated intrapelvic pressure ⇒recurrent UTIs ⇒progressive renal scarring ⇒secondary focal segmental glomerulosclerosis (FSGS) ⇒CKD/ESRD.

Clinical Features

- **Antenatal:** Oligohydramnios, antenatal hydronephrosis (ANH), absent fetal bladder filling.
- **Postnatal (Neonates):** Palpable abdominal mass (MCDK, UPJO), poor urinary stream/dribbling (PUV), Potter facies (flat nose, low-set ears, micrognathia).
- **Infants/Children:** Recurrent febrile UTIs, failure to thrive, unexplained hypertension, daytime incontinence/enuresis.

Diagnosis

- **Prenatal:** Fetal USG (Society for Fetal Urology grading for hydronephrosis).
- **Postnatal Imaging:**

- *USG KUB:* First-line investigation. Best done at 48–72 hours of life (to avoid false negatives from physiological neonatal dehydration).
- *Micturating Cystourethrogram (MCU / VCUG):* Gold standard for VUR grading and PUV diagnosis (shows "keyhole sign" in PUV).
- *Diuretic Renogram (MAG3 / DTPA):* Differentiates true obstruction (e.g., UPJO) from non-obstructive dilatation (e.g., megaureter). Done after 4–6 weeks of life.
- *DMSA Scan:* Gold standard for detecting renal cortical scarring and differential renal function (DRF). Done $\geq$ 6 months post-UTI.

- **Laboratory:** Serum creatinine (reflects maternal Cr in first 24-48 hours), electrolytes, urinalysis (proteinuria indicates hyperfiltration injury).

Management

- **Antenatal:**
  - Serial USG monitoring.
  - Vesicoamniotic shunting (selected cases of severe bilateral obstruction/PUV with progressive oligohydramnios to preserve lung development).
- **Postnatal Medical:**
  - **Continuous Antibiotic Prophylaxis (CAP):**
    - *AAP/IAP Update:* CAP is no longer universally recommended for all VUR. Indicated for high-grade VUR (Grade III-V), recurrent UTIs, or severe obstructive uropathy.
    - *Drugs:* Cephalexin/Amoxicillin (< 2 months); TMP-SMX or Nitrofurantoin (> 2 months).
  - **CKD Management:** BP control (ACEi/ARB for proteinuria—*Contraindicated in bilateral renal artery stenosis*), acidosis correction (bicarbonate), nutrition (maximize caloric intake for growth).
- **Postnatal Surgical:**
  - *PUV:* Primary valve ablation (fulguration) via cystoscopy ⇒temporizing vesicostomy if urethra is too small.
  - *UPJO:* Anderson-Hynes dismembered pyeloplasty (if DRF <40% or progressively falling, or symptomatic).
  - *VUR:* Endoscopic Deflux injection or open ureteric reimplantation (if breakthrough UTIs on CAP, or non-resolving high-grade VUR).

Complications

- End-Stage Renal Disease (ESRD).
- Reflux nephropathy / Renal scarring.
- Hypertension (renin-mediated).
- Growth retardation / Renal osteodystrophy.

Prognosis & Prevention

- **Prognosis:** Directly dependent on the degree of renal dysplasia and remaining functional nephron mass. Bilateral severe anomalies have high mortality due to pulmonary hypoplasia.
- **Prevention:** Avoidance of maternal teratogens (ACEi/ARBs). Genetic counseling for familial syndromes (e.g., HNF1B, BOR).

Exam Summary

- **Most common CAKUT:** UPJO (pelviureteric junction obstruction).
- **Leading cause of pediatric ESRD:** CAKUT.
- **PUV Triad:** Bladder distension, bilateral hydroureteronephrosis, oligohydramnios (exclusively males).
- **Imaging sequence:** USG (structural) ⇒MCU (lower tract/reflux) ⇒DMSA (scarring) / MAG3 (obstruction).
- **Crucial Trap:** Do not do postnatal USG on day 1 (physiological oliguria hides hydronephrosis); wait until 48–72 hours.

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50. Lupus nephritis management

Subject: Nephrology

Basics

- Severe, common manifestation of pediatric Systemic Lupus Erythematosus (pSLE).
- Occurs in 50–80% of pSLE patients (higher incidence and severity than adults).
- Pathogenesis: Immune complex deposition (IgG, IgA, IgM, C3, C1q - "full house" immunofluorescence), complement consumption.

Clinical Features

- Asymptomatic microscopic hematuria and/or non-nephrotic proteinuria (earliest signs).
- Nephrotic syndrome (edema, severe proteinuria, hypoalbuminemia).
- Acute nephritic syndrome / Rapidly Progressive Glomerulonephritis (RPGN).
- Hypertension and acute kidney injury (AKI).

Diagnosis

- **Urinalysis:** Active sediment (dysmorphic RBCs, RBC casts, cellular casts).
- **Serology:** High anti-dsDNA titers, low complement (C3, C4, CH50).
- **Renal Biopsy:** Mandatory for all suspected cases to determine ISN/RPS class and guide therapy.

ISN/RPS Classification (2003, revised 2018)

- **Class I:** Minimal mesangial.
- **Class II:** Mesangial proliferative.

- **Class III:** Focal lupus nephritis (<50% glomeruli).
- **Class IV:** Diffuse lupus nephritis (≥50% glomeruli) – *most common and severe*.
- **Class V:** Membranous lupus nephritis.
- **Class VI:** Advanced sclerosing (>90% globally sclerosed).

General Management (All Classes)

- **Hydroxychloroquine (HCQ):** Universal for all SLE patients (reduces flares, improves survival, antithrombotic).
- **Renoprotection:** ACE inhibitors or ARBs for proteinuria (UPCR > 0.5 mg/mg) and hypertension.
- **Bone protection:** Calcium and Vitamin D supplementation (due to steroid use).
- **Lipid control:** Statins for persistent dyslipidemia (target LDL < 100 mg/dL).
- **Infection prevention:** Pneumococcal, influenza, and HPV vaccines; PCP prophylaxis (TMP-SMX) during heavy immunosuppression.

Induction Therapy (Class III & IV - Proliferative)

- *Goal:* Rapid control of inflammation (Duration: 3–6 months).
- **Corticosteroids:** IV Methylprednisolone pulses (10–30 mg/kg/day for 3 days) followed by oral Prednisolone (tapering rapidly per KDIGO 2024 guidelines to minimize toxicity).
- **PLUS First-line Agent (Choose one):**
    - **Mycophenolate Mofetil (MMF):** Preferred for Hispanics/Africans, better side-effect profile (less gonadal toxicity).
    - **IV Cyclophosphamide (IVCYC):** Preferred for severe/RPGN presentations or non-compliance. *Euro-Lupus regimen* (low dose, 6 fortnightly doses) is preferred over *NIH regimen* (high dose, monthly) for lower toxicity.

Induction Therapy (Class V - Membranous)

- *Goal:* Control proteinuria.
- **First-line:** MMF + oral Corticosteroids.
- **Alternative:** Calcineurin Inhibitors (CNI) like Tacrolimus or Cyclosporine (especially if nephrotic-range proteinuria) + Corticosteroids.

Maintenance Therapy

- *Goal:* Prevent relapses, minimize steroid use.
- **First-line:** MMF (preferred) OR Azathioprine (AZA).
- **Steroids:** Taper to lowest possible dose (target ≤ 5 mg/day) or withdraw completely if stable.
- *Duration:* Minimum 3–5 years; often longer in pSLE.
- *Note:* Do not use Cyclophosphamide for maintenance.

Refractory / Relapsing Disease & Updates

- **KDIGO 2024 Update:** Emphasizes earlier integration of novel therapies and aggressive steroid sparing.

- **Rituximab (Anti-CD20):** Used for refractory Class III/IV or frequent relapsers.
- **Belimumab (Anti-BAFF):** FDA approved for pSLE; used as add-on therapy to improve renal response and reduce steroid burden.
- **Voclosporin (Novel CNI):** Approved for adult LN; increasingly used off-label in pSLE as part of multi-target therapy (MMF + CNI + Steroids) for refractory proteinuria.

Complications & Prognosis

- **Complications:** End-Stage Renal Disease (ESRD) in 10-20%, severe infections, premature atherosclerosis, macrophage activation syndrome (MAS).
- **Class VI Management:** Discontinue immunosuppression; prepare for Renal Replacement Therapy (RRT) / transplant. Transplant deferred until SLE is clinically inactive for ≥6 months.

Exam Summary

- Renal biopsy is the absolute prerequisite for classifying and treating lupus nephritis.
- "Full house" immunofluorescence is the classic biopsy buzzword.
- HCQ and ACEi/ARB are mandatory baseline therapies for all active LN patients.
- Class III/IV requires aggressive Induction (Steroids + MMF or IVCYC) followed by Maintenance (MMF or AZA).
- KDIGO 2024 emphasizes rapid steroid tapering and favors Euro-Lupus IVCYC or MMF over high-dose IVCYC to preserve fertility and reduce toxicity.

Endocrinology

51. Diabetic ketoacidosis in children

Subject: Endocrinology

Definition & Criteria (ISPAD 2022)

- **Hyperglycemia:** Blood glucose > 200 mg/dL (11.1 mmol/L)
- **Acidosis:** Venous pH < 7.30 or Bicarbonate < 15 mmol/L
- **Ketosis:** Blood β-hydroxybutyrate (BOHB) ≥ 3.0 mmol/L or moderate/large urine ketones

Severity Grading

- **Mild:** pH < 7.30 or HCO3 < 15 mmol/L
- **Moderate:** pH < 7.20 or HCO3 < 10 mmol/L
- **Severe:** pH < 7.10 or HCO3 < 5 mmol/L

Etiology & Triggers

- **New-onset T1DM:** ~30% of cases
- **Known T1DM:** Missed insulin doses, insulin pump failure
- **Stressors:** Infection (pneumonia, UTI, gastroenteritis), trauma, surgery, medications (steroids, atypical antipsychotics)

Pathophysiology

- **Hormonal imbalance:** Absolute/relative insulin deficiency + Excess counter-regulatory hormones (glucagon, catecholamines, cortisol, GH)
- **Hyperglycemia:** Increased gluconeogenesis and glycogenolysis + decreased peripheral utilization
- **Ketogenesis:** Uninhibited lipolysis → free fatty acids → hepatic conversion to ketoacids (BOHB, acetoacetate) → high anion gap metabolic acidosis
- **Fluid/Electrolytes:** Osmotic diuresis → profound dehydration (typically 5–10% deficit) + massive total body potassium and phosphorus depletion

Clinical Features

- **General:** Polyuria, polydipsia, weight loss, severe dehydration (sunken eyes, poor turgor, tachycardia)
- **Respiratory:** Kussmaul breathing (deep, sighing respirations), fruity/acetone breath odor
- **GI:** Nausea, vomiting, severe abdominal pain (can mimic acute surgical abdomen)
- **Neurological:** Ranging from lethargy to coma (correlates with degree of acidosis/hyperosmolarity)

Diagnosis & Investigations

- **Bedside:** Capillary blood glucose (CBG), blood/urine ketones
- **Labs:** Venous blood gas (VBG), electrolytes, BUN, creatinine, HbA1c, CBC
- **Calculations:**
    - *Anion Gap:* Na - (Cl + HCO3) [Normal: 12 ± 2; DKA: > 20]
    - *Corrected Sodium:* Add 1.6 mEq/L to measured Na for every 100 mg/dL glucose > 100 mg/dL
- **Trigger hunt:** Blood/urine cultures, CXR (if indicated)

Management (Stepwise ISPAD 2022 Protocol)

1. Resuscitation & Initial Fluids

- **ABC:** 100% O2 if shocked; secure airway if comatose
- **Bolus:** 10–20 mL/kg 0.9% Normal Saline (NS) over 20–30 mins (repeat only if hemodynamically unstable)

2. Deficit & Maintenance Fluids

- **Rate:** Replace deficit + maintenance over 24–48 hours (PECARN trial showed no difference in cerebral edema risk between fast/slow or 0.45%/0.9% NS, but ISPAD recommends steady correction)
- **Fluid choice:** 0.9% NS or 0.45% NS initially

3. Insulin Therapy

- **Dose:** 0.05 to 0.1 U/kg/hr regular insulin continuous IV infusion

- **Timing:** Start 1–2 hours *after* starting fluid therapy (prevents rapid osmolar shifts)
- **Contraindication:** *Never* give an IV insulin bolus (increases cerebral edema risk)

4. Potassium Replacement

- **Requirement:** Total body K+ is depleted despite normal/high serum K+ (due to acidosis shift)
- **Action:** Add 40 mEq/L K+ to IV fluids (usually 50% KCl, 50% K-Phos)
- **Timing:** Start immediately if K+ < 5.5 mEq/L and patient is voiding. If K+ < 2.5 mEq/L, delay insulin until K+ is replaced.

5. Dextrose Addition

- **Trigger:** When blood glucose falls to 250–300 mg/dL (14–17 mmol/L)
- **Action:** Add 5% or 10% Dextrose to IV fluids
- **Rule:** Do *not* decrease/stop insulin to manage falling glucose (insulin is needed to clear ketones); increase IV dextrose instead.

6. Bicarbonate (Avoid)

- **Indication:** Only for life-threatening hyperkalemia or severe acidosis (pH < 6.9) with impaired cardiac contractility
- **Risk:** Paradoxical CNS acidosis, delayed ketone clearance, increased cerebral edema risk

Complications

- **Cerebral Edema (Most lethal):**
    - *Risk factors:* Age < 5 yrs, new onset, severe acidosis, high BUN, rapid drop in corrected Na, early insulin bolus
    - *Signs:* Headache, vomiting, bradycardia, hypertension, declining GCS, cranial nerve palsies (CN III, VI)
    - *Management:* Elevate head of bed 30°, reduce IV fluid rate by 33%, give **Mannitol** (0.5–1 g/kg IV) or **3% Hypertonic Saline** (2.5–5 mL/kg IV). Do not wait for CT scan to treat.
- **Other Complications:** Hypokalemia, hypoglycemia, acute kidney injury (AKI), venous thromboembolism (VTE)

Prevention

- **Sick Day Rules:** Never stop basal insulin during illness; monitor glucose/ketones every 2–4 hours; push sugary fluids if eating poorly; contact provider early.

Exam Summary (Must-Write Points)

- **Diagnostic Triad:** Glucose > 200 mg/dL + pH < 7.3/HCO3 < 15 + Blood BOHB ≥ 3.0 mmol/L.
- **Golden Rule of Fluids:** 10-20 mL/kg NS bolus first; replace remaining deficit evenly over 24-48 hours.
- **Golden Rule of Insulin:** 0.05–0.1 U/kg/hr infusion. Start 1 hour *after* fluids. **No bolus.**

- **Potassium:** Total body K+ is always low. Add to fluids once urine output is established and K+ < 5.5.
- **Cerebral Edema:** Suspect if headache/bradycardia/altered GCS. Treat clinically and immediately with Mannitol or 3% Saline before neuroimaging.

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52. Recent advances in diabetic ketoacidosis management

Subject: Endocrinology

Definition & Criteria (ISPAD 2022)

- **Hyperglycemia:** Blood glucose (BG) > 200 mg/dL (11.1 mmol/L)
- **Acidosis:** Venous pH < 7.3 or serum bicarbonate < 15 mmol/L
- **Ketosis:** Blood β-hydroxybutyrate (BOHB) ≥3.0 mmol/L or moderate/large urine ketones
- **Severity grading:** Mild (pH < 7.3), Moderate (pH < 7.2), Severe (pH < 7.1)

Pathophysiology & Clinical Clues

- **Mechanism:** Absolute/relative insulin deficiency + counter-regulatory hormone excess (glucagon, catecholamines, cortisol, GH)
- **Metabolic derangement:** Accelerated gluconeogenesis, glycogenolysis, and lipolysis (ketogenesis)
- **Clinical:** Polyuria, polydipsia, weight loss, Kussmaul breathing, fruity breath, abdominal pain (mimics acute abdomen), altered sensorium

Diagnosis & Monitoring

- **Primary tests:** Plasma BG, venous blood gas (VBG), blood BOHB (preferred over urine ketones), electrolytes, BUN/Cr
- **Calculations:**
    - Anion gap = Na - (Cl + HCO3) [Normal: 12 $\pm$ 2 mmol/L]
    - Corrected Sodium = Measured Na + 1.6 $\times$ [(Glucose - 100) / 100]
- **Monitoring:** Hourly BG, neuro vitals, fluid input/output; 2-4 hourly VBG and electrolytes

Recent Advances: The Paradigm Shifts (ISPAD 2022 / PECARN Trial)

- **Fluid rate (The PECARN Shift):**
    - *Previously:* Strict 48-hour deficit replacement to avoid cerebral edema.
    - *Now:* Faster fluid delivery (replacing deficit over 24–36 hours) does **not** increase the risk of clinically apparent brain injury.
- **Fluid type:** Balanced crystalloids (Ringer's Lactate/Plasma-Lyte) are increasingly preferred over 0.9% Saline to reduce hyperchloremic non-anion gap metabolic acidosis.
- **Subcutaneous (SC) Insulin:** Rapid-acting SC insulin analogs (lispro/aspart) every 1–2 hours are now an accepted alternative to IV insulin for **mild-to-moderate** DKA in non-ICU settings (uncomplicated cases).

- **Two-bag system:** Simultaneous use of two IV bags (identical electrolytes/insulin, but one with 0% dextrose and one with 10% dextrose) titrated to maintain BG while clearing ketones, reducing fluid waste and nursing errors.

Stepwise Management Protocol

- **1. Resuscitation (0-1 Hour):**
  - 10–20 mL/kg of 0.9% NaCl or balanced crystalloids over 20–30 mins.
  - Repeat up to 30 mL/kg if peripheral perfusion remains poor.
- **2. Maintenance & Deficit Fluids:**
  - Calculate maintenance + deficit (assume 5-10% dehydration based on severity).
  - Subtract bolus volume; replace remainder over 24–48 hours.
- **3. Insulin Therapy (Starts at Hour 1):**
  - **Never** give IV insulin bolus (increases cerebral edema risk).
  - Start continuous IV regular insulin at 0.05 to 0.1 U/kg/hr.
  - Add 5%–10% Dextrose to IV fluids when BG falls to 250–300 mg/dL to allow continued insulin infusion for ketone clearance.
- **4. Potassium Replacement:**
  - Patients have total-body K+ depletion despite normal/high serum levels.
  - Start K+ replacement (40 mEq/L) concurrently with insulin if serum K+ < 5.5 mEq/L and patient is voiding.
- **5. Bicarbonate:**
  - **Contraindicated** for routine use (paradoxical CNS acidosis, delayed ketone clearance).
  - *Exception:* Life-threatening hyperkalemia or profound acidosis (pH < 6.9) with impaired cardiac contractility.

Complications & Red Flags

- **Cerebral Edema (Brain Injury):**
  - *Peak risk:* First 4–12 hours of therapy.
  - *Warning signs:* Headache, bradycardia, hypertension, declining GCS, cranial nerve palsies.
  - *Action:* Stop fluids, elevate head of bed 30°, give Mannitol (0.5–1 g/kg) or 3% Hypertonic Saline (2.5–5 mL/kg). Order head CT *only after* treatment.
- **Other:** Hypokalemia (arrhythmias), Hypoglycemia, Acute Kidney Injury (AKI), Venous Thromboembolism (VTE - high risk with central lines).

Prognosis & Prevention

- **Resolution criteria:** pH > 7.3, HCO_3 > 15, BOHB < 1.0 mmol/L, anion gap closed, tolerating oral intake.

- **Transition:** Give SC basal/bolus insulin 1–2 hours *before* stopping IV insulin infusion to prevent rebound DKA.
- **Prevention:** Sick-day management education, widespread screening for early polyuria/polydipsia, access to BOHB meters at home.

Exam Summary

- **ISPAD 2022 Update:** Fast rehydration (24-36 hrs) is safe; PECARN trial proved it does not cause cerebral edema.
- **Ketone monitoring:** Blood BOHB > 3.0 mmol/L is superior to urine ketones for diagnosis and resolution tracking.
- **Insulin rule:** No IV bolus; delay infusion until 1 hour *after* fluid expansion; SC rapid-acting insulin is now valid for mild/moderate DKA.
- **Fluid choice:** Balanced crystalloids (Plasma-Lyte/RL) minimize hyperchloremic acidosis compared to 0.9% NS.
- **Cerebral Edema management:** Clinical diagnosis; treat immediately with Mannitol or 3% Saline *before* neuroimaging.

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53. Ketotic hypoglycemia

Subject: Endocrinology

Definition

- Most common cause of hypoglycemia in early childhood (idiopathic ketotic hypoglycemia)
- Diagnosis of exclusion (requires ruling out endocrine and metabolic disorders)

Epidemiology

- **Age of onset:** 18 months to 5 years
- **Resolution:** Spontaneously outgrown by 8–9 years of age
- **Risk factors:** History of Small for Gestational Age (SGA), Low Birth Weight (LBW), thin/slender body habitus, males > females

Pathophysiology

- **Demand-supply mismatch:** High brain-to-body mass ratio in toddlers demands high glucose; limited muscle mass provides inadequate gluconeogenic precursors
- **Substrate limitation:** Primary defect is relative hypoalaninemia (insufficient alanine for gluconeogenesis during fasting)
- **Glycogen depletion:** Rapid exhaustion of limited hepatic glycogen stores during fasting or illness
- **Alternative fuel shift:** Accelerated lipolysis leads to increased free fatty acids and secondary profound ketogenesis

Clinical Features

- **Timing:** Classically occurs in the early morning after an overnight fast, a skipped meal, or minor intercurrent illness (especially gastrointestinal)
- **Neuroglycopenic symptoms:** Lethargy, irritability, confusion, unresponsiveness, seizures
- **Autonomic symptoms:** Pallor, diaphoresis, tachycardia, tremors, vomiting
- **Physical Examination:** Completely normal between episodes; **no** hepatomegaly, normal growth and development

Diagnosis (Critical Sample)

- *Must be drawn during the hypoglycemic episode (Blood Glucose <50 mg/dL)*
- **Ketones:** Elevated serum beta-hydroxybutyrate and large ketonuria
- **Insulin:** Suppressed (<2 µU/mL) – rules out hyperinsulinism
- **Counter-regulatory hormones:** Appropriate elevation of Growth Hormone (>5 ng/mL) and Cortisol (>18 µg/dL)
- **Lactate & Uric Acid:** Normal (rules out Glycogen Storage Diseases)
- **Acylcarnitine profile & Urine organic acids:** Normal (rules out Fatty Acid Oxidation Defects)
- **Glucagon stimulation test:** No glycemic rise given during hypoglycemia (glycogen stores are already depleted)

Management

- **Acute Episode:**
    - Conscious: Immediate oral fast-acting carbohydrates (juice, glucose gel)
    - Unconscious/Seizing: IV 10% Dextrose bolus (2–5 mL/kg/dose), followed by maintenance IV fluids (D10W) until oral intake is established
- **Preventive/Maintenance:**
    - Avoid prolonged fasting (maximum fasting time depends on age)
    - Frequent, regular meals and snacks
    - Uncooked cornstarch (UCCS) or a high-protein/complex carbohydrate snack at bedtime
- **Sick Day Rules:** Ensure frequent intake of sugar-containing fluids during intercurrent illnesses; early hospital admission for IV dextrose if oral intake fails

Prognosis

- Excellent; self-limiting condition
- Brain damage is rare unless episodes are prolonged, severe, and untreated
- Total resolution expected by late childhood as muscle mass increases and brain-to-body size ratio normalizes

Exam Summary

- **Classic profile:** 2-year-old, slender, history of SGA, presents with morning seizure after missing dinner.
- **Key labs:** Hypoglycemia + Ketonuria + Low Insulin + Normal Lactate/Ammonia.

- **Physical exam:** Absolutely NO hepatomegaly (differentiates from Glycogen Storage Diseases).
- **Core mechanism:** Hypoalaninemia leading to impaired gluconeogenesis.
- **Treatment:** Acute IV D10W bolus; prevention via frequent feeds and bedtime complex carbs.

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54. Short stature evaluation and role of growth hormone

Subject: Endocrinology

Definition

- Height < 3rd percentile or < -2 Standard Deviations (SD) for age, sex, and population.
- Height velocity < 25th percentile (typically < 4–5 cm/year in mid-childhood).
- Projected adult height falls below the Mid-Parental Height (MPH) range (MPH ± 6.5 cm).
- Crossing two major centile lines downwards on the growth chart after age 2.

Etiology

- **Normal Variants (80%):** Familial Short Stature (FSS), Constitutional Delay of Growth and Puberty (CDGP).
- **Pathological Proportionate:**
    - Nutritional: Malnutrition (most common globally).
    - Systemic/Chronic: Celiac disease, Chronic Kidney Disease (CKD), Congenital Heart Disease (CHD), severe asthma.
    - Endocrine: Hypothyroidism, Growth Hormone Deficiency (GHD), Cushing syndrome, poorly controlled Type 1 Diabetes (Mauriac syndrome).
    - Genetic/Syndromic: Turner syndrome, Prader-Willi syndrome (PWS), Noonan syndrome.
- **Pathological Disproportionate:** Skeletal dysplasias (Achondroplasia, Hypochondroplasia), Rickets.

Clinical Clues & Dysmorphology

- **GHD:** Cherubic facies, central adiposity, prominent forehead, microphallus, neonatal hypoglycemia/prolonged jaundice.
- **Turner Syndrome:** Webbed neck, wide-spaced nipples, cubitus valgus, short 4th metacarpal.
- **CDGP:** Delayed puberty, family history of "late bloomers."
- **Cushing Syndrome:** Weight gain with simultaneous growth deceleration (height velocity drops while BMI rises).

Diagnostic Evaluation (Stepwise)

Step 1: Anthropometry & Clinical

- Plot height, weight, and head circumference on WHO/IAP charts.
- Calculate MPH: (Father's height + Mother's height ± 13 cm) / 2. [Add 13 for boys, subtract 13 for girls].

- Assess proportions: Upper Segment/Lower Segment (US/LS) ratio and arm span.

Step 2: Bone Age (BA)

- X-ray of left hand and wrist (Greulich-Pyle method).
- **FSS:** Bone Age = Chronological Age (BA = CA).
- **CDGP:** Bone Age = Height Age < Chronological Age (BA = HA < CA).
- **Endocrine (GHD/Hypothyroid):** Bone Age severely delayed (< CA).

Step 3: Tier 1 Investigations (Rule out systemic)

- CBC, ESR/CRP (chronic infection/inflammation).
- KFT, Urine routine, venous blood gas (CKD, RTA).
- LFT, Tissue Transglutaminase (TTG)-IgA with Total IgA (Celiac disease).
- TSH, free T4 (Hypothyroidism).
- **Karyotype (45,X0):** Mandatory in *all* girls with unexplained short stature.

Step 4: GH Axis Evaluation

- **Screening:** Serum IGF-1 and IGFBP-3 (correlate with bone age and pubertal status).
- **GH Stimulation Tests:** Required because GH secretion is pulsatile.
    - Agents: Clonidine, Glucagon, Insulin tolerance test (ITT), Levodopa, Arginine.
    - Diagnosis requires failure to peak (< 10 ng/mL) on **two** different pharmacological tests.
    - *Note:* Sex steroid priming is recommended in peripubertal children to prevent false positives.

Step 5: Imaging

- MRI Brain with pituitary cuts: Indicated if GHD is confirmed (look for ectopic posterior pituitary, pituitary hypoplasia, craniopharyngioma, septo-optic dysplasia).

Role of Growth Hormone (rhGH Therapy)

Mechanism

- Recombinant human GH (rhGH) stimulates hepatic and tissue production of IGF-1, promoting chondrocyte proliferation at the epiphyseal plates.

Approved Indications (FDA/IAP)

- Growth Hormone Deficiency (GHD)
- Turner Syndrome
- Prader-Willi Syndrome (PWS)
- Small for Gestational Age (SGA) with failure of catch-up growth by 2–4 years of age
- Chronic Kidney Disease (CKD) prior to transplant
- Idiopathic Short Stature (ISS) (Height < -2.25 SD with poor predicted adult height)
- SHOX gene deficiency

- Noonan Syndrome

Administration & Dosing

- **Standard:** Subcutaneous injection, daily at bedtime (mimics physiologic nighttime GH surge).
- **Dose:** Varies by condition (GHD: 0.16–0.24 mg/kg/week; Turner/SGA/CKD require higher doses: 0.33–0.37 mg/kg/week).
- **Update (FDA 2021/2023):** Long-acting once-weekly GH preparations (Somapacitan, Lonapegsomatropin) are now approved for pediatric GHD.

Monitoring

- Assess height velocity, weight, and pubertal staging every 3–6 months.
- Measure IGF-1 levels (target upper half of normal range for age/sex).
- Monitor bone age annually.
- Check thyroid function (GH therapy can unmask central hypothyroidism).

Complications & Adverse Effects

- Slipped Capital Femoral Epiphysis (SCFE) – suspect if child develops a limp or knee/hip pain.
- Benign Intracranial Hypertension (Pseudotumor cerebri) – suspect if severe headaches/vomiting occur.
- Worsening of pre-existing scoliosis (due to rapid growth).
- Insulin resistance and transient hyperglycemia.
- Prepubertal gynecomastia.

Contraindications

- Closed epiphyses.
- Active malignancy or active intracranial tumor.
- Severe obesity or severe respiratory impairment in Prader-Willi Syndrome (risk of sudden death).
- Active proliferative diabetic retinopathy.

Exam Summary

- **Must-write Definition:** Height < -2 SD or crossing two major centile lines.
- **Golden Rule:** Always check a karyotype in any short female to rule out Turner syndrome, even without classic dysmorphism.
- **Diagnosis trap:** A single random GH level is useless; diagnosis of GHD requires failure to peak (< 10 ng/mL) on **two** stimulation tests.
- **Key GH Side Effects:** SCFE, Pseudotumor cerebri, unmasking of hypothyroidism, and insulin resistance.
- **Update:** Once-weekly long-acting GH (e.g., Somapacitan) is the latest advancement in improving patient compliance.

55. Precocious puberty evaluation and management

Subject: Endocrinology

Definition

- **Girls:** Onset of secondary sexual characteristics (thelarche) before **8 years**.
- **Boys:** Testicular enlargement (volume ≥4 mL or length ≥2.5 cm) before **9 years**.
- *Note:* AAP updates acknowledge earlier onset in certain demographics (e.g., normal breast budding at 7 years in Black/Hispanic girls), but 8/9 years remains the strict exam threshold.

Classification & Etiology

- **Central Precocious Puberty (CPP):** Gonadotropin (GnRH) dependent.
    - *Idiopathic:* Most common cause in girls (80–90%).
    - *CNS Lesions:* Hypothalamic hamartoma (classic: gelastic seizures), optic glioma (NF-1), astrocytoma, hydrocephalus.
    - *Acquired:* Post-meningitis, cranial irradiation, trauma.
    - *Exam Trap:* Idiopathic CPP is rare in boys (<40%); always suspect and rule out a CNS tumor.
- **Peripheral Precocious Puberty (PPP):** Gonadotropin (GnRH) independent.
    - *Adrenal:* Congenital Adrenal Hyperplasia (CAH - 21-OHase deficiency), adrenal tumors.
    - *Gonadal:* Ovarian cysts/tumors (Granulosa cell), Testicular tumors (Leydig cell).
    - *Genetic Syndromes:*
        - **McCune-Albright Syndrome:** GNAS mutation, café-au-lait macules (Coast of Maine), polyostotic fibrous dysplasia, recurrent ovarian cysts.
        - **Familial Male-Limited PP (Testotoxicosis):** Activating mutation of LH receptor.
    - *Ectopic:* hCG-secreting tumors (hepatoblastoma, germ cell tumors - causes PPP in boys only).
    - *Severe Hypothyroidism:* Van Wyk-Grumbach syndrome (cross-reactivity of high TSH on FSH receptors).
- **Benign Variants:** Premature thelarche, premature adrenarche, isolated premature menarche.

Clinical Features

- **Growth:** Accelerated height velocity, somatic advancement.
- **Girls:** Breast budding, estrogenization of vaginal mucosa, menses.
- **Boys:** Testicular enlargement (indicates central/gonadal) vs. small testes with penile growth (indicates adrenal source).
- **Adrenarche signs:** Pubic/axillary hair, acne, adult body odor.

Stepwise Diagnosis

- **Step 1: Bone Age (BA)**

- X-ray left hand/wrist.
- Advanced BA (>2 SD above chronological age) confirms true precocious puberty.

- **Step 2: Basal Hormones**
  - Check Basal LH (ultrasensitive assay).
  - Basal LH **>0.3 mIU/mL** suggests CPP.
- **Step 3: GnRH Stimulation Test (Gold Standard)**
  - Administer GnRH analog; measure LH at 0, 30, and 60 minutes.
  - **Peak LH >5.0 mIU/mL:** Confirms CPP.
  - **Flat/Suppressed LH response:** Confirms PPP.
- **Step 4: Etiology-Specific Imaging & Labs**
  - *MRI Brain with contrast:* Mandatory in ALL boys with CPP, and girls with CPP <6 years or with neurological signs.
  - *Pelvic USG:* Uterine length >34 mm, fundus > cervix ratio, ovarian volume >1–3 mL (supports CPP).
  - *PPP Labs:* Estradiol, Testosterone, 17-OHP, DHEAS, TSH, beta-hCG.

Management

- **Central Precocious Puberty (CPP):**
  - *Drug of choice:* **GnRH Agonists** (Leuprolide acetate depot, Triptorelin, or Histrelin subcutaneous implant).
  - *Mechanism:* Continuous (non-pulsatile) administration causes downregulation and desensitization of pituitary GnRH receptors.
  - *Monitoring:* Re-evaluate height velocity, Tanner staging, and BA every 6 months. Random LH should remain suppressed (<0.6 mIU/mL).
  - *Discontinuation:* Stop at appropriate age for puberty (typically bone age 12 in girls, 13 in boys) to allow normal pubertal progression and growth spurt.
- **Peripheral Precocious Puberty (PPP):**
  - *McCune-Albright:* Aromatase inhibitors (Letrozole) or estrogen receptor modulators (Tamoxifen).
  - *Testotoxicosis:* Antiandrogens (Spironolactone/Bicalutamide) + Aromatase inhibitors (Letrozole) to prevent bone maturation.
  - *CAH:* Glucocorticoids (Hydrocortisone).
  - *Tumors:* Surgical resection.
  - *Van Wyk-Grumbach:* Levothyroxine.

Complications

- **Physical:** Premature epiphyseal fusion leading to compromised final adult short stature.

- **Psychosocial:** Behavioral issues, emotional lability, distress due to physical differences from peers, risk of early sexual debut/abuse.

Exam Summary

- **Cut-offs:** Girls <8 years, Boys <9 years.
- **Initial test:** Bone Age X-ray (advanced in true PP, normal in benign variants).
- **Gold Standard:** GnRH stimulation test (Peak LH >5 mIU/mL = Central).
- **Red Flag:** CPP in a boy is a CNS tumor (hamartoma) until proven otherwise → MRI is mandatory.
- **Treatment for CPP:** Long-acting GnRH agonists (continuous stimulation = downregulation).
- **Buzzword:** "Coast of Maine" spots + fractures + precocious puberty = McCune-Albright syndrome.

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56. Congenital adrenal hyperplasia

Subject: Endocrinology

Definition & Genetics

- Autosomal recessive disorders of adrenal steroidogenesis
- Characterized by specific enzyme deficiencies impairing cortisol synthesis
- Most common: 21-Hydroxylase deficiency (21-OHD) accounting for >95% cases
- Gene: *CYP21A2* located on chromosome 6p21.3

Enzyme Variants & Key Differences

- **21-Hydroxylase (95%):** Virilization, salt-wasting (hypotension, hyperkalemia)
- **11-β-Hydroxylase (5%):** Virilization, salt-retention (hypertension, hypokalemia) due to deoxycorticosterone (DOC) accumulation
- **3-β-Hydroxysteroid Dehydrogenase (Rare):** Ambiguous genitalia in both sexes, severe salt-wasting
- **17-α-Hydroxylase (Rare):** Hypertension, hypokalemia, sexual infantilism (delayed puberty)

Pathophysiology (21-OHD)

- Enzyme block prevents conversion of 17-hydroxyprogesterone (17-OHP) to 11-deoxycortisol
- Decreased cortisol → loss of negative feedback → increased ACTH secretion
- Elevated ACTH → bilateral adrenal cortical hyperplasia
- Accumulated precursors (17-OHP) shunt into the intact androgen synthesis pathway
- Result: Excess testosterone/androstenedione and deficient cortisol/aldosterone

Clinical Features (21-OHD)

1. Classic Salt-Wasting (75%)

- **Neonatal period (Days 7–14):** Adrenal crisis (lethargy, vomiting, poor feeding, shock)

- **Females (46,XX):** Ambiguous genitalia at birth (clitoromegaly, labial fusion, urogenital sinus)
- **Males (46,XY):** Normal genitalia at birth, present with unexplained shock/salt-wasting crisis

2. Classic Simple Virilizing (25%)

- Adequate aldosterone prevents salt-wasting crisis
- **Infancy/Childhood:** Rapid somatic growth, accelerated bone maturation, premature adrenarche
- **Signs:** Pubic hair, body odor, acne, phallic enlargement (without testicular enlargement in males)

3. Non-Classic (Late-Onset)

- Mild enzyme deficiency; normal cortisol/aldosterone
- **Childhood/Adolescence:** Premature pubarche, severe acne, hirsutism, oligomenorrhea, PCOS-like phenotype

Diagnosis

- **Newborn Screening (NBS):** Filter paper blood spot for 17-OHP (high false-positive rate in premature/sick infants)
- **Hormonal Profile (Gold Standard):** Markedly elevated basal serum 17-OHP (>3,000 ng/dL is diagnostic for classic CAH)
- **Electrolytes:** Hyponatremia, hyperkalemia, metabolic acidosis, hypoglycemia
- **ACTH Stimulation Test:** Confirmatory test for borderline/non-classic cases (measures 17-OHP at 0 and 60 mins)
- **Imaging:** Pelvic USG (confirms presence of uterus/ovaries in virilized females); Adrenal USG (bilateral hyperplasia)
- **Karyotype/Genetics:** 46,XX in virilized females; *CYP21A2* gene sequencing for definitive diagnosis

Management: Acute Adrenal Crisis

- **Fluid Resuscitation:** IV 0.9% Normal Saline 20 mL/kg bolus (treat shock)
- **Glucocorticoids:** IV Hydrocortisone 50–100 mg/m^2 immediately (stress dose)
- **Hypoglycemia:** IV 10% Dextrose (2–4 mL/kg)
- **Hyperkalemia correction:** Calcium gluconate, Insulin+Glucose, Salbutamol nebulization if ECG changes are present

Management: Chronic Maintenance

- **Glucocorticoids:** Oral Hydrocortisone 10–15 mg/m^2/day divided in 3 doses (suppresses ACTH and androgens)
- **Mineralocorticoids:** Oral Fludrocortisone 0.05–0.2 mg/day (for salt-wasters)
- **Salt Supplementation:** NaCl 1–2 g/day (17–34 mEq/day) in infants until age 6–12 months
- **Stress Dosing:** Double or triple oral hydrocortisone dose during fever (>38.5°C), surgery, or severe illness. Give IM if vomiting.

Surgical Management

- **Feminizing Genitoplasty:** Clitoroplasty and vaginoplasty for severe virilization (Prader stage III-V)
- **Update (Endocrine Society/AAP):** Timing is highly debated. Multidisciplinary DSD (Disorders of Sex Development) team approach is mandatory. Trend is moving toward delaying surgery until the patient can participate in decision-making, unless anatomically necessary for urinary drainage.

Monitoring & Follow-up

- **Clinical:** Growth velocity, weight gain, blood pressure, signs of virilization
- **Radiological:** Bone age annually (monitor for premature epiphyseal fusion)
- **Biochemical:** 17-OHP, Androstenedione, Testosterone (aim for upper-normal range, do not suppress completely to avoid Cushingoid effects); Plasma Renin Activity (target: lower half of normal to titrate fludrocortisone)

Complications

- Short adult stature (due to early epiphyseal closure from excess androgens)
- Testicular Adrenal Rest Tumors (TARTs) in males (causes infertility; monitor with testicular USG)
- Iatrogenic Cushing syndrome (over-treatment)
- Polycystic ovaries and reduced fertility in females

Prenatal Diagnosis & Prevention

- **Diagnosis:** Chorionic villus sampling (CVS) at 10–12 weeks or amniocentesis for *CYP21A2* mutation
- **Update (Prenatal Dexamethasone):**
    - *Previously:* Given to mothers early in pregnancy to prevent female virilization.
    - *Now (Endocrine Society 2018/Current):* Routine use is **not recommended** due to maternal side effects and potential fetal cognitive/metabolic risks. Should only be done under approved institutional research protocols.

Exam Summary

- **Classic SW CAH:** Shock, hyponatremia, hyperkalemia, hypoglycemia at days 7-14.
- **Classic SV CAH:** Virilization, early pubarche, advanced bone age, normal electrolytes.
- **Key differentiator:** 21-OHD has high K+ and low BP; 11-β-OHD has low K+ and high BP.
- **Diagnostic marker:** Elevated 17-OHP (basal or post-ACTH).
- **Core treatment:** Hydrocortisone (10-15 mg/m^2/day) + Fludrocortisone + Salt (in infants).
- **Must-know:** Always educate parents on stress dosing (double/triple dose) and emergency IM hydrocortisone injection for sick days.

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57. Vitamin D deficiency in children

Subject: Endocrinology

Definition (Global Consensus / IAP)

- Based on serum 25(OH)D levels:
    - **Deficiency:** <12 ng/mL (<30 nmol/L)
    - **Insufficiency:** 12–20 ng/mL (30–50 nmol/L)
    - **Sufficiency:** >20 ng/mL (>50 nmol/L)
    - **Toxicity:** >100 ng/mL (>250 nmol/L)

Etiology

- **Decreased Intake:** Exclusive breastfeeding without supplementation (breast milk contains only ~20 IU/L).
- **Decreased Synthesis:** Dark skin pigmentation (melanin absorbs UV-B), indoor lifestyle, sunscreen use, high latitude, winter season.
- **Malabsorption:** Celiac disease, Cystic Fibrosis, biliary atresia, short bowel syndrome.
- **Altered Metabolism:**
    - Hepatic disease (decreased 25-hydroxylation).
    - Chronic Kidney Disease (decreased 1-alpha-hydroxylation).
    - Drugs: Anticonvulsants (Phenytoin, Phenobarbital) induce hepatic CYP450, accelerating vitamin D degradation.

Pathophysiology

- Low Vitamin D → ↓ intestinal absorption of Calcium (Ca) and Phosphorus (PO4).
- Transient hypocalcemia triggers **Secondary Hyperparathyroidism** (↑ PTH).
- ↑ PTH causes bone resorption (normalizes serum Ca) and renal phosphaturia (↓ serum PO4).
- Net result: Normal/low Ca, low PO4, ↑ Alkaline Phosphatase (ALP).
- Deficient Ca/PO4 product → failure of apoptosis of hypertrophic chondrocytes → defective osteoid mineralization at the growth plate (**Rickets** in growing bones, **Osteomalacia** in mature bones).

Clinical Features

- **Infants (<1 year):**
    - **Craniotabes:** "Ping-pong ball" skull (softening of occipital/parietal bones); earliest bony sign.
    - Delayed closure of anterior fontanelle, frontal bossing, caput quadratum.
    - Hypocalcemic seizures or tetany.
    - Dilated cardiomyopathy (severe cases).
- **Toddlers & Children:**

- **Chest:** Rachitic rosary (enlarged costochondral junctions), Harrison sulcus (indentation at diaphragmatic insertion).
- **Extremities:** Widened wrists and ankles, bowing of legs (genu varum) in toddlers, knock knees (genu valgum) in older children.
- **General:** Hypotonia, delayed motor milestones (walking), delayed dentition, enamel hypoplasia.

Diagnosis

- **Biochemical Labs:**
  - **Serum 25(OH)D:** Best indicator of body stores (Low).
  - **ALP:** Elevated (earliest marker of active disease and best marker to monitor treatment response).
  - **PTH:** Elevated (Secondary hyperparathyroidism).
  - **PO4:** Low.
  - **Calcium:** Normal or Low.
- **Radiology (X-ray Wrist / Knee):**
  - **Cupping:** Concavity of the metaphysis.
  - **Splaying:** Widening of metaphyseal ends.
  - **Fraying:** Irregular, brush-like metaphyseal margins.
  - Widened epiphyseal growth plate.
  - Generalized osteopenia.

Management

- **Principle:** Replenish Vitamin D stores rapidly, followed by maintenance. Always co-administer Calcium to prevent "Hungry Bone Syndrome."
- **IAP Treatment Guidelines (2021 Update):**
  - **< 1 year:** 2,000 IU/day for 3 months OR 60,000 IU/week for 6 weeks.
  - **1–18 years:** 3,000–6,000 IU/day for 3 months OR 60,000 IU/week for 6 weeks.
  - *Preferred Route:* Oral (IM depot injections are erratic and generally avoided unless compliance/malabsorption is an issue).
- **Calcium Supplementation:**
  - 500 mg/day of elemental calcium for at least the first 2–4 weeks of Vitamin D therapy.
- **Monitoring:**
  - Check ALP and radiographic healing at 1 and 3 months.
  - Radiological healing (calcification line at metaphysis) appears in 2–4 weeks.

Complications

- Hypocalcemic seizures and tetany.

- Pathological fractures.
- Permanent skeletal deformities (e.g., contracted pelvis leading to future obstructed labor in females).
- Severe hypotonia and recurrent respiratory infections.

Prevention (AAP & IAP Guidelines)

- **Infants (<1 year):** 400 IU/day starting from the first few days of life, regardless of feeding mode (breastfed or formula-fed).
- **Children (>1 year) & Adolescents:** 600 IU/day.
- **Sun Exposure:** 15–30 minutes of midday sun exposure (10 AM to 3 PM) on 15–30% of body surface area.

Exam Summary

- **Cut-off:** Deficiency is <12 ng/mL (IAP/Global Consensus).
- **Classic Lab Profile:** Normal/Low Ca, Low PO4, High ALP, High PTH, Low 25(OH)D.
- **Radiology Triad:** Cupping, splaying, fraying of metaphyses.
- **Must-Write Treatment Rule:** Always add oral Calcium (500 mg/day) to Vitamin D therapy to avoid Hungry Bone Syndrome.
- **Prevention:** Universal supplementation of 400 IU/day for all infants starting at birth.

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58. Rickets classification and management

Subject: Endocrinology

Definition

- Defective mineralization of osteoid at the epiphyseal growth plates of long bones in growing children.
- Osteomalacia: Defective mineralization of mature cortical/spongy bone (occurs after epiphyseal closure).

Classification

1. Calcipenic Rickets (Low Calcium/Vitamin D)

- **Nutritional:** Vitamin D deficiency (most common), Calcium deficiency.
- **Vitamin D Dependent Rickets (VDDR):**
    - *Type 1A:* 1-alpha-hydroxylase deficiency (renal).
    - *Type 1B:* 25-hydroxylase deficiency (hepatic).
    - *Type 2A:* Vitamin D receptor (VDR) mutation.
    - *Type 2B:* VDR-retinoid X receptor heterodimerization defect.

- **Secondary:** Malabsorption (Celiac, Biliary atresia), Drugs (Phenytoin, Phenobarbital - induce hepatic P450).

2. Phosphopenic Rickets (Low Phosphorus)

- **FGF23-Mediated (Renal phosphate wasting):**
    - X-linked Hypophosphatemic rickets (XLH) - *PHEX* gene mutation.
    - Autosomal Dominant (ADHR) / Autosomal Recessive (ARHR).
    - Tumor-induced osteomalacia.
- **Non-FGF23-Mediated:**
    - Fanconi syndrome (global proximal tubular dysfunction).
    - Dent disease, Lowe syndrome.
    - Prematurity (osteopenia of prematurity).

3. Renal Rickets

- Chronic Kidney Disease (Renal osteodystrophy - mixed calcipenic/phosphopenic).

Pathophysiology (Nutritional)

- ↓ Vitamin D/Dietary Calcium → ↓ Serum Calcium.
- Triggers Secondary Hyperparathyroidism (↑ PTH).
- ↑ PTH causes:
    - Bone resorption (normalizes serum Ca temporarily).
    - Renal phosphate excretion (phosphaturia) → Hypophosphatemia.
- Low Phosphorus + Low/Normal Calcium → Failure of osteoid mineralization at growth plate.

Clinical Features

- **Head:** Craniotabes (ping-pong skull, earliest sign), frontal bossing, delayed anterior fontanelle closure, delayed dentition.
- **Chest:** Rachitic rosary (enlarged costochondral junctions), Harrison sulcus (diaphragmatic pull on softened ribs), pigeon chest.
- **Extremities:** Widened wrists/ankles, double malleoli, genu varum (bow legs - in toddlers), genu valgum (knock knees - in older children).
- **Systemic:** Hypotonia, delayed motor milestones, pot-belly, hypocalcemic tetany/seizures (especially infants <6 months).

Diagnosis

Biochemical Profile

- **Nutritional:** ↓/Normal Ca, ↓ P, ↑ ALP, ↑ PTH, ↓ 25(OH)D (<12 ng/mL).
- **VDDR Type 1:** Normal 25(OH)D, ↓ 1,25(OH)2D, ↑ PTH.
- **VDDR Type 2:** Normal 25(OH)D, ↑↑ 1,25(OH)2D, ↑ PTH.
- **XLH:** Normal Ca, ↓↓ P, Normal PTH, Normal 25(OH)D, Inappropriately normal/low 1,25(OH)2D.

Radiology (X-ray Wrist/Knee)

- **Earliest sign:** Loss of zone of provisional calcification.
- **Classic triad:** Cupping, Fraying, and Splaying of metaphyses.
- Widened epiphyseal plate.
- Osteopenia, looser zones (pseudofractures).

Management

1. Nutritional Rickets (Global Consensus / IAP Guidelines)

- **Vitamin D Therapy:**
  - *Age < 1 month:* 1,000 IU/day for 2–3 months.
  - *Age 1–12 months:* 2,000 IU/day for 3 months OR Stoss therapy: 50,000 IU as single dose.
  - *Age > 12 months:* 3,000–6,000 IU/day for 3 months OR Stoss therapy: 150,000–300,000 IU as single dose.
- **Calcium Supplementation (Mandatory):**
  - 500 mg/day of elemental calcium for 2–4 weeks.
  - *Rationale:* Prevents "Hungry Bone Syndrome" (precipitous hypocalcemia as bone remineralizes).
- **Maintenance:** 400–600 IU/day of Vitamin D after therapeutic phase.

2. Genetic / Refractory Rickets

- **VDDR Type 1:** Active Vitamin D (Calcitriol) 10–50 ng/kg/day.
- **VDDR Type 2:** High-dose Calcitriol + Extremely high oral Calcium (may require prolonged IV Calcium infusions).
- **XLH (Hypophosphatemic):**
  - *Conventional:* Oral Phosphate (frequent dosing) + Calcitriol (to prevent secondary hyperparathyroidism).
  - *Update (AAP/Recent):* **Burosumab** (Monoclonal antibody against FGF23) is now the definitive treatment for XLH >6 months of age.

Complications

- Hypocalcemic seizures (most common presentation in early infancy).
- Dilated cardiomyopathy (infantile hypocalcemia).
- Permanent skeletal deformities (pelvic disproportion, short stature).
- Recurrent respiratory infections (due to poor chest mechanics).

Prognosis

- Nutritional rickets resolves completely with early treatment.
- Radiological healing (appearance of provisional line of calcification) begins within 1–2 weeks.
- ALP normalizes by 3 months (best biochemical marker of healing).

Prevention

- **IAP 2021 / Global Consensus:** 400 IU/day of Vitamin D for all infants (breastfed and formula-fed) from birth to 1 year of age.
- Adequate sunlight exposure and maternal Vitamin D supplementation during pregnancy/lactation.

Exam Summary (Must-Write Points)

- **Triad of X-ray findings:** Cupping, fraying, splaying of metaphyses.
- **Earliest biochemical marker:** Elevated Alkaline Phosphatase (ALP).
- **Stoss Therapy limit:** Never exceed 300,000 IU total (risk of hypercalcemia).
- **Hungry Bone Syndrome prevention:** Always co-administer Calcium 500 mg/day with Vitamin D therapy.
- **XLH vs VDDR:** XLH has normal PTH and normal Ca; VDDR has high PTH and low Ca.
- **Alopecia** is a classic exam clue for VDDR Type 2 (receptor defect).
- **Recent Advance:** Burosumab (anti-FGF23) is the game-changer for X-linked Hypophosphatemia.

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59. Ambiguous genitalia evaluation

Subject: Endocrinology

Topic: Evaluation of Ambiguous Genitalia (Disorders of Sex Development - DSD)

Definition & Terminology

- **DSD:** Congenital conditions with atypical development of chromosomal, gonadal, or anatomic sex.
- *Note:* The term "ambiguous genitalia" is clinically descriptive, but "DSD" is the accepted diagnostic nomenclature (Chicago Consensus).

Indications for Evaluation

- Overt genital ambiguity (e.g., cloacal exstrophy).
- Apparent female: Clitoromegaly (>9 mm), posterior labial fusion, or inguinal/labial mass (palpable gonad).
- Apparent male: Bilateral non-palpable testes, micropenis (<2.5 cm stretched length at term), or severe hypospadias (perineal/penoscrotal).
- Discordance: Prenatal karyotype vs. postnatal phenotype.

Etiology (Chicago Classification)

- **46, XX DSD (Virilized Female):**
    - Congenital Adrenal Hyperplasia (CAH) (21-hydroxylase deficiency >90%; 11β-OHD, 3β-HSD).

- Maternal androgens (luteoma, exogenous progestins).
- Aromatase deficiency.

- **46, XY DSD (Undermasculinized Male):**
  - Gonadal dysgenesis (complete/partial).
  - Androgen synthesis defects (5α-reductase deficiency, 17β-HSD deficiency).
  - Androgen action defects (Complete or Partial Androgen Insensitivity Syndrome - CAIS/PAIS).
  - AMH or AMH receptor defects (Persistent Mullerian Duct Syndrome).
- **Sex Chromosome DSD:**
  - 45,X/46,XY (Mixed Gonadal Dysgenesis).
  - 46,XX/46,XY (Chimerism).
  - Ovotesticular DSD (True hermaphroditism).

Clinical Evaluation (History & Exam)

- **History:** Consanguinity, sibling neonatal deaths (unrecognized CAH crisis), maternal virilization, maternal drug exposure.
- **Palpable Gonads (The crucial branch point):**
  - *Palpable gonad = Contains Y chromosome* (Testis or Ovotestis). Ovaries do not descend into the labia/scrotum.
  - Bilateral palpable gonads: Excludes 46,XX CAH.
- **Genital Exam:**
  - Prader Staging (0 = normal female, 5 = normal male).
  - Stretched Penile Length (SPL): Measure pubic ramus to tip (exclude prepuce).
  - Urethral meatus position (hypospadias severity).
  - Anogenital ratio: >0.5 suggests androgen exposure in females.
- **Systemic Exam:**
  - Hyperpigmentation (areola, scrotum): Suggests high ACTH (CAH).
  - Blood pressure: Hypertension seen in 11β-OHD and 17α-OHD.
  - Dysmorphism: Denys-Drash / WAGR (WT1 mutations), Campomelic dysplasia (SOX9).

Diagnostic Algorithm (Stepwise)

- **Step 1: Life-Threatening Rule-Out (Day 1)**
  - Serum electrolytes (Na+, K+) and blood glucose.
  - *Red Flag:* Hyponatremia, hyperkalemia, hypoglycemia = Salt-wasting CAH (Medical Emergency).
- **Step 2: Core Baseline (Day 2-3)**

- **Karyotype + FISH for SRY:** Rapid turnaround to establish chromosomal sex.
- **Serum 17-OHP:** *Must draw after 48 hours* (Day 3 is ideal) to avoid false elevation from maternal/physiologic stress.

- **Step 3: Imaging**
  - Pelvic/Abdominal USG: Check for Mullerian structures (uterus/upper vagina), locate gonads, assess adrenal size.
- **Step 4: Endocrine Profiling (Based on Karyotype)**
  - *If 46, XY:* Serum Testosterone, DHT, Androstenedione, LH, FSH. AMH (evaluates Sertoli cell function).
  - *hCG Stimulation Test:* Differentiates testicular dysgenesis (no testosterone rise) from androgen insensitivity/5α-reductase deficiency (testosterone rises).
  - *Testosterone/DHT ratio:* >10 post-hCG suggests 5α-reductase deficiency.
- **Step 5: Molecular Genetics**
  - Targeted DSD gene panels or Whole Exome Sequencing (WES) if hormonal workup is inconclusive.

Management

- **MDT Approach:** Care must involve Pediatric Endocrinology, Urology, Genetics, Psychology, and Social Work.
- **Gender Assignment:** Do not rush. Based on underlying diagnosis, fertility potential, surgical options, and anticipated pubertal brain virilization.
- **Medical:**
  - CAH: Hydrocortisone (10-15 mg/m^2/day) + Fludrocortisone + NaCl supplementation.
  - Sex steroid replacement at puberty (based on gender of rearing).
- **Surgical (AAP/International Consensus Updates):**
  - *Current Trend:* Delay irreversible cosmetic genitoplasty until the patient is old enough to participate in gender identity decisions.
  - *Early surgery indications:* Medically necessary procedures (e.g., severe urogenital sinus causing recurrent UTI/obstruction).
- **Gonadectomy:** Prophylactic removal of intra-abdominal dysgenetic gonads containing Y-chromosome material (high risk of gonadoblastoma).

Prognosis & Complications

- **Adrenal Crisis:** Fatal if 21-OHD is missed.
- **Malignancy:** 15-30% risk of germ cell tumors in dysgenetic XY gonads.
- **Psychosocial:** High risk of gender dysphoria, depression, and impaired sexual function. Infertility is common in most DSDs (except treated CAH).

Exam Summary: Absolute Must-Write Points

- **Palpable gonad rule:** A palpable gonad in the groin/labia rules out 46,XX CAH; it indicates the presence of testicular tissue (Y chromosome).
- **CAH is the most common cause:** 46,XX DSD with 21-hydroxylase deficiency accounts for the majority of ambiguous genitalia.
- **Timing of 17-OHP:** Never draw on Day 1; draw after 48-72 hours to prevent false positives.
- **Life-saving step:** Always check electrolytes and glucose immediately to rule out salt-wasting adrenal crisis.
- **Modern surgical paradigm:** Delay cosmetic/irreversible reconstructive surgery until patient consent is possible, unless medically urgent.

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60. Childhood hypertension evaluation and management

Subject: Endocrinology

Definition & Classification (AAP 2017 Guidelines)

- **Routine Screening:** Annually starting at $\ge$3 years; check at every visit if obese, on high-risk meds, or has renal disease/aortic arch anomalies.
- **Classification (< 13 years):** Based on age, sex, and height percentiles.
    - *Normal:* <90th percentile
    - *Elevated:* $\ge$90th to <95th percentile (or 120/80 to <95th, whichever is lower)
    - *Stage 1 HTN:* $\ge$95th to <95th percentile + 12 mmHg (or 130/80 to 139/89)
    - *Stage 2 HTN:* $\ge$95th percentile + 12 mmHg (or $\ge$140/90)
- **Classification (≥13 years):** Uses absolute adult cut-offs.
    - *Normal:* <120/<80 mmHg
    - *Elevated:* 120–129/<80 mmHg
    - *Stage 1 HTN:* 130–139/80–89 mmHg
    - *Stage 2 HTN:* $\ge$140/90 mmHg

Etiology (Age-Stratified)

- **Neonates:** Umbilical artery catheterization (thrombus), congenital renal anomalies, renal artery stenosis (RAS), coarctation of aorta (CoA).
- **Infants to 6 years:** Renal parenchymal disease (most common secondary cause overall), RAS, CoA.
- **>6 years to Adolescence:** Primary/Essential HTN (obesity-related; now most common overall), renal parenchymal disease.
- **Endocrine Causes (Must-know for secondary HTN):**
    - *Catecholamine excess:* Pheochromocytoma, Neuroblastoma.
    - *Corticosteroid excess:* Cushing syndrome, Exogenous steroids.

- *Mineralocorticoid excess:* Primary hyperaldosteronism (Conn syndrome), Liddle syndrome, Apparent Mineralocorticoid Excess (AME).
- *Enzyme defects:* Congenital Adrenal Hyperplasia (11-β hydroxylase and 17-α hydroxylase deficiencies).
- *Thyroid:* Hyperthyroidism (isolated systolic HTN).

Clinical Features & Clues

- **General:** Often asymptomatic; discovered incidentally.
- **Symptoms of severe HTN:** Headache, epistaxis, vomiting, visual changes, facial palsy (classic association with severe HTN in infants).
- **Etiological Clues:**
  - *Radio-femoral delay / weak lower pulses:* CoA.
  - *Episodic flushing, sweating, palpitations:* Pheochromocytoma.
  - *Ambiguous genitalia / virilization:* CAH (11-β hydroxylase deficiency).
  - *Abdominal bruit:* Renal artery stenosis (fibromuscular dysplasia).
  - *Flash pulmonary edema:* Bilateral RAS.

Diagnosis & Evaluation

- **Measurement Rules:**
  - Right arm, seated, resting for 3–5 minutes.
  - *Cuff size:* Bladder width must cover 40% of mid-arm circumference; length must cover 80–100%. (Too small cuff = falsely high BP).
  - *Confirmation:* Auscultatory method is the gold standard; must confirm any elevated oscillometric reading.
- **Ambulatory BP Monitoring (ABPM):**
  - Gold standard to confirm HTN before starting meds.
  - Identifies White-Coat HTN, Masked HTN, and loss of nocturnal dipping (non-dippers have higher cardiovascular risk).
- **Tier 1 Workup (All confirmed HTN):**
  - Urinalysis, BUN, Creatinine, Electrolytes (Na, K, Ca).
  - Lipid profile, Fasting glucose/HbA1c (if overweight/obese).
  - Renal USG (mandated if <6 years or abnormal renal labs).
- **Tier 2 Workup (Targeted for Secondary HTN):**
  - *Endocrine labs:* Plasma free metanephrines, Aldosterone/Renin ratio, Morning cortisol, Thyroid profile.
  - *Imaging:* Renal Doppler / CT Angiography / MR Angiography (for RAS).
  - *Sleep study:* Polysomnography for Obstructive Sleep Apnea (OSA).

- **Target Organ Damage (TOD) Assessment:**
    - *Echocardiogram:* Mandatory to assess Left Ventricular Hypertrophy (LVH) *before* initiating pharmacotherapy.
    - *Retinal exam:* For hypertensive retinopathy.

Management

- **Lifestyle Modifications (First-line for Elevated BP & Stage 1 without TOD):**
    - DASH diet (high fruit/veg, low fat dairy).
    - Sodium restriction (<1.5 to 2 g/day).
    - Moderate-to-vigorous physical activity (30–60 mins, 3–5 days/week).
    - Weight reduction if BMI $\ge$85th percentile.
- **Indications for Pharmacotherapy:**
    - Symptomatic HTN.
    - Stage 2 HTN.
    - Presence of Target Organ Damage (LVH, retinopathy, proteinuria).
    - Secondary HTN.
    - Stage 1 HTN failing 6 months of lifestyle changes.
    - Comorbidities: CKD, Type 1 or Type 2 Diabetes.
- **First-Line Antihypertensives:**
    - *ACE inhibitors (Enalapril, Lisinopril) or ARBs (Losartan):* Drug of choice for CKD, proteinuria, or diabetes. (Contraindicated in pregnancy and bilateral RAS).
    - *Calcium Channel Blockers (Amlodipine):* Highly effective, no routine lab monitoring required.
    - *Thiazide diuretics (Hydrochlorothiazide):* Good adjunct; useful in Liddle syndrome (Amiloride preferred).
- **Hypertensive Emergency Management:**
    - *Definition:* Severe HTN with acute TOD (encephalopathy, heart failure, AKI).
    - *Goal:* Reduce BP by no more than 25% of planned reduction in the first 8 hours (prevents cerebral ischemia/infarction).
    - *Drugs:* IV Labetalol, Nicardipine, or Sodium Nitroprusside.

Complications

- Left Ventricular Hypertrophy (earliest and most common TOD).
- Posterior Reversible Encephalopathy Syndrome (PRES) / Hypertensive encephalopathy.
- Progression of Chronic Kidney Disease.
- Accelerated atherosclerosis / premature coronary artery disease.

Exam Summary

- **AAP 2017 Update:** $\ge$13 years uses adult cut-offs (120/80 is elevated, 130/80 is Stage 1).
- **Cuff Trap:** Undersized cuff is the most common cause of falsely elevated BP.
- **Echo Rule:** Always obtain an Echocardiogram to check for LVH before starting antihypertensive drugs.
- **Endocrine Trap:** Hypokalemia + HTN = suspect hyperaldosteronism, Liddle syndrome, or diuretic abuse.
- **Drug of Choice:** ACEi/ARBs are first-line for proteinuric renal disease/diabetes but strictly contraindicated in bilateral renal artery stenosis.

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61. Obesity and metabolic syndrome in children

Subject: Endocrinology

Definitions

- **Overweight:** BMI ≥85th to < 95th percentile for age and sex.
- **Obesity:** BMI ≥95th percentile (CDC/WHO) or Adult Equivalent BMI ≥27 (IAP).
- **Severe Obesity:** BMI ≥120% of 95th percentile.
- **Metabolic Syndrome (MetS):** Cluster of cardiometabolic risk factors. *IDF Criteria (Age ≥10 years):* Central obesity (Waist circumference ≥90th percentile) **PLUS** ≥2 of the following:
    - Triglycerides ≥150 mg/dL
    - HDL < 40 mg/dL
    - Systolic BP ≥130 or Diastolic BP ≥85 mm Hg
    - Fasting blood glucose ≥100 mg/dL (or known T2DM)

Etiology

- **Primary (Exogenous) [95%]:** Caloric excess, sedentary lifestyle, sleep deprivation, low socioeconomic status.
- **Secondary (Endogenous) [<5%]:**
    - *Endocrine:* Hypothyroidism, Cushing syndrome, Growth Hormone deficiency, Pseudohypoparathyroidism.
    - *Monogenic:* Leptin deficiency, Leptin receptor mutation, MC4R mutation (most common monogenic cause).
    - *Syndromic:* Prader-Willi, Bardet-Biedl, Alström, Cohen syndromes.
    - *Iatrogenic:* Glucocorticoids, atypical antipsychotics (olanzapine, risperidone), antiepileptics (valproate).

Pathophysiology

- **Adiposopathy:** Hypertrophied visceral adipocytes shift to a pro-inflammatory state.
- **Adipokines:** Increased secretion of IL-6, TNF-α, and leptin (leptin resistance); decreased adiponectin.

- **Insulin Resistance (IR):** Core mechanism of MetS. Excess free fatty acids impair insulin signaling in muscle/liver ⇒hyperinsulinemia ⇒exhaustion of pancreatic β-cells (T2DM).
- **Vascular impact:** Hyperinsulinemia and inflammation cause endothelial dysfunction and sodium retention (hypertension).

Clinical Features

- **Primary vs. Secondary Clue:** Primary obesity presents with **tall stature and normal/advanced bone age**. Secondary obesity presents with **short stature and delayed bone age**.
- **Skin:** Acanthosis nigricans (neck, axillae - marker of IR), striae (pink/white in simple obesity; purple/wide in Cushing), intertrigo.
- **Adiposity distribution:** Central/visceral adiposity correlates highest with MetS.
- **Syndromic clues:** Hypotonia/hypogonadism (Prader-Willi), retinitis pigmentosa/polydactyly (Bardet-Biedl), red hair/hyperphagia (MC4R).

Diagnosis & Screening

- **Routine Screening:** Calculate BMI annually starting at age 2 years.
- **Metabolic Screening (AAP/IAP):** Initiate at age 10 (or onset of puberty) if BMI ≥85th percentile + risk factors, OR universally if BMI ≥95th percentile.
    - *Fasting Lipid Profile*
    - *Fasting Glucose* or HbA1c
    - *ALT/AST* (Screening for MASLD)
- **Endocrine Workup:** *Not routinely recommended.* Indicated ONLY if height velocity is attenuated (short stature), or specific features of Cushing/hypothyroidism are present.
- **Sleep Study (Polysomnography):** If snoring or daytime somnolence (OSA screening).

Complications

- **Endocrine:** Type 2 Diabetes, Polycystic Ovary Syndrome (PCOS), premature adrenarche.
- **GI/Hepatic:** MASLD (*Metabolic Dysfunction-Associated Steatotic Liver Disease* - formerly NAFLD), gallstones.
- **Respiratory:** Obstructive Sleep Apnea (OSA), Obesity-hypoventilation syndrome, Asthma exacerbation.
- **Orthopedic:** Slipped Capital Femoral Epiphysis (SCFE), Blount disease (tibia vara), flat feet.
- **Neurologic:** Idiopathic Intracranial Hypertension (Pseudotumor cerebri).
- **Psychosocial:** Depression, bullying, binge eating disorder.

Management

- **AAP 2023 Paradigm Shift:** *Previously:* "Watchful waiting" or stepwise approach. *Now:* Early, intensive, proactive treatment at the time of diagnosis.
- **Lifestyle Modification:** Intensive Health Behavior and Lifestyle Treatment (IHBLT) ≥26 hours/year of face-to-face counseling.

    - Dietary modifications (low glycemic index, eliminate sugary drinks).
    - Physical activity: ≥60 mins moderate-vigorous activity daily.
- **Pharmacotherapy (AAP 2023 Update):** Indicated as adjunct to lifestyle for age ≥12 years with obesity.
    - *GLP-1 Agonists:* Liraglutide, Semaglutide (Current first-line for severe obesity/T2DM).
    - *Phentermine/Topiramate:* Approved for ≥12 years.
    - *Orlistat:* Lipase inhibitor (causes steatorrhea).
    - *Metformin:* Used if concurrent prediabetes/T2DM or PCOS (not approved for weight loss alone).
- **Metabolic & Bariatric Surgery (MBS):**
    - *Indications:* Adolescents with severe obesity (BMI ≥120% of 95th percentile) + severe comorbidities (T2DM, severe OSA, MASLD).
    - *Procedures:* Roux-en-Y gastric bypass, Vertical sleeve gastrectomy.

Prevention

- **5-2-1-0 Rule:**
    - **5** servings of fruits and vegetables daily.
    - **< 2** hours of recreational screen time.
    - **≥1** hour of physical activity.
    - **0** sugar-sweetened beverages.
- Promote exclusive breastfeeding for first 6 months (protective against childhood obesity).
- Ensure adequate sleep duration for age.

Exam Summary

- **Primary vs Secondary Obesity:** Tall stature = primary/exogenous; Short stature = secondary/endocrine.
- **MetS Core:** Driven by Insulin Resistance; screen with waist circumference, fasting glucose, lipids, and BP.
- **Acanthosis Nigricans:** High-yield clinical marker for hyperinsulinemia/insulin resistance.
- **Screening Rule:** Do not order thyroid/cortisol tests for simple obesity unless height velocity is poor.
- **AAP 2023 Update:** Abandon watchful waiting; initiate pharmacotherapy (GLP-1 agonists) for age ≥12 and consider bariatric surgery for severe adolescent obesity.

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62. Disorders of sexual development

Subject: Endocrinology

Definition & Terminology

- Congenital conditions with atypical development of chromosomal, gonadal, or anatomic sex.
- *Update (Chicago Consensus 2006):* Replaced outdated terms (intersex, hermaphroditism) with DSD to reduce stigma.

Classification & Etiology Classified into three major groups based on karyotype:

- **Sex Chromosome DSD:**
  - *45,X/46,XY:* Mixed gonadal dysgenesis (streak gonad + dysgenetic testis).
  - *46,XX/46,XY:* Chimerism (ovotesticular DSD).
  - *45,X (Turner)* and *47,XXY (Klinefelter)*: Typically present with delayed puberty/infertility rather than ambiguous genitalia.
- **46,XX DSD (Androgen Excess):**
  - *Ovaries present, virilized external genitalia*.
  - *Fetal origin:* Congenital Adrenal Hyperplasia (CAH) – 21-hydroxylase deficiency is the **most common cause of ambiguous genitalia in neonates**.
  - *Maternal origin:* Luteoma of pregnancy, exogenous androgens.
  - *Placental:* Aromatase deficiency.
- **46,XY DSD (Undermasculinization):**
  - *Testes present, incomplete virilization*.
  - *Disorders of Testicular Development:* Complete/Partial Gonadal Dysgenesis (Swyer syndrome - SRY mutation).
  - *Disorders of Androgen Synthesis:* 5-alpha-reductase deficiency (impaired Testosterone to DHT conversion), 17-beta-hydroxysteroid dehydrogenase deficiency.
  - *Disorders of Androgen Action:* Complete/Partial Androgen Insensitivity Syndrome (CAIS/PAIS) – androgen receptor defect.

Clinical Features (Red Flags)

- **Neonatal period:**
  - Overt ambiguous genitalia (assess using Prader staging).
  - Apparent female with clitoromegaly (>9 mm), posterior labial fusion, or inguinal mass (testis).
  - Apparent male with bilateral non-palpable testes, micropenis (<2.5 cm at term), or severe perineoscrotal hypospadias.
  - *Emergency presentation:* Vomiting, lethargy, shock at 1–2 weeks of life (Salt-wasting CAH).
- **Adolescence:**
  - Primary amenorrhea in females.
  - Virilization at puberty in females.

- Delayed puberty or severe gynecomastia in males.
- Cyclic gross hematuria in phenotypic males (menstruation via urogenital sinus).

Diagnostic Approach

- *Initial Step:* DO NOT assign gender in the delivery room.
- **Tier 1 (Stat/Immediate):**
  - *Karyotype & FISH for SRY:* Determines chromosomal sex rapidly.
  - *Serum 17-OH Progesterone (17-OHP):* Rule out CAH (draw after 48 hours of life to avoid false positives from maternal transfer).
  - *Serum Electrolytes & Glucose:* Check for hyponatremia, hyperkalemia, hypoglycemia (CAH salt-wasting).
  - *Pelvic/Abdominal USG:* Identify Mullerian structures (uterus/vagina) and locate gonads.
- **Tier 2 (Hormonal & Functional):**
  - *Anti-Mullerian Hormone (AMH):* Marker of Sertoli cell function (presence confirms functional testicular tissue).
  - *Testosterone, DHT, LH, FSH:* Baseline and post-hCG stimulation test (differentiates synthesis vs. action defects).
- **Tier 3 (Molecular/Genetics):**
  - Targeted gene panels or Whole Exome Sequencing (WES) for precise molecular diagnosis.

Management

- **Acute Medical:**
  - Treat salt-wasting CAH immediately: IV fluids, IV Hydrocortisone, oral Fludrocortisone.
- **Multidisciplinary Team (MDT):**
  - Involve Pediatric Endocrinologist, Urologist/Surgeon, Geneticist, and Psychologist.
- **Gender Assignment:**
  - Based on exact diagnosis, genital appearance, surgical options, potential for fertility, hormone responsiveness, and parental/cultural factors.
- **Surgical Interventions:**
  - *Update (AAP/Human Rights consensus):* Defer irreversible genitoplasty/cosmetic surgery until the patient is old enough to participate in decision-making (assent/consent).
  - *Early surgery indications:* Relief of severe urinary obstruction, removal of streak gonads with Y-chromosome material (high malignancy risk).
- **Endocrine Therapy:**
  - Hormone replacement therapy (HRT) at expected time of puberty (estrogen/testosterone) to induce secondary sexual characteristics and optimize bone mass.

Complications & Prognosis

- **Malignancy:** High risk of gonadoblastoma/dysgerminoma in dysgenetic gonads containing Y-chromosome material (e.g., 45,X/46,XY or Swyer syndrome). Prophylactic gonadectomy is indicated.
- **Fertility:** Often impaired; CAH females can be fertile; AIS and gonadal dysgenesis patients are infertile.
- **Psychosocial:** High risk of gender dysphoria, depression, and psychosexual distress.

Exam Summary: Must-Write Points

- CAH (21-OH deficiency) is the most common cause of DSD; always rule out life-threatening salt-wasting crisis first.
- Never assign sex hastily in the delivery room; utilize an MDT approach.
- AMH is the best marker for the presence of functional Sertoli cells (testicular tissue).
- Dysgenetic gonads with Y-chromosome material carry a high risk of malignancy and require prophylactic removal.
- Current guidelines strongly advocate delaying cosmetic genitoplasty until the patient can provide informed consent.

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63. Short notes on important electrolyte disorders in children

Subject: Endocrinology

HYPONATREMIA (Serum Na < 135 mEq/L)

Etiology (by volume status)

- **Hypovolemic:** Gastroenteritis (GE), Congenital Adrenal Hyperplasia (CAH), Cerebral Salt Wasting (CSW), diuretics.
- **Euvolemic:** SIADH, Hypothyroidism, Glucocorticoid deficiency, Water intoxication.
- **Hypervolemic:** Nephrotic syndrome, Heart failure, Cirrhosis.

Clinical Features

- Mild/Moderate: Anorexia, nausea, lethargy, headache.
- Severe (<120 mEq/L or rapid fall): Seizures, coma, brain herniation.

Diagnosis

- Serum osmolality (differentiates true vs. pseudo/translocational).
- Urine osmolality and Urine Na (SIADH: U.Osm >100 mOsm/kg, U.Na >30 mEq/L).

Management

- **Symptomatic (Seizures/Coma):** 3% NaCl (Hypertonic saline) 3–5 mL/kg IV over 10–15 minutes (raises Na by ~3–5 mEq/L).
- **Asymptomatic:** Treat underlying cause (Fluid restriction in SIADH; Normal Saline in hypovolemia).

- **Correction Limit:** Max 8–10 mEq/L/day.
- **Complication:** Rapid correction causes **Osmotic Demyelination Syndrome (ODS)** (central pontine myelinolysis).

HYPERNATREMIA (Serum Na > 145 mEq/L)

Etiology

- **Water Loss:** Diabetes Insipidus (Central/Nephrogenic), insensible losses (fever, burns), inadequate breast milk intake.
- **Sodium Excess:** Improperly mixed ORS, hypertonic saline administration.

Clinical Features

- "Doughy" skin texture, high-pitched cry, extreme irritability, hyperreflexia.
- Severe: Intracranial hemorrhage (due to brain shrinkage tearing bridging veins), thrombosis.

Management

- **Rule of thumb:** Correct slowly over 48–72 hours.
- **Target drop rate:** <0.5 mEq/L/hr (max 10–12 mEq/L/day).
- **Fluids:** Use Isotonic fluids initially if in shock; then switch to 0.45% NaCl + 5% Dextrose to replace free water deficit.
- **Complication:** Rapid correction causes **Cerebral Edema** and seizures.

HYPOKALEMIA (Serum K < 3.5 mEq/L)

Etiology

- **GI losses:** Diarrhea, vomiting (causes metabolic alkalosis and secondary renal K loss).
- **Renal losses:** Renal Tubular Acidosis (RTA), Bartter/Gitelman syndromes, Diuretics, Hyperaldosteronism.
- **Transcellular shift:** Alkalosis, Insulin therapy (classic in DKA management), Beta-2 agonists (salbutamol).

Clinical Features

- Muscle weakness (ascending), hyporeflexia, paralytic ileus, respiratory failure.
- **ECG changes:** Flattened T waves → **U waves** → ST depression → Arrhythmias.

Management

- **Mild/Asymptomatic:** Oral KCl (1–4 mEq/kg/day).
- **Severe/Symptomatic:** IV KCl.
- **IV Rules:** Max peripheral concentration = 40 mEq/L; Max central concentration = 80 mEq/L; Max infusion rate = 0.5 mEq/kg/hr.

- **Trap:** Always check and correct Magnesium; hypokalemia is refractory if hypomagnesemia is untreated.

HYPERKALEMIA (Serum K > 5.5 mEq/L)

Etiology

- **Spurious:** Hemolysis from traumatic venipuncture (most common).
- **Decreased Excretion:** Acute Kidney Injury (AKI), CAH (salt-wasting), K-sparing diuretics.
- **Transcellular shift/Release:** Acidosis, Tumor Lysis Syndrome, Rhabdomyolysis, burns.

Clinical Features

- Paresthesias, palpitations, ascending flaccid paralysis.
- **ECG changes: Tall peaked T waves** (earliest) → Loss of P wave → Widened QRS → Sine wave pattern → VFib/Asystole.

Management (Stepwise Approach)

1. **Membrane Stabilization:** IV 10% Calcium Gluconate (0.5–1 mL/kg over 5–10 mins) — *Does not lower K, prevents arrhythmias*.
2. **Intracellular Shift:**
    - Insulin + Glucose (0.1 U/kg regular insulin with 0.5 g/kg dextrose).
    - Salbutamol nebulization.
    - IV Sodium Bicarbonate (if acidotic).
3. **Elimination:** Loop diuretics (Furosemide), GI binders (Sodium polystyrene sulfonate - *use with caution due to bowel necrosis risk*), Hemodialysis (definitive).

HYPOCALCEMIA (Ionized Ca < 4.4 mg/dL or Total Ca < 8.5 mg/dL)

Etiology

- Vitamin D deficiency (Rickets), Hypoparathyroidism (DiGeorge syndrome, post-thyroidectomy), Pseudohypoparathyroidism.
- Neonatal: Prematurity, Infant of Diabetic Mother (IDM), asphyxia.

Clinical Features

- Tetany, carpopedal spasm, seizures, laryngospasm.
- **Signs:** Chvostek sign (facial nerve tapping), Trousseau sign (carpal spasm with BP cuff).
- **ECG changes: Prolonged QTc interval**.

Management

- **Acute/Symptomatic:** IV 10% Calcium Gluconate (1–2 mL/kg diluted 1:1 in D5W/NS) given slowly over 10–15 mins with HR monitoring (stop if bradycardia occurs).
- **Maintenance:** Oral Calcium + Calcitriol (Active Vitamin D).

EXAM SUMMARY (Must-Write Points)

- **Symptomatic Hyponatremia:** Give 3% NaCl (3-5 ml/kg); correct slowly to prevent **Osmotic Demyelination Syndrome**.
- **Hypernatremia:** Correct slowly (<0.5 mEq/L/hr) to prevent **Cerebral Edema**.
- **Hypokalemia ECG:** U waves. **Refractory cases:** Check and correct Magnesium.
- **Hyperkalemia ECG:** Tall peaked T waves. **First step:** IV Calcium Gluconate for cardioprotection.
- **Hypocalcemia ECG:** Prolonged QTc. Stop IV Calcium if bradycardia develops during infusion.

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64. Pediatric thyroid disorders

Subject: Endocrinology

Classification

- **Congenital Hypothyroidism (CH):** Most common preventable cause of intellectual disability.
- **Acquired Hypothyroidism:** Hashimoto thyroiditis (most common).
- **Hyperthyroidism:** Graves disease (most common).

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1. Congenital Hypothyroidism (CH)

Etiology

- **Thyroid Dysgenesis (85%):** Ectopia (most common, e.g., lingual), aplasia, hypoplasia (sporadic).
- **Dyshormonogenesis (10-15%):** Enzyme defects (e.g., Thyroid peroxidase deficiency); Autosomal Recessive. Associated with goiter (e.g., Pendred syndrome: deafness + goiter).
- **Central (Secondary):** Pituitary/hypothalamic defects (TSH/TRH deficiency).
- **Transient:** Maternal anti-thyroid drugs, maternal TSH-receptor blocking antibodies (TRBAb), iodine deficiency/excess.

Clinical Features

- **Birth:** Mostly asymptomatic (protected by maternal transplacental T4).
- **Early signs:** Prolonged neonatal jaundice (unconjugated), large posterior fontanelle (>1 cm), birth weight > 90th centile.
- **Classic signs (Late):** Coarse facies, macroglossia, umbilical hernia, hypotonia, hoarse cry, constipation, mottled/cool skin, bradycardia.

Diagnosis

- **Newborn Screening (NBS):** Heel prick at 48–72 hours of life. Primary TSH with backup T4, or primary T4 with backup TSH.
- **Confirmatory:** Venous sample for Free T4 (FT4) and TSH. (Primary CH = ↓FT4, ↑TSH).

- **Imaging:** Thyroid Ultrasound and Radionuclide scan (Tc-99m or I-123) to differentiate dysgenesis vs. dyshormonogenesis. *Do not delay treatment for imaging*.
- **Bone Age:** X-ray knee/foot shows absent distal femoral/proximal tibial epiphyses.

Management

- **Drug of choice:** Levothyroxine (L-T4).
- **Dose:** 10–15 mcg/kg/day (start immediately, ideally by 2 weeks of life).
- **Administration:** Crush tablet, mix with breastmilk/formula/water.
- **Contraindications:** Do not mix with soy formula, iron, or calcium supplements (impairs absorption).
- **Monitoring targets:** Keep TSH in lower half of normal range, FT4 in upper half. Recheck 2-4 weeks after initiation, then every 1-2 months in the first year.

Prognosis

- Excellent IQ if treated < 2 weeks of age.
- Irreversible intellectual disability if treatment delayed.

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2. Acquired Hypothyroidism (Hashimoto Thyroiditis)

Etiology & Pathophysiology

- **Mechanism:** Autoimmune destruction of thyroid gland (Chronic lymphocytic thyroiditis).
- **Associations:** Down syndrome, Turner syndrome, Type 1 Diabetes, Celiac disease, Vitiligo.

Clinical Features

- **Growth:** Severe growth deceleration/short stature (hallmark).
- **General:** Weight gain (fluid retention, not severe obesity), cold intolerance, lethargy, constipation.
- **Neck:** Firm, non-tender, pebbly goiter.
- **Puberty:** Delayed puberty.
- **Exam Buzzword:** *Van Wyk-Grumbach Syndrome* (Severe primary hypothyroidism causing precocious puberty, galactorrhea, and multicystic ovaries due to TSH cross-reacting with FSH receptors).

Diagnosis

- **Profile:** ↑ TSH, ↓ or Normal FT4 (subclinical).
- **Antibodies:** Positive Anti-Thyroid Peroxidase (Anti-TPO) and Anti-Thyroglobulin (Anti-Tg).
- **Bone Age:** Significantly delayed.

Management

- **Treatment:** L-T4 replacement.
- **Dose:** Age-dependent (approx. 2–4 mcg/kg/day in children; 1.6 mcg/kg/day in adolescents).

- **Caution:** Monitor for transient behavioral changes/poor school performance upon initiation.

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3. Hyperthyroidism (Graves Disease)

Etiology & Pathophysiology

- **Mechanism:** Autoimmune; TSH-receptor stimulating antibodies (TRAb/TSI) continuously stimulate thyroid hormone production.

Clinical Features

- **General:** Weight loss despite polyphagia, heat intolerance, diaphoresis.
- **Cardiovascular:** Tachycardia, wide pulse pressure, flow murmur.
- **Neuro/Psych:** Tremor, emotional lability, poor school performance, sleep disturbances.
- **Neck:** Diffuse, smooth goiter with audible bruit.
- **Eyes:** Exophthalmos, lid lag, stare (less severe than in adults).
- **Growth:** Accelerated linear growth and advanced bone age.

Diagnosis

- **Profile:** Suppressed TSH (<0.1 mIU/L), ↑ FT4, ↑ FT3 (T3 toxicosis common).
- **Antibodies:** Positive TRAb / TSI (Thyroid Stimulating Immunoglobulin).

Management

- **1. Medical (First-line):** Methimazole (MMI).
    - *Update/Red Flag:* Propylthiouracil (PTU) is strictly contraindicated in children due to FDA Black Box warning for fulminant hepatic failure.
    - *Adverse effects:* Agranulocytosis (warn about fever/sore throat), rash, transaminitis.
- **2. Symptomatic:** Beta-blockers (Propranolol) for severe tachycardia/tremors until euthyroid.
- **3. Definitive Therapy (if medical failure/relapse):**
    - **Radioactive Iodine (RAI - I-131):** Preferred in older children (>10 years).
    - **Surgery:** Near-total thyroidectomy (Indicated for huge goiters, severe ophthalmopathy, or children <10 years failing MMI).

Neonatal Graves Disease

- **Pathophysiology:** Transplacental passage of maternal TRAb (even if mother is euthyroid/post-ablation).
- **Clinical:** Fetal tachycardia, IUGR, premature closure of fontanelles (craniosynostosis), heart failure, irritability.
- **Management:** Methimazole + Lugol's iodine + Propranolol.
- **Prognosis:** Self-limiting over 3–4 months as maternal antibodies clear.

Exam Summary (Must-Write Points)

- **CH Treatment:** L-T4 @ 10–15 mcg/kg/day must be started before 2 weeks of age to prevent irreversible intellectual disability.
- **CH Screening:** TSH/T4 screening via heel prick at 48-72 hours; never delay treatment for confirmatory imaging.
- **Acquired Hypothyroidism:** Hallmark is falling off the growth chart (short stature) + firm goiter + Anti-TPO antibodies.
- **Graves Treatment:** Methimazole is the only oral anti-thyroid drug used in pediatrics; PTU is absolutely contraindicated (hepatotoxicity).
- **Van Wyk-Grumbach:** Profound hypothyroidism presenting paradoxically as precocious puberty.

Gastroenterology / Hepatology

65. Chronic diarrhea in toddlers

Subject: Gastroenterology / Hepatology

Definition

- **Chronic Diarrhea:** Alteration in stool consistency and/or frequency lasting **> 14 days**.
- **Toddler's Diarrhea:** Also known as Chronic Nonspecific Diarrhea (CNSD); the most common functional cause of chronic diarrhea in children aged 1–3 years.

Etiology (Toddler Age Group)

- **Functional (Most Common):** Toddler's diarrhea (CNSD).
- **Infectious:** Post-infectious enteropathy, *Giardia lamblia*, *Clostridioides difficile*.
- **Malabsorption:** Celiac disease, Cystic fibrosis, Disaccharidase deficiency (Lactose/Sucrase-isomaltase).
- **Allergic/Immune:** Cow's milk protein allergy (CMPA), Eosinophilic gastroenteropathies.
- **Other Organic:** Inflammatory Bowel Disease (rare in toddlers but must not be missed), Immunodeficiency.

Pathophysiology (Toddler's Diarrhea)

- **Dietary Imbalance:** Excessive intake of clear fluids and fruit juices (especially apple, pear, prune).
- **Osmotic Load:** High fructose/sorbitol content in juice exceeds absorptive capacity, drawing water into the lumen.
- **Rapid Transit:** Low dietary fat intake (fat normally triggers cholecystokinin release, delaying gastric emptying; low fat = rapid transit).
- **Immaturity:** Exaggerated gastrocolic reflex and altered intestinal motility.

Clinical Features

- **Classic CNSD Presentation:** Age 6–36 months.

- **Stool Pattern:** 3–10 loose, mushy, or watery stools per day.
- **Timing:** Occurs strictly during waking hours (no nocturnal diarrhea).
- **Appearance:** Often contains undigested food particles (classic "peas and carrots" stool) and mucus; **no blood**.
- **Systemic:** Child is active, playful, with a normal appetite.
- **Growth: Normal weight gain and linear growth** (Hallmark feature).

Red Flags (Indicating Organic Disease)

- Failure to thrive (FTT) / crossing percentiles downward.
- Nocturnal diarrhea (wakes the child from sleep).
- Blood or pus in the stool.
- Systemic symptoms: Persistent fever, severe vomiting, rash, or joint pain.
- Severe abdominal distension or localized pain.
- Onset temporarily related to introduction of gluten or cow's milk.

Diagnosis

- **Clinical Diagnosis:** Primarily based on a classic history and normal growth chart.
- **Dietary History:** Quantify juice, water, fat, and fiber intake.
- **First-line Investigations (if organic disease suspected):**
    - **Stool:** Routine microscopy (Ova & Parasites for *Giardia*), pH and reducing substances (carbohydrate malabsorption).
    - **Fecal Calprotectin:** Highly sensitive to rule out mucosal inflammation (IBD).
    - **Blood:** CBC (anemia), CRP/ESR.
- **Specific Workup (Guided by Red Flags):**
    - **Celiac Screen:** Total Serum IgA + Anti-Tissue Transglutaminase (tTG) IgA (Note: Child must be consuming a gluten-containing diet).
    - **Cystic Fibrosis:** Sweat chloride test (if FTT, respiratory symptoms, or greasy stools present).

Management

- **Reassurance:** Validate parental concerns but firmly explain the benign, functional nature of CNSD.
- **Dietary Modification (The "4 Fs"):**
    - **F**ruit Juice: Discontinue or strictly limit. *AAP 2017 Guideline:* Limit 100% fruit juice to ≤ 4 oz/day for toddlers (1–3 years).
    - **F**at: Increase dietary fat to 35–40% of total calories (e.g., whole milk, butter, avocados) to slow intestinal transit.
    - **F**iber: Normalize dietary fiber to add bulk to stools (Age in years + 5g = daily requirement).

- **F**luid: Restrict excessive grazing on clear fluids/water between meals.

- **Medical Therapy:**
  - **Contraindicated:** Antidiarrheals (e.g., loperamide) and anticholinergics are not recommended in toddlers due to toxicity risks.
  - **Probiotics:** *Saccharomyces boulardii* or *Lactobacillus rhamnosus* GG may help if a post-infectious component is suspected, but lack strong evidence for pure CNSD.

Complications & Prognosis

- **Prognosis:** Excellent. CNSD is self-limiting and typically resolves spontaneously by age 4–5 years (often coinciding with toilet training).
- **Complications:** The major risk is **iatrogenic Failure to Thrive** caused by parents placing the child on overly restrictive elimination diets (e.g., dairy-free, gluten-free) without medical supervision.

Exam Summary

- **Toddler's diarrhea (CNSD)** is the most common cause of chronic diarrhea in ages 1–3.
- **Diagnostic hallmark:** Frequent loose stools with undigested food, but **normal growth and no nocturnal symptoms**.
- **Red Flags:** FTT, blood in stool, and nocturnal diarrhea mandate a workup for organic causes (Celiac, Giardia, CMPA, CF).
- **Management Mnemonic:** The **4 Fs** (restrict **F**ruit juice/excess **F**luid, increase **F**at and **F**iber).
- **Avoid:** Unnecessary dietary restrictions (prevents iatrogenic FTT) and antidiarrheal medications.

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66. Persistent diarrhea management

Subject: Gastroenterology / Hepatology

Definition

- **Persistent Diarrhea (PD):** Diarrhea of acute onset (presumed infectious) lasting ≥14 days.
- **Differentiate:** Chronic diarrhea (often insidious onset, non-infectious/congenital malabsorptive etiologies).

Etiology & Risk Factors

- **Pathogens:** Enteroaggregative *E. coli* (EAEC), Enteropathogenic *E. coli* (EPEC), *Shigella*, *Cryptosporidium*, *Giardia*, *Entamoeba histolytica*.
- **Host Risk Factors:** Severe acute malnutrition (SAM), young age (<18 months), immunodeficiency (HIV, zinc/vitamin A deficiency), lack of exclusive breastfeeding.
- **Iatrogenic:** Injudicious use of empirical antibiotics or antimotility drugs during acute diarrhea.

Pathophysiology

- **Vicious Cycle:** Acute infection ⇒intestinal mucosal injury ⇒villous atrophy ⇒secondary lactase deficiency & bile acid deconjugation ⇒malabsorption/osmotic diarrhea ⇒worsening malnutrition ⇒impaired gut immunity ⇒persistent infection.

Clinical Features

- **Primary:** Frequent loose stools ≥14 days.
- **Assessment:** Signs of dehydration (sunken eyes, delayed skin pinch, lethargy).
- **Nutritional:** Weight loss, growth faltering, visible severe wasting, edema (kwashiorkor).
- **Systemic:** Signs of concurrent infections (pneumonia, UTI, sepsis).

Investigations

- **Stool Analysis:** Routine microscopy (RBCs, WBCs, ova, cysts, parasites), pH (<5.5 suggests carbohydrate malabsorption), reducing substances (>0.5% indicates lactose intolerance).
- **Stool Culture & Sensitivity:** To isolate *Shigella*, *Salmonella*, *Campylobacter*.
- **Blood:** CBC, electrolytes (K+, Na+), acid-base status (ABG/VBG), HIV serology (if clinically indicated).

Management (WHO / IAP Guidelines)

- **1. Resuscitation & Hydration**
    - Assess and correct dehydration using standard WHO Plan A, B, or C.
    - Prefer Oral Rehydration Solution (low-osmolarity ORS). Use IV fluids (Ringer's Lactate) only for severe dehydration or shock.
- **2. Nutritional Therapy (Core Pillar)**
    - **Goal:** Provide adequate calories (at least 110 kcal/kg/day) while avoiding malabsorbed nutrients.
    - **Diet A (Reduced Lactose):** First-line for mild/moderate cases. Max lactose 2–3 g/kg/day. Use yogurt/curd, cereals, cooked vegetables, and breastmilk. Monitor for 7 days.
    - **Diet B (Lactose-Free):** If Diet A fails (diarrhea worsens or ≥10 stools/day). Milk-free diet. Provide calories via chicken, egg, rice, soy-based protein, and oil. Monitor for 7 days.
    - **Diet C (Monosaccharide-based):** If Diet B fails or in SAM. Excludes lactose and complex carbohydrates. Elemental formulas containing glucose, amino acids, and MCT oil.
    - *Note:* Breastfeeding must continue uninterrupted across all diets.
- **3. Micronutrient Supplementation**
    - **Zinc:** Mandatory. 10 mg/day (<6 months) or 20 mg/day (>6 months) for 14 days. Promotes enterocyte regeneration.
    - **Vitamin A:** Single high dose as per age (50,000 to 200,000 IU) if not given in the last 1 month.
    - **Multivitamins:** Supplement folic acid, copper, magnesium, and iron (iron *only* after diarrhea resolves and appetite returns).

- **4. Antimicrobial Therapy**
    - **Routine antibiotics:** Strictly contraindicated (worsen dysbiosis).
    - **Indications for antibiotics:** Blood in stool (*Shigella* - use Cefixime/Ceftriaxone/Azithromycin), stool microscopy positive for *Giardia* or *Amoeba* (use Metronidazole), or suspected systemic sepsis.

Complications

- Severe malnutrition (SAM).
- Electrolyte derangements (severe hypokalemia, hyponatremia).
- Secondary systemic infections (sepsis, pneumonia).
- Death (PD accounts for up to 15% of all diarrhea-related pediatric deaths).

Prevention

- Exclusive breastfeeding for the first 6 months.
- Timely and hygienic complementary feeding.
- Vaccination: Rotavirus and Measles vaccines drastically reduce PD incidence.
- WASH practices (Water, Sanitation, and Hygiene).

Exam Summary

- **Definition:** Presumed infectious diarrhea lasting ≥14 days.
- **Pathogenesis:** Mucosal injury ⇒Secondary lactose intolerance ⇒Malnutrition ⇒Vicious cycle.
- **Dietary Steps (WHO):** Diet A (Reduced lactose) ⇒Diet B (Lactose-free) ⇒Diet C (Elemental/Monosaccharide).
- **Mandatory Rx:** Zinc (14 days), Vitamin A, uninterrupted breastfeeding.
- **Trap:** Do NOT prescribe empirical antibiotics or antimotility agents (Loperamide is strictly contraindicated).

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67. Malabsorption syndromes in children

Subject: Gastroenterology / Hepatology

Definition

- Defective digestion (maldigestion) or absorption (malabsorption) of dietary nutrients, vitamins, and minerals leading to impaired growth and specific deficiency states.

Etiology (By Phase of Absorption)

- **Luminal Phase (Defective Hydrolysis/Solubilization):**
    - *Pancreatic insufficiency:* Cystic Fibrosis (most common), Shwachman-Diamond syndrome, Chronic pancreatitis.

- *Bile salt deficiency:* Cholestasis (Biliary atresia, neonatal hepatitis), Short bowel syndrome (terminal ileum resection), Small Intestinal Bacterial Overgrowth (SIBO - deconjugates bile salts).

- **Mucosal Phase (Defective Epithelial Transport):**
  - *Loss of surface area:* Celiac disease, Cow's Milk Protein Allergy (CMPA), Short bowel syndrome, Rotavirus/post-enteritis syndrome.
  - *Infection/Inflammation:* Giardiasis, Crohn's disease, Tropical sprue, HIV enteropathy.
  - *Specific defects:* Acrodermatitis enteropathica (Zinc), Congenital lactase deficiency.
- **Post-Absorptive/Transport Phase (Defective Lymphatic/Vascular Delivery):**
  - Intestinal lymphangiectasia (primary or secondary to right heart failure).
  - Abetalipoproteinemia (defective chylomicron formation).

Clinical Features

- **Gastrointestinal:**
  - Chronic diarrhea (>14 days).
  - Steatorrhea: Pale, bulky, foul-smelling, greasy stools that are difficult to flush.
  - Abdominal distension, excessive flatulence, borborygmi.
- **Growth & Development:**
  - Failure to thrive (FTT), severe weight loss, muscle wasting (buttocks/thighs).
  - Short stature, delayed puberty.
- **Specific Micronutrient Deficiencies:**
  - *Protein:* Peripheral edema, ascites (Kwashiorkor-like state).
  - *Iron/Folate/B12:* Pallor, fatigue, glossitis, stomatitis.
  - *Vitamin A:* Night blindness, Bitot's spots, xerophthalmia.
  - *Vitamin D & Calcium:* Rickets, osteopenia, tetany (Chvostek/Trousseau signs).
  - *Vitamin E:* Spinocerebellar ataxia, peripheral neuropathy, hemolytic anemia.
  - *Vitamin K:* Bleeding diathesis, easy bruising, prolonged PT/INR.
  - *Zinc:* Periorificial rash, alopecia, diarrhea.

Diagnosis

- **First-Line / Screening:**
  - *Stool Routine:* Ova and parasites (Giardia cysts/trophozoites).
  - *Stool pH & Reducing substances:* pH <5.5 and positive reducing substances indicate carbohydrate malabsorption.
  - *Stool Fat Exam:* Sudan III stain (qualitative screening for steatorrhea).
  - *Blood Basics:* CBC, reticulocyte count, peripheral smear, total protein, albumin, LFTs, Ca, PO4, ALP, PT/INR.

- **Specific / Confirmatory Tests:**
    - *Celiac Disease:* Total serum IgA + IgA anti-tissue transglutaminase (tTG).
        - **ESPGHAN 2020 Update:** Biopsy can be avoided if IgA tTG is >10x Upper Limit of Normal + positive Endomysial Antibodies (EMA) in a second sample.
    - *Cystic Fibrosis:* Sweat chloride test (>60 mEq/L is diagnostic).
    - *Pancreatic Exocrine Insufficiency:* Fecal elastase-1 (<200 µg/g stool).
    - *SIBO:* Glucose or Lactulose breath test.
    - *Protein-Losing Enteropathy:* Elevated fecal alpha-1 antitrypsin clearance.
- **Gold Standard:**
    - *Upper GI Endoscopy with Biopsy:* Duodenal biopsies show villous atrophy, crypt hyperplasia, intraepithelial lymphocytosis (Celiac) or dilated lacteals (Lymphangiectasia).

Management

- **Nutritional Rehabilitation:**
    - High-calorie, high-protein diet (120–150% of RDA for ideal body weight).
    - Use Medium Chain Triglycerides (MCT) oil for fat malabsorption/lymphangiectasia (absorbs directly into portal vein, bypassing lymphatics).
- **Micronutrient Supplementation:**
    - Water-miscible forms of fat-soluble vitamins (A, D, E, K).
    - Iron, Zinc, Calcium, and Folic acid supplementation.
- **Disease-Specific Therapy:**
    - *Celiac Disease:* Strict, lifelong Gluten-Free Diet (GFD) - avoid Wheat, Barley, Rye (Oats permitted if uncontaminated).
    - *Cystic Fibrosis:* Pancreatic Enzyme Replacement Therapy (PERT) with meals + high-fat diet.
    - *CMPA:* Extensively Hydrolyzed Formula (eHF); if severe/refractory, use Amino Acid-based formula (AAF).
    - *Infections:* Metronidazole (Giardia), Rifaximin or Metronidazole (SIBO).
    - *Lactose Intolerance:* Lactose-free formula/diet.

Complications

- Severe Acute Malnutrition (SAM) and immunosuppression.
- Refractory rickets and permanent short stature.
- Osteoporosis and pathological fractures (chronic Vit D/Ca malabsorption).
- Enteropathy-associated T-cell lymphoma (rare late complication of untreated Celiac).

Exam Summary

- **Phase-based approach:** Always classify into luminal (CF), mucosal (Celiac), and transport (Lymphangiectasia) defects.
- **Celiac Buzzwords:** Villous atrophy, anti-tTG IgA, lifelong GFD, ESPGHAN no-biopsy criteria (>10x tTG + EMA).
- **CF Buzzwords:** Steatorrhea + recurrent pneumonia, low fecal elastase, sweat chloride >60, PERT.
- **MCT Oil Indication:** Bypasses lymphatics; crucial for managing intestinal lymphangiectasia and severe cholestasis.
- **Steatorrhea screening:** Sudan III stain (qualitative); Fecal elastase-1 is the best non-invasive test for pancreatic function.

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68. Infantile and neonatal cholestasis

Subject: Gastroenterology / Hepatology

Definition

- Prolonged conjugated (direct) hyperbilirubinemia occurring in the newborn period or early infancy.
- **NASPGHAN 2017 Update:** Defined as serum conjugated bilirubin >1.0 mg/dL (17 µmol/L) regardless of the total bilirubin level.
- *Previously:* Defined as direct bilirubin >20% of total (if total >5 mg/dL) or >1.0 mg/dL (if total <5 mg/dL).
- **Red Flag:** Any jaundice persisting beyond 14 days (term) or 21 days (preterm) mandates fractionation of bilirubin.

Etiology

Extrahepatic (Obstructive) - 40%

- Biliary Atresia (BA) – Most common surgical cause; most common indication for pediatric liver transplant.
- Choledochal cyst.
- Inspissated bile syndrome (often post-hemolysis).

Intrahepatic (Hepatocellular) - 60%

- **Infections:** Sepsis, UTI (E. coli), TORCH (CMV, Syphilis, Toxoplasmosis, Rubella).
- **Metabolic:** Galactosemia, Tyrosinemia type 1, Alpha-1 antitrypsin (A1AT) deficiency (most common genetic cause), Cystic Fibrosis.
- **Genetic/Familial:** Alagille syndrome, Progressive Familial Intrahepatic Cholestasis (PFIC).
- **Endocrine:** Hypothyroidism, Panhypopituitarism (septo-optic dysplasia).
- **Toxic:** Total Parenteral Nutrition (TPN) associated cholestasis.
- **Idiopathic:** Neonatal giant cell hepatitis (diagnosis of exclusion).

Pathophysiology

- Impaired bile formation (hepatocellular) or obstructed bile flow (ductal).
- Retention of bile acids → Hepatocyte apoptosis, localized inflammation, and progressive fibrosis/cirrhosis.
- Lack of bile in gut → Fat malabsorption, fat-soluble vitamin (A, D, E, K) deficiency, and acholic stools.
- Retention of bilirubin → Jaundice and dark urine.

Clinical Features

- **Classic Triad:** Jaundice, dark urine (stains diaper), pale/acholic stools.
- **Hepatomegaly:** Firm/hard liver suggests BA or cirrhosis; soft suggests hepatitis.
- **Splenomegaly:** Indicates early portal hypertension.
- **Bleeding diathesis:** Intracranial or mucosal bleeding due to Vitamin K deficiency.
- **Failure to thrive:** Due to severe fat malabsorption.
- **Syndromic clues:**
    - *Alagille:* Butterfly vertebrae, peripheral pulmonary stenosis, triangular facies, posterior embryotoxon.
    - *A1AT deficiency:* Positive family history, early emphysema in relatives.
    - *Galactosemia:* Cataracts, E. coli sepsis, vomiting after milk feeds.

Diagnosis

First-Line Investigations

- **Fractionated Bilirubin:** Confirm conjugated hyperbilirubinemia.
- **LFTs:** AST, ALT, ALP.
- **GGT (Crucial discriminator):**
    - *High GGT:* Biliary atresia, Alagille syndrome, A1AT deficiency, PFIC type 3.
    - *Low/Normal GGT:* PFIC types 1 and 2, Bile acid synthesis defects.
- **Coagulation profile:** PT/INR, aPTT (correctable with parenteral Vitamin K suggests malabsorption; uncorrectable suggests liver failure).

Etiology-Specific Tests

- **Metabolic:** Urine reducing substances (Galactosemia), A1AT phenotype (PiZZ), Thyroid profile (T4, TSH).
- **Infectious:** Urine culture (rule out UTI), Viral PCRs (CMV).

Imaging & Histology

- **USG Abdomen (Fasting for 4 hours):** Evaluate gallbladder size/presence, rule out choledochal cyst.
    - *Buzzword for BA:* "Triangular cord sign" (fibrous cone at porta hepatis), absent/contracted gallbladder.

- **Hepatobiliary Scintigraphy (HIDA):** Demonstrates hepatic uptake with absent bowel excretion in BA (high sensitivity, low specificity; rarely delays biopsy now).
- **Liver Biopsy (Percutaneous):** Most definitive pre-operative test.
    - *Biliary Atresia:* Bile duct proliferation, portal tract edema/fibrosis, bile plugs.
    - *Neonatal Hepatitis:* Multinucleated giant cells, lobular disarray, inflammatory infiltrates.
- **Intraoperative Cholangiogram (IOC):** Gold standard to confirm/exclude Biliary Atresia.

Management

1. Medical & Supportive (All causes)

- **Nutrition:** 125–150% of RDA for calories. Use formulas enriched with Medium-Chain Triglycerides (MCT) as they do not require bile salts for absorption (e.g., Pregestimil, Pepti-Junior).
- **Fat-Soluble Vitamins (ADEK):** Provide water-miscible forms.
    - *Vit K:* 2.5–5 mg IM/IV immediately if bleeding/prolonged PT, then oral maintenance.
- **Choleretics:** Ursodeoxycholic acid (UDCA) 20–30 mg/kg/day to stimulate bile flow and displace toxic hydrophobic bile acids.
- **Pruritus relief:** Rifampin, Cholestyramine, Naltrexone (if older/refractory).

2. Specific Therapy

- *Galactosemia:* Stop lactose; start soy-based formula.
- *Tyrosinemia:* Nitisinone (NTBC) + Tyrosine/Phenylalanine-restricted diet.
- *Hypothyroidism:* Levothyroxine.
- *Sepsis/UTI:* Appropriate IV antibiotics.

3. Surgical Therapy

- **Kasai Portoenterostomy (for BA):** Roux-en-Y loop of jejunum anastomosed to porta hepatis.
    - *Timing is critical:* Best results if done **<60 days** of life. Success drops precipitously after 90 days.
- **Liver Transplantation:** Definitive treatment for failed Kasai, decompensated cirrhosis, or specific metabolic diseases (e.g., severe A1AT).

Complications

- Progressive biliary cirrhosis.
- Portal hypertension (variceal bleeding, ascites, hypersplenism).
- Ascending cholangitis (post-Kasai).
- Metabolic bone disease (Rickets) due to Vitamin D malabsorption.
- Neuropathy/ataxia due to Vitamin E deficiency.

Prognosis

- **Neonatal Hepatitis:** 70-80% recover completely with supportive care.

- **Biliary Atresia:** Without surgery, fatal by age 2. With Kasai <60 days, 1/3 achieve normal bile flow long-term, 1/3 need transplant in childhood, 1/3 need transplant in infancy. Ultimately, 70-80% will require a liver transplant in their lifetime.

Exam Summary (Must-Write Points)

- **Definition:** Conjugated bilirubin >1.0 mg/dL is abnormal; any jaundice >14 days needs fractionated bilirubin.
- **Key Clinical Clue:** Always check stool color (acholic/pale) and urine color (dark).
- **GGT Utility:** Differentiates high GGT (BA, Alagille) from low/normal GGT (PFIC 1/2) cholestasis.
- **Biliary Atresia:** Suspect if acholic stools + high GGT + triangular cord sign on USG.
- **Kasai Timing:** Must be performed before 60 days of life for optimal bile drainage.
- **Supportive Rx:** MCT oil formula and water-miscible ADEK vitamins are mandatory.

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69. Neonatal hepatitis versus biliary atresia

Subject: Gastroenterology / Hepatology

Overview

- **Neonatal Cholestasis:** Conjugated hyperbilirubinemia (Conjugated bilirubin >1.0 mg/dL if total <5.0 mg/dL, or >20% of total bilirubin).
- **Biliary Atresia (BA):** Progressive, idiopathic fibro-obliterative disease of the extrahepatic biliary tree. Surgical emergency.
- **Neonatal Hepatitis (NH):** Broad term for hepatocellular injury/inflammation; often idiopathic (giant cell hepatitis) or secondary to specific medical causes. Medical management.
- **Core Dilemma:** Differentiating surgical BA from medical NH rapidly to perform Kasai portoenterostomy before 60 days of life.

Etiology & Pathogenesis

- **Biliary Atresia:**
    - *Etiology:* Unknown. Suspected viral trigger (CMV, Reovirus type 3, Rotavirus) + dysregulated immune response in a genetically susceptible host.
    - *Pathology:* Progressive inflammatory obliteration of extrahepatic ducts → bile stasis → rapidly progressive secondary biliary cirrhosis.
- **Neonatal Hepatitis:**
    - *Etiology:* Idiopathic (most common), Infections (TORCH, Syphilis, sepsis), Metabolic (Alpha-1 antitrypsin deficiency, Galactosemia, Tyrosinemia), Endocrine (Hypothyroidism).
    - *Pathology:* Hepatocellular necrosis, lobular disarray, and giant cell transformation → impaired bile excretion.

Clinical Differentiation

- **Biliary Atresia:**

- **Birth details:** Usually full-term, normal birth weight.
- **Appearance:** Thrives initially, looks well ("happy jaundiced baby").
- **Stools:** Persistently acholic (white/pale/clay-colored) from onset or progressing over weeks.
- **Urine:** Dark yellow (stains diaper).
- **Abdomen:** Hepatomegaly (firm to hard consistency); splenomegaly develops late (portal hypertension).

- **Neonatal Hepatitis:**
  - **Birth details:** Often premature, IUGR, or low birth weight.
  - **Appearance:** Ill-looking, lethargic, poor feeding.
  - **Stools:** Fluctuating color (intermittently pale and yellow).
  - **Abdomen:** Hepatosplenomegaly early (liver is soft/normal consistency).
  - **Associated features:** Microcephaly, chorioretinitis, purpura (if TORCH).

Diagnostic Workup

- **Biochemical Profile:**
  - *BA:* Disproportionately elevated GGT and Alkaline Phosphatase (ALP). Mild-moderate AST/ALT elevation.
  - *NH:* Markedly elevated AST/ALT. Normal or mildly elevated GGT/ALP.
- **Ultrasonography (Fasting for 4 hours):**
  - *BA:* **Triangular cord sign** (fibrous cone at porta hepatis - highly specific), absent or small gallbladder (<1.5 cm), absent gallbladder contraction post-feed.
  - *NH:* Normal biliary tree, normal/contracting gallbladder.
- **Hepatobiliary Scintigraphy (HIDA/Tc-99m DISIDA scan):**
  - *Pre-requisite:* Pre-treat with Phenobarbital (5 mg/kg/day for 3–5 days) to enhance bile flow.
  - *BA:* Normal hepatic uptake, **absent intestinal excretion** at 24 hours.
  - *NH:* Sluggish/delayed hepatic uptake, **present intestinal excretion** (eventually appears in bowel).
- **Liver Biopsy (Gold Standard):**
  - *BA:* **Bile duct proliferation**, bile plugs in portal tracts, portal tract edema/fibrosis, preserved lobular architecture.
  - *NH:* **Giant cell transformation** (fusion of hepatocytes), lobular disarray, hepatocellular necrosis, focal inflammatory infiltrates.

Management

- **Biliary Atresia:**
  - **Surgical:** Kasai portoenterostomy (Roux-en-Y hepatoportoenterostomy).

- **Timing:** Optimal outcome if done **<60 days of life** (success drops drastically >90 days).
- **Post-op:** Prophylactic antibiotics (prevent ascending cholangitis), Ursodeoxycholic acid (UDCA), steroids (controversial/center-dependent).
- **Definitive:** Liver transplantation (if Kasai fails or cirrhosis develops).

- **Neonatal Hepatitis:**
  - **Specific:** Treat underlying cause (e.g., Galactose-free diet for galactosemia, thyroxine for hypothyroidism).
  - **Medical/Supportive (Both BA & NH require this):**
    - *Choleretics:* UDCA (20–30 mg/kg/day).
    - *Nutrition:* High-calorie formula with Medium Chain Triglycerides (MCTs) which bypass lymphatic absorption.
    - *Vitamins:* Water-miscible fat-soluble vitamins (ADEK).

Complications & Prognosis

- **Biliary Atresia:**
  - *Complications:* Ascending cholangitis (most common post-Kasai), portal hypertension, bleeding varices, biliary cirrhosis, fat-soluble vitamin deficiency (rickets, coagulopathy).
  - *Prognosis:* Without surgery, fatal by 2 years. Even with successful Kasai, ~80% eventually require a liver transplant by adulthood.
- **Neonatal Hepatitis:**
  - *Complications:* Chronic liver disease, cirrhosis (if metabolic/alpha-1 antitrypsin).
  - *Prognosis:* Idiopathic cases generally have a good prognosis (80% recover completely without sequelae).

Prevention & Screening Updates

- **AAP/NASPGHAN Guidelines:** All infants jaundiced at **2 weeks of age** must be screened with fractionated (total and direct) bilirubin.
- **Stool Color Cards:** Implemented globally (e.g., Taiwan, AAP endorsed) to empower parents to identify acholic stools early, drastically reducing the age of BA diagnosis.

Exam Summary (Must-Write Points)

- **BA** = Well baby, firm liver, persistently acholic stools, high GGT.
- **NH** = Ill/IUGR baby, soft liver, fluctuating stools, high AST/ALT.
- **USG Buzzword:** Triangular cord sign = Biliary Atresia.
- **Biopsy Buzzwords:** Bile duct proliferation = BA; Giant cell transformation = NH.
- **Crucial Timeline:** BA is a surgical emergency requiring Kasai portoenterostomy ideally before 60 days of life to prevent irreversible secondary biliary cirrhosis.

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70. Portal hypertension in children

Subject: Gastroenterology / Hepatology

Definition

- **Absolute pressure:** Portal vein pressure > 10–12 mmHg (Normal: 1–4 mmHg)
- **Gradient:** Hepatic Venous Pressure Gradient (HVPG) > 5 mmHg
- **Clinically Significant Portal Hypertension (CSPH):** HVPG ≥ 10 mmHg (threshold for variceal formation)

Etiology

- **Pre-hepatic (Presinusoidal):**
    - Extrahepatic Portal Vein Obstruction (EHPVO) — *Most common cause in India/developing nations*
    - Risk factors: Umbilical sepsis/catheterization, severe dehydration, prothrombotic states (Protein C/S deficiency)
- **Hepatic:** *Most common cause in developed nations*
    - *Presinusoidal:* Congenital hepatic fibrosis, Schistosomiasis
    - *Sinusoidal:* Cirrhosis (Biliary atresia, Wilson disease, Autoimmune hepatitis, Viral hepatitis)
    - *Postsinusoidal:* Veno-occlusive disease (Sinusoidal Obstruction Syndrome)
- **Post-hepatic:**
    - Budd-Chiari syndrome (hepatic vein thrombosis)
    - Right-sided heart failure, constrictive pericarditis

Pathophysiology

- **Ohm's Law equivalent:** Pressure = Flow (Q) × Resistance (R)
- **Increased Resistance (Primary event):** Structural (fibrosis, thrombosis, nodular regeneration) and dynamic (hepatic stellate cell contraction)
- **Increased Flow (Secondary event):** Splanchnic vasodilation (mediated by excessive nitric oxide) → hyperdynamic circulatory state → exacerbates portal pressure
- **Collateral formation:** Shunting of blood to systemic circulation (gastroesophageal varices, caput medusae, anorectal varices)

Clinical Features

- **Splenomegaly:** Earliest and most consistent sign; massive in EHPVO
- **GI Bleeding:** Painless, often massive hematemesis/melena (ruptured esophageal or gastric varices)
- **Hypersplenism:** Thrombocytopenia (first to appear), leukopenia, anemia
- **Abdominal signs:** Dilated superficial abdominal veins (flow away from umbilicus), ascites

- **Signs of Chronic Liver Disease (CLD):** Jaundice, spider angiomas, palmar erythema (present in hepatic causes; *absent in EHPVO*)
- **Growth failure:** Common in chronic EHPVO (portal biliopathy and malabsorption)

Diagnosis

- **Laboratory:** CBC (cytopenias indicate hypersplenism), LFTs (normal in EHPVO, deranged in cirrhosis), Coagulation profile (PT/INR)
- **USG Abdomen with Doppler (1st line):**
    - Detects portal vein thrombosis, flow reversal (hepatofugal flow), collateral vessels
    - *Buzzword:* "Cavernous transformation" of the portal vein (diagnostic of EHPVO)
- **Upper GI Endoscopy (Gold Standard):** Grades esophageal/gastric varices and detects portal hypertensive gastropathy
- **CT/MRI Portovenography:** Essential for vascular mapping prior to shunt surgery
- **Transient Elastography (FibroScan):** Non-invasive assessment of liver stiffness (Baveno VII criteria to predict CSPH and rule out high-risk varices)

Management: Acute Variceal Bleed

- **Resuscitation:** ABCs, two large-bore IV lines, cautious PRBC transfusion (Target Hb: 7–8 g/dL; over-transfusion worsens portal pressure)
- **Vasoactive drugs (Start immediately):**
    - Octreotide (bolus 1–2 mcg/kg, then 1–2 mcg/kg/hr infusion) OR
    - Terlipressin (proven mortality benefit in adults/older children)
- **Antibiotic prophylaxis:** IV Ceftriaxone (prevents SBP and rebleeding; *mandatory even in non-cirrhotics*)
- **Endoscopic intervention (within 12–24 hours):**
    - Endoscopic Band Ligation (EBL): Treatment of choice
    - Endoscopic Sclerotherapy (EST): Used if EBL technically difficult in small infants
- **Rescue therapy (Refractory bleed):** Balloon tamponade (Sengstaken-Blakemore tube - max 24 hrs) or Transjugular Intrahepatic Portosystemic Shunt (TIPS)

Management: Prophylaxis & Definitive

- **Primary Prophylaxis (Prevent first bleed):** Non-selective beta-blockers (NSBB - Propranolol or Carvedilol) OR Endoscopic band ligation
- **Secondary Prophylaxis (Prevent rebleed):** Combination of EBL + NSBB
- **Definitive Surgical Management:**
    - *EHPVO:* **Meso-Rex Bypass** (Rex shunt) is the gold standard/curative (restores physiological portal flow to the liver, reversing hypersplenism and growth failure)
    - *Non-shuntable EHPVO/Refractory:* Portosystemic shunts (e.g., Warren distal splenorenal shunt)

- *Cirrhosis:* Liver transplantation (curative for the underlying liver disease and portal hypertension)

Complications

- Variceal hemorrhage (esophageal, gastric, ectopic)
- Hepatic encephalopathy (precipitated by bleeding/constipation)
- Ascites and Spontaneous Bacterial Peritonitis (SBP)
- Hepatopulmonary syndrome (hypoxemia, intrapulmonary vascular dilations)
- Portopulmonary hypertension (pulmonary arterial hypertension)
- Portal biliopathy (biliary strictures due to compression by cavernoma in EHPVO)

Exam Summary

- **EHPVO vs Cirrhosis:** EHPVO has massive splenomegaly, normal liver function, and no encephalopathy. Cirrhosis has stigmata of CLD and deranged LFTs.
- **Cavernous transformation** on USG Doppler is the hallmark of EHPVO.
- **Acute bleed triad:** Restrictive transfusion (Hb 7-8) + Vasoactive drug (Octreotide) + Antibiotic (Ceftriaxone) before endoscopy.
- **Meso-Rex bypass** is the physiological and curative surgery for EHPVO.
- **Thrombocytopenia** is the most sensitive non-invasive indicator of portal hypertension and hypersplenism.

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71. Hepatic encephalopathy in children

Subject: Gastroenterology / Hepatology

Definition

- Reversible spectrum of neurocognitive and psychiatric abnormalities occurring in acute liver failure (ALF) or chronic liver disease (CLD).

Classification (AASLD/ISHE)

- **Type A:** Associated with Acute Liver Failure (ALF). High risk of rapid cerebral edema.
- **Type B:** Associated with Portosystemic Bypass (shunts) without intrinsic liver disease.
- **Type C:** Associated with Cirrhosis/CLD. Subdivided into episodic, persistent, or covert (minimal).

Pathophysiology

- **Ammonia Hypothesis:** Failing liver/shunts fail to clear gut-derived ammonia ⇒crosses blood-brain barrier.
- **Astrocyte Swelling:** Ammonia is detoxified into glutamine within astrocytes ⇒osmotic gradient ⇒astrocyte swelling (cerebral edema).
- **Neuroinflammation:** Systemic inflammation and cytokines (TNF-α, IL-6) increase BBB permeability to ammonia.

- **Histopathology:** Alzheimer Type II astrocytes (enlarged, pale nuclei) seen in chronic HE.

Precipitating Factors (Mnemonic: HELP BICS)

- **H**ypokalemia / Hyponatremia (Hypokalemia increases renal ammonia production)
- **E**xcess dietary protein (rarely the sole trigger)
- **L**iver insult (superimposed hepatitis, hepatotoxic drugs)
- **P**ortosystemic shunting (TIPS procedure)
- **B**leeding (Gastrointestinal variceal bleed ⇒protein load in gut)
- **I**nfection (Spontaneous bacterial peritonitis, UTI, pneumonia)
- **C**onstipation (increased gut transit time ⇒more ammonia absorption)
- **S**edatives/Tranquilizers (Benzodiazepines, narcotics)

Clinical Features (Pediatric Modified West Haven Criteria)

- **Infants:** Poor feeding, altered cry, irritability, reversed sleep-wake cycle.
- **Older Children:**
    - *Stage I:* Mild confusion, mood changes, sleep inversion.
    - *Stage II:* Lethargy, ataxia, dysarthria, **asterixis** (flapping tremor).
    - *Stage III:* Somnolent but arousable, marked confusion, hyperreflexia, clonus, Babinski positive.
    - *Stage IV:* Coma, decerebrate/decorticate posturing, absent reflexes.

Diagnosis

- **Clinical:** Primarily a clinical diagnosis based on history and neuro-exam.
- **Biomarkers:** Serum ammonia (arterial preferred; confirms hyperammonemia but *does not* correlate linearly with HE severity).
- **EEG:** Shows classic symmetrical high-voltage **triphasic waves** (Stages II-III) ⇒generalized slowing (Stage IV).
- **Neuroimaging (CT/MRI):** Rule out intracranial bleed. MRI in CLD shows bilateral T1 hyperintensity in basal ganglia (manganese deposition). MRI in ALF shows cerebral edema.
- **Psychometry:** Number Connection Test / Block Design for Covert/Minimal HE in older children.

Management

- **General & Supportive:**
    - Admit to ICU if ≥Stage II.
    - Intubate for airway protection if Stage III/IV.
    - Elevate head of bed to 30° (reduces intracranial pressure).
- **Treat Precipitants:**
    - Correct electrolytes (especially potassium).

- Treat infections (empiric broad-spectrum antibiotics / treat SBP).
- Stop GI bleeding (octreotide, endoscopy).

- **Ammonia Lowering Therapy:**
  - **Lactulose (1st line):** Non-absorbable disaccharide. Lowers colonic pH ⇒converts NH_3 to non-absorbable NH_4^+ (ion trapping) + cathartic effect. Titrate to 2–3 soft stools/day.
  - **Rifaximin (2nd line/Adjunct):** Non-absorbable antibiotic. Eradicates ammonia-producing gut flora. Used if unresponsive to lactulose or for secondary prophylaxis.
  - **L-Ornithine L-Aspartate (LOLA):** Substrates for the urea cycle; increases hepatic ammonia clearance (adjunct).
- **Nutrition (Updated Guidelines):**
  - *Previously:* Severe protein restriction.
  - *Now:* **Do not restrict protein** long-term (causes muscle breakdown, which worsens hyperammonemia since muscle clears ammonia). Target 1–2 g/kg/day (dairy/vegetable protein preferred over meat).
- **Cerebral Edema Management (Crucial in Type A / ALF):**
  - 3% Hypertonic saline (Target serum Na: 145–155 mEq/L).
  - IV Mannitol (0.5–1 g/kg) for acute ICP spikes.
  - Mild hypothermia (34–35°C) and continuous renal replacement therapy (CRRT) for rapid ammonia clearance in fulminant ALF.
- **Definitive:** Urgent Liver Transplantation evaluation.

Complications & Prognosis

- **ALF (Type A):** Brain herniation secondary to severe cerebral edema is the leading cause of death.
- **CLD (Type C):** Recurrent HE leads to permanent cognitive deficits, poor school performance, and impaired quality of life. Resolves significantly post-transplant.

Exam Summary: Must-Write Points

- HE is driven by gut-derived ammonia bypassing the liver, converting to glutamine in the brain, causing astrocyte swelling.
- Always actively search for and treat precipitants (Infection, GI bleed, Hypokalemia, Constipation).
- Diagnosis is clinical; arterial ammonia confirms etiology but doesn't track stage severity perfectly.
- EEG buzzword: Symmetrical high-voltage triphasic waves.
- First-line treatment: Lactulose (ion trapping) + treat precipitants. Rifaximin is the standard add-on.
- *Trap:* Never severely restrict protein in chronic HE; malnutrition worsens muscle wasting and hyperammonemia.

72. Gastrointestinal bleeding diagnostic approach

Subject: Gastroenterology / Hepatology

Definitions & Classification

- **Upper GI Bleed (UGIB):** Bleeding originating proximal to the Ligament of Treitz (esophagus, stomach, duodenum).
- **Lower GI Bleed (LGIB):** Bleeding originating distal to the Ligament of Treitz (jejunum, ileum, colon, rectum).
- **Obscure GI Bleed:** Source remains unidentified after standard Esophagogastroduodenoscopy (EGD) and colonoscopy.

False GI Bleeding (Must Rule Out First)

- **Dietary/Medications:** Beetroot, red food dyes, iron supplements (black stools), bismuth, rifampin.
- **Swallowed Blood:** Epistaxis, hemoptysis, or swallowed maternal blood during breastfeeding.
- **Apt-Downey Test:** Differentiates fetal vs. maternal blood in neonates (Fetal Hb is alkali-resistant and stays pink; adult Hb denatures and turns yellow/brown).

Etiology (Age-Stratified)

- **Neonates (0–1 month):** Swallowed maternal blood, Vitamin K Deficiency Bleeding (VKDB), Necrotizing Enterocolitis (NEC), Cow's Milk Protein Allergy (CMPA).
- **Infants/Toddlers (1 mo–3 yrs):** Anal fissures (most common LGIB), Intussusception, Meckel diverticulum, CMPA.
- **Children/Adolescents (>3 yrs):** Peptic Ulcer Disease (PUD), Esophageal varices, Mallory-Weiss tears, Inflammatory Bowel Disease (IBD), Juvenile polyps, infectious enteritis.

Clinical Clues to Localization

- **Hematemesis:** Bright red (active UGIB) or coffee-ground (slow/stopped UGIB).
- **Melena:** Black, tarry, foul-smelling stool (usually UGIB; requires ~50 mL of blood to form).
- **Hematochezia:** Bright red blood per rectum (usually LGIB; can be massive, rapid-transit UGIB).
- **Painless massive LGIB:** Classic for Meckel diverticulum.
- **Currant jelly stool + colicky pain:** Classic for Intussusception.
- **Blood-streaked stool + constipation:** Classic for Anal fissure.
- **Mucocutaneous pigmentation:** Think Peutz-Jeghers syndrome.
- **Cutaneous hemangiomas:** Think Blue Rubber Bleb Nevus syndrome.

Diagnostic Approach (Stepwise Algorithm)

- **Step 1: Hemodynamic Assessment & Resuscitation (Always precedes diagnosis)**
    - Assess ABCs, tachycardia, orthostatic hypotension, capillary refill.

- Place 2 large-bore IV lines; send blood for Type & Crossmatch immediately.

- **Step 2: Confirm & Localize True Bleed**
  - Perform perianal exam (fissures, polyps, trauma).
  - Nasogastric (NG) lavage: Clears stomach for endoscopy; presence of blood confirms UGIB; clearing with coffee grounds suggests stopped UGIB (Note: negative aspirate does *not* rule out duodenal bleed).
- **Step 3: Laboratory Evaluation**
  - **CBC:** Serial Hb/Hct (may be falsely normal initially due to hemoconcentration), platelets.
  - **BUN/Creatinine Ratio:** Ratio >30:1 strongly suggests UGIB (due to blood protein digestion/absorption).
  - **Coagulation:** PT/INR, aPTT (evaluate for liver disease, DIC, VKDB).
  - **LFTs:** If variceal bleed/liver disease is suspected.
- **Step 4: Imaging**
  - **Abdominal X-Ray:** Rule out perforation (pneumoperitoneum) or NEC (pneumatosis intestinalis).
  - **Ultrasound:** First-line for suspected intussusception ("target sign") or portal hypertension (Doppler).
  - **Meckel Scan (Tc-99m pertechnetate):** Diagnostic test of choice for Meckel diverticulum (enhanced by pre-treatment with H2 blockers/PPI).
- **Step 5: Endoscopy (Gold Standard for Diagnosis & Therapy)**
  - **EGD:** Procedure of choice for UGIB; ideally performed within 24 hours of presentation.
  - **Colonoscopy:** Procedure of choice for LGIB (after bowel prep, if stable).
  - **Video Capsule Endoscopy / Push Enteroscopy:** For obscure GI bleeding (evaluates small bowel).
- **Step 6: Angiography/RBC Tagged Scan**
  - Reserved for massive, active bleeding where endoscopy is unfeasible or non-diagnostic (requires bleeding rate >0.1–0.5 mL/min).

Brief Management Principles

- **Fluid Resuscitation:** 20 mL/kg Normal Saline boluses.
- **Blood Transfusion:** PRBCs indicated if hemodynamically unstable despite fluids, or Hb <7 g/dL (target Hb 7–9 g/dL).
- **Pharmacotherapy:**
  - IV PPI (Omeprazole/Pantoprazole) for suspected PUD/UGIB.
  - IV Octreotide (somatostatin analog) for suspected variceal bleeding.
  - IV Vitamin K for neonates/liver disease.

- IV Antibiotics (Ceftriaxone) for cirrhotic patients with GI bleed (prevents SBP).

- **Endoscopic Hemostasis:** Band ligation (varices), epinephrine injection + clips/cautery (ulcers).

Exam Summary: Must-Write Points

- **Resuscitation first:** Never begin diagnostic testing on an unstable patient without securing ABCs and IV access.
- **Apt-Downey test:** Essential mention for neonatal hematemesis to rule out swallowed maternal blood.
- **BUN/Cr ratio >30:** Classic, high-yield biochemical marker differentiating UGIB from LGIB.
- **Age-specific etiologies:** Anal fissures (infants), Meckel (toddlers), Varices/PUD (older children).
- **Meckel Scan:** Specify Tc-99m pertechnetate for painless lower GI bleeding in a toddler.

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73. Wilson disease

Subject: Gastroenterology / Hepatology

Basics & Genetics

- **Definition:** Inherited disorder of copper metabolism leading to toxic accumulation in tissues (liver, brain, cornea).
- **Genetics:** Autosomal Recessive (AR).
- **Gene:** *ATP7B* gene mutation on Chromosome 13q14.3.
- **Protein:** Defective ATP7B protein (a copper-transporting P-type ATPase).

Pathophysiology

- **Normal state:** ATP7B mediates copper transport into the trans-Golgi network for incorporation into ceruloplasmin and excretion into bile.
- **Defect:** Failure of biliary copper excretion and failure to incorporate copper into apoceruloplasmin.
- **Accumulation:** Free copper accumulates first in the liver → hepatocellular death → release of free copper into blood → deposition in extrahepatic tissues (brain, cornea, kidneys, RBCs).
- **Oxidative stress:** Free copper generates reactive oxygen species (Fenton reaction) causing lipid peroxidation and cell damage.

Clinical Features

Age of onset: Rarely symptomatic <3 years; hepatic presentation usually in first decade, neurologic in second/third decade.

- **Hepatic (Most common pediatric presentation):**
  - Incidental asymptomatic hepatomegaly / transaminitis.
  - Acute hepatitis (jaundice, anorexia).

  - Acute Liver Failure (ALF): Rapid onset with coagulopathy and encephalopathy.
  - Chronic liver disease / Compensated or decompensated cirrhosis.
- **Neurologic (Basal ganglia involvement):**
  - Movement disorders: Asymmetric resting/intention tremor, dystonia, choreoathetosis.
  - Bulbar signs: Dysarthria, dysphagia, drooling, pseudobulbar palsy (classic "sardonic smile").
  - Deteriorating school performance / handwriting changes (micrographia).
- **Psychiatric:**
  - Personality changes, emotional lability, depression, psychosis.
- **Ophthalmologic:**
  - Kayser-Fleischer (KF) rings: Copper deposition in Descemet membrane of the cornea (best seen on slit-lamp exam).
  - Sunflower cataracts (rare).
- **Hematologic:** Coombs-negative hemolytic anemia (due to direct RBC toxicity by massive free copper release).
- **Renal:** Fanconi syndrome (renal tubular acidosis, aminoaciduria, glycosuria), nephrolithiasis.

Diagnosis

Based on Leipzig Scoring System (Score ≥4 establishes diagnosis).

- **Serum Ceruloplasmin:** Low (<20 mg/dL). *Trap: Acute phase reactant; can be falsely normal in acute inflammation/ALF or falsely low in malabsorption/protein-losing states.*
- **24-Hour Urinary Copper:** Elevated (>40 µg/24h is abnormal; >100 µg/24h is classic).
- **Slit-Lamp Exam:** Presence of KF rings (absent in up to 50% of isolated hepatic presentations).
- **Liver Biopsy (Gold Standard):** Hepatic copper >250 µg/g dry weight. (Special stains: Rhodanine, Timm's, Orcein).
- **Genetic Testing:** *ATP7B* mutation analysis (confirmatory).
- **Labs specific to Wilson ALF (Must-know):**
  - Alkaline Phosphatase (ALP) to Total Bilirubin ratio < 4.
  - AST to ALT ratio > 2.2.
  - Low serum uric acid (due to renal tubular wasting).

Management

- **Dietary Modification:** Avoid high-copper foods (organ meats/liver, shellfish, nuts, chocolate, mushrooms).
- **Chelation Therapy (Induction / Symptomatic patients):**
  - **Trientine (First-line):** Promotes renal excretion. Preferred due to better safety profile.

    - **D-Penicillamine (Alternative):** Must be given with Pyridoxine (Vitamin B6). *Adverse effects:* Worsening of neuro symptoms initially, SLE-like syndrome, nephrotic syndrome, bone marrow suppression, elastosis perforans serpiginosa.

- **Maintenance Therapy (Asymptomatic / Post-induction):**
    - **Oral Zinc (Zinc acetate/sulfate):** Induces enterocyte metallothionein, which binds dietary copper and prevents its systemic absorption (excreted in feces).
- **Acute Liver Failure / Decompensated Cirrhosis:**
    - **Liver Transplantation (Curative):** Reverses hepatic and hematologic defects; neurologic improvement is variable.
    - Plasmapheresis / Hemofiltration: Bridge to transplant to remove massive free copper.

Monitoring & Prognosis

- **Monitoring efficacy:** 24-hour urine copper (high during chelation, low on zinc therapy), Non-ceruloplasmin bound copper (Free copper) levels (target 5–15 µg/dL).
- **Prognosis:** Excellent if diagnosed early and strictly adherent to lifelong therapy. Fatal if untreated.
- **Family Screening:** Siblings of index cases must be screened (clinical exam, LFTs, ceruloplasmin, genetic testing).

💡 **Exam Summary**

- **Genetics:** AR, *ATP7B* gene, Chromosome 13.
- **Classic ALF Triad:** Coombs-negative hemolytic anemia + ALP/Bilirubin ratio < 4 + AST > ALT.
- **Diagnosis:** Ceruloplasmin <20 mg/dL, 24h Urine Cu >100 µg, Hepatic Cu >250 µg/g.
- **KF Rings:** In Descemet membrane; diagnostic but NOT mandatory (often absent in pure hepatic presentations).
- **Treatment:** Trientine/Penicillamine (chelation/symptomatic) → Zinc (maintenance/asymptomatic). Liver transplant is curative.

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74. Indications for liver transplantation

Subject: Gastroenterology / Hepatology

Overview

- **Definition:** Surgical replacement of a native diseased liver with a healthy allograft (living or deceased donor).
- **Most common indication:** Biliary Atresia (accounts for ~50% of all pediatric liver transplants).
- **Primary goal:** Extend survival and improve quality of life in end-stage liver disease, acute liver failure, or specific metabolic/malignant conditions.

Indications by Category

1. Cholestatic Liver Diseases

- **Biliary Atresia (BA):** Indicated if Kasai portoenterostomy fails (persistent jaundice >3 months post-op), recurrent severe cholangitis, or late presentation (>120 days of life) with established cirrhosis.
- **Progressive Familial Intrahepatic Cholestasis (PFIC):** Types 1, 2, and 4 with intractable pruritus, growth failure, or cirrhosis (note: PFIC-1 may develop severe steatohepatitis post-transplant).
- **Alagille Syndrome:** For intractable pruritus, severe osteodystrophy, or synthetic failure (must rule out severe cardiac/vascular anomalies first).
- **Primary Sclerosing Cholangitis (PSC):** End-stage disease or recurrent cholangitis.

2. Metabolic Liver Diseases

- *Group A: Resulting in Cirrhosis/Hepatic Damage*
    - Alpha-1 Antitrypsin Deficiency (PiZZ phenotype).
    - Wilson Disease (fulminant presentation or progressive chronic liver failure).
    - Tyrosinemia Type 1 (if unresponsive to NTBC or if hepatocellular carcinoma develops).
    - Glycogen Storage Disease (GSD) Type IV.
    - Cystic Fibrosis–associated liver disease.
- *Group B: Structurally Normal Liver (Transplant as Enzyme Replacement)*
    - Crigler-Najjar Syndrome Type I (to prevent kernicterus).
    - Urea Cycle Defects (e.g., Ornithine Transcarbamylase deficiency) with recurrent severe hyperammonemia.
    - Primary Hyperoxaluria Type 1 (often requires combined Liver-Kidney transplant).
    - Homozygous Familial Hypercholesterolemia.

3. Acute Liver Failure (ALF)

- **Viral:** HAV, HBV, HEV, indeterminate (Non-A-Non-E).
- **Toxins/Drugs:** Acetaminophen toxicity, Valproate, Isoniazid, mushroom poisoning (*Amanita phalloides*).
- **Autoimmune:** Seronegative or seropositive fulminant autoimmune hepatitis.
- **Criteria for ALF Transplant:** King's College Criteria (differentiates acetaminophen vs. non-acetaminophen causes based on pH, INR, encephalopathy grade, bilirubin, and age).

4. Chronic Liver Disease / Cirrhosis

- **Autoimmune Hepatitis (AIH):** Decompensated cirrhosis unresponsive to immunosuppression.
- **Viral Hepatitis:** Chronic HBV/HCV with decompensation (rare in modern pediatric practice due to DAAs and vaccination).
- **Cryptogenic Cirrhosis.**

5. Hepatic Malignancies

- **Hepatoblastoma:** Unresectable tumors (PRETEXT III or IV) after neoadjuvant chemotherapy, or multifocal disease without extrahepatic spread.
- **Hepatocellular Carcinoma (HCC):** Within Milan criteria (single tumor ≤5 cm, or up to 3 tumors ≤3 cm, no vascular invasion/extrahepatic spread). *Note: Expanded criteria are often used in pediatrics.*

Decision Criteria & Scoring

- **PELD Score (Pediatric End-Stage Liver Disease):** Used for children <12 years. Variables: Bilirubin, INR, Albumin, Growth failure (< -2 SD), Age at listing (<1 year).
- **MELD Score (Model for End-Stage Liver Disease):** Used for children ≥12 years. Variables: Bilirubin, INR, Creatinine, Serum Sodium.
- **Clinical triggers:** Recurrent variceal bleeding, refractory ascites, hepatopulmonary syndrome, portopulmonary hypertension, severe malnutrition.

Contraindications

- **Absolute:**
    - Severe, irreversible neurologic injury (e.g., fixed dilated pupils in ALF).
    - Uncontrolled systemic sepsis.
    - Extrahepatic malignancy (or metastatic liver tumors).
    - Severe uncorrectable cardiopulmonary disease.
    - Mitochondrial depletion syndromes with severe extrahepatic manifestations (e.g., Alpers disease, POLG mutations).
- **Relative:** Active substance abuse (in adolescents), severe psychosocial non-compliance, portal vein thrombosis (Grade IV).

Complications (Post-Transplant)

- **Early (<1 month):** Primary non-function, Hepatic Artery Thrombosis (HAT - highest risk in pediatrics, leads to biliary necrosis), biliary leaks/strictures, acute cellular rejection, bacterial/fungal infections.
- **Late (>1 month):** Chronic rejection (vanishing bile duct syndrome), CMV/EBV infections, Post-Transplant Lymphoproliferative Disorder (PTLD), calcineurin inhibitor nephrotoxicity.

Exam Summary

- **Biliary Atresia** is the single most common indication for pediatric liver transplant (~50%).
- Metabolic indications are split: those that destroy the liver (Alpha-1 AT, Wilson) and those with a normal liver but missing enzyme (Crigler-Najjar, Urea cycle defects).
- **Hepatic Artery Thrombosis (HAT)** is the most dreaded early vascular complication in pediatrics.
- **PELD score** (<12 years) uniquely incorporates **growth failure** and **age <1 year** alongside bilirubin, INR, and albumin.
- **Contraindication trap:** Do not transplant if fixed neurologic injury (brain death) has already occurred in fulminant hepatic failure.

75. Protein losing enteropathy

Subject: Gastroenterology / Hepatology

Definition

- Condition characterized by excessive loss of serum proteins into the gastrointestinal (GI) tract.
- Results in hypoproteinemia when protein loss exceeds hepatic synthetic capacity.
- Non-selective loss: Affects albumin, globulins, transferrin, ceruloplasmin, and clotting factors.

Pathophysiology & Etiology

Classified by three distinct mechanisms of GI protein leakage:

- **1. Mucosal Injury with Ulceration (Exudation):**
  - Inflammatory Bowel Disease (Crohn's disease, Ulcerative Colitis).
  - Infectious enteritis (Pseudomembranous colitis, Shigella, Salmonella).
  - Peptic ulcer disease / Erosive gastritis.
- **2. Mucosal Disease without Ulceration (Increased Permeability):**
  - Celiac disease.
  - Cow's Milk Protein Allergy (CMPA) / Allergic enteropathy.
  - Menetrier disease (hypertrophic gastropathy).
  - Eosinophilic gastroenteritis.
  - Small intestinal bacterial overgrowth (SIBO).
- **3. Lymphatic Obstruction / Hypertension (Leakage of chyle):**
  - *Congenital:* Primary intestinal lymphangiectasia (PIL).
  - *Cardiac:* Post-Fontan procedure (classic exam association), Right heart failure, Constrictive pericarditis.
  - *Acquired:* Lymphoma, tuberculosis, mesenteric venous thrombosis.

Clinical Features

- **Generalized:** Pitting edema (dependent, periorbital), ascites, pleural/pericardial effusions.
- **GI Symptoms:** Chronic diarrhea, steatorrhea, abdominal pain, vomiting.
- **Systemic:** Failure to thrive (FTT), severe malnutrition, muscle wasting.
- **Lymphatic-specific clues:** Chylous ascites, profound lymphopenia, opportunistic infections, fat-soluble vitamin (A, D, E, K) deficiency.

Diagnosis

1. Confirm Hypoproteinemia (Rule out other causes):

- **Blood:** Low serum albumin, low total protein, low IgG, low fibrinogen. Normal liver enzymes/synthetic function.

- **Urine:** Normal urinalysis (rules out nephrotic syndrome).
- **CBC:** Lymphopenia (specifically points to lymphatic etiology).

2. Confirm GI Protein Loss:

- **Fecal Alpha-1-Antitrypsin (α1-AT) Clearance:** Gold standard diagnostic test.
    - α1-AT is resistant to intestinal degradation (unlike other proteins).
    - *Diagnostic criteria:* Clearance > 27 mL/24 hours (or > 56 mL/24h if accompanied by diarrhea).
    - *Trap:* Degraded in high stomach acid. If gastric PLE (e.g., Menetrier) is suspected, patient must be on a Proton Pump Inhibitor (PPI) before the test.

3. Identify Underlying Etiology:

- **Endoscopy & Biopsy:** For IBD, Celiac, Menetrier, CMPA, or intestinal lymphangiectasia (shows dilated lacteals).
- **Imaging:** Echocardiogram (rule out right heart failure/pericarditis), Abdominal US/CT, MR Enterography.
- **Specialized:** Technetium-99m labeled human serum albumin scintigraphy (localizes the exact site of GI protein leak).

Management

1. Dietary & Nutritional Support:

- **High-protein diet:** 2–3 grams/kg/day to compensate for losses.
- **Fat modification (Crucial for Lymphatic causes):**
    - Strict Low-Fat Diet (reduces lymphatic flow/pressure).
    - Supplement with **Medium-Chain Triglycerides (MCT oil)**.
    - *Mechanism:* MCTs bypass the intestinal lacteals/lymphatic system and are absorbed directly into the portal vein.
- **Micronutrients:** Supplement fat-soluble vitamins (A, D, E, K), calcium, iron, and zinc.

2. Disease-Specific Therapy:

- *CMPA:* Extensively hydrolyzed or amino acid-based formula.
- *Celiac:* Strict gluten-free diet.
- *IBD:* Corticosteroids, immunomodulators, biologics.
- *Fontan-associated PLE:* Sildenafil, bosentan, budesonide, or surgical fenestration/heart transplant.

3. Symptomatic & Supportive Care:

- **Edema control:** Diuretics (Spironolactone, Furosemide).
- **Acute severe anasarca:** IV Albumin infusion followed by IV Furosemide (temporary bridge, not a definitive treatment).

Complications

- **Infections:** Due to loss of immunoglobulins (IgG) and lymphocytes (impaired cellular immunity).
- **Thrombosis:** Due to loss of antithrombin III and protein C/S.
- **Endocrine:** Hypocalcemia (loss of vitamin D binding protein and albumin).
- **Growth:** Severe stunting and delayed puberty.

Exam Summary

- **Definition:** Hypoalbuminemia + edema with NORMAL liver function and NO proteinuria.
- **Gold Standard Test:** 24-hour fecal Alpha-1-Antitrypsin (α1-AT) clearance.
- **Lymphatic PLE Triad:** Hypoproteinemia + Lymphopenia + Hypocholesterolemia.
- **Classic Cardiac Cause:** Post-Fontan procedure.
- **Key Dietary Intervention:** MCT oil (bypasses lacteals directly to portal circulation).

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76. Electrolyte disturbances in diarrhea

Subject: Gastroenterology / Hepatology

Basics & Pathophysiology

- **Core Mechanism:** Diarrheal fluid is rich in water, sodium (Na+), potassium (K+), and bicarbonate (HCO3-).
- **Most Common State:** Isonatremic dehydration (Na+ 130–150 mEq/L) accounts for 70–80% of cases.
- **Stool Composition:** Cholera stool is high in Na+ (secretory); viral diarrhea (Rotavirus) is high in water relative to Na+ (osmotic).
- **Secondary Mechanisms:** Volume depletion triggers RAAS activation → secondary hyperaldosteronism → increased renal K+ wasting.

Sodium Disturbances

Hyponatremia (<130 mEq/L)

- **Etiology:** High Na+ loss (cholera, Shigella) or replacing fluid losses with free water/dilute fluids.
- **Clinical:** Lethargy, headache, nausea, seizures, coma (due to cerebral edema).
- **Management:**
    - *Asymptomatic:* Correct with standard WHO low-osmolarity ORS or Normal Saline (NS).
    - *Symptomatic (Seizures):* 3% Hypertonic Saline (3–5 mL/kg IV over 10–15 minutes).
- **Red Flag:** Do not correct serum Na+ faster than 8–10 mEq/L/24 hours to prevent **Osmotic Demyelination Syndrome (Central Pontine Myelinolysis)**.

Hypernatremia (>150 mEq/L)

- **Etiology:** Disproportionate water loss (viral diarrhea), fever, poor fluid intake, improperly mixed (concentrated) ORS/formula.

- **Clinical:** "Doughy" skin turgor, high-pitched cry, extreme irritability, hyperreflexia, seizures. Intracellular dehydration causes brain shrinkage.
- **Management:**
    - Restore intravascular volume first with isotonic fluid (NS or RL) if in shock (10–20 mL/kg).
    - Deficit replacement: Use 0.45% NS in 5% Dextrose.
    - **Pivotal Rule:** Correct SLOWLY over 48–72 hours. Drop Na+ by **<0.5 mEq/L/hour** (max 10–12 mEq/L/day) to prevent **Cerebral Edema**.

Potassium Disturbances

Hypokalemia (<3.5 mEq/L)

- **Etiology:** Direct stool losses, secondary hyperaldosteronism, intracellular shift during acidosis correction.
- **Clinical:** Progressive muscle weakness, absent deep tendon reflexes, paralytic ileus (abdominal distension), respiratory failure.
- **ECG Changes:** Flattened/inverted T waves, prominent **U waves**, ST depression, arrhythmias.
- **Management:**
    - Enteral: WHO ORS contains 20 mEq/L of K+ (usually sufficient for mild cases).
    - IV Correction: Add KCl to maintenance fluids. Max concentration: 40 mEq/L via peripheral line. Max rate: 0.3–0.5 mEq/kg/hour.
    - **Absolute Rule:** Never administer IV potassium until urine output is established (>1 mL/kg/hr).

Acid-Base Disturbances

Metabolic Acidosis

- **Etiology:** Fecal loss of bicarbonate (Normal Anion Gap) + lactic acidosis from hypovolemic shock/poor tissue perfusion (High Anion Gap).
- **Clinical:** Deep, rapid breathing (**Kussmaul respiration**), poor peripheral perfusion, lethargy.
- **Management:**
    - Fluid resuscitation with Ringer's Lactate (RL) is first-line (lactate is metabolized to bicarbonate in the liver).
    - Avoid IV Sodium Bicarbonate unless pH < 7.10, severe base deficit, or accompanied by hyperkalemia.

Diagnosis

- **Serum Chemistries:** Na+, K+, Cl-, HCO3-, Urea, Creatinine (to assess prerenal AKI).
- **Blood Gas (ABG/VBG):** Assess pH, pCO2 (respiratory compensation), and base excess.
- **ECG:** Mandatory if hypokalemia is suspected or patient has arrhythmias/ileus.
- **Stool Osmotic Gap:** Differentiates secretory (<50 mOsm/kg) from osmotic (>100 mOsm/kg) diarrhea.

Prevention & Standard Therapy

- **WHO Low-Osmolarity ORS:** The cornerstone of prevention and treatment.
    - *Composition:* Na+ 75, K+ 20, Cl- 65, Citrate 10, Glucose 75 (Total osmolarity: **245 mOsm/L**).
    - *Mechanism:* Utilizes the intact Sodium-Glucose cotransporter (SGLT-1) in the gut to facilitate equimolar absorption of Na+ and water.
- **Zinc Supplementation:** Reduces duration and severity of diarrhea; promotes enterocyte regeneration.
    - *Dose:* <6 months: 10 mg/day; >6 months: 20 mg/day (for 14 days).

Complications & Prognosis

- **Neurological:** Seizures (from dysnatremia), cerebral edema (rapid hypernatremia correction), pontine myelinolysis (rapid hyponatremia correction).
- **Renal:** Prerenal AKI progressing to acute tubular necrosis (ATN) if uncorrected.
- **Gastrointestinal:** Paralytic ileus (hypokalemia) exacerbating fluid sequestration.
- **Prognosis:** Excellent with timely, protocol-based fluid and electrolyte resuscitation. Mortality is primarily linked to unrecognized shock or iatrogenic correction errors.

Exam Summary

- **Most common disturbance:** Isonatremic dehydration with normal anion gap metabolic acidosis.
- **WHO ORS:** 245 mOsm/L (Na 75, Glucose 75); utilizes SGLT-1 cotransporter.
- **Hyponatremia rescue:** 3% NaCl (3-5 mL/kg) for seizures. Max correction 8-10 mEq/L/day to avoid central pontine myelinolysis.
- **Hypernatremia management:** Doughy skin. Correct slowly over 48-72 hrs (<0.5 mEq/L/hr) to avoid cerebral edema.
- **Hypokalemia trap:** Paralytic ileus + U waves. *Never give IV K+ without established urine output.*
- **Acidosis:** Treat with Ringer's Lactate fluid boluses; avoid routine $NaHCO_3$.

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77. Diagnosis and management of celiac disease

Subject: Gastroenterology / Hepatology

Basics

- **Definition:** Systemic immune-mediated enteropathy triggered by dietary gluten in genetically susceptible individuals.
- **Genetics:** >99% carry HLA-DQ2 or HLA-DQ8.
- **Triggers:** Gliadin (fraction of gluten) found in wheat, barley, and rye.

Pathophysiology

- Gliadin resists complete digestion, crossing intestinal epithelium.
- Tissue transglutaminase (tTG) deamidates gliadin, increasing immunogenicity.
- Antigen-presenting cells bind deamidated gliadin via HLA-DQ2/DQ8.
- CD4+ T-cell activation drives cytokine release (IFN-γ) and autoantibody production.
- Result: Crypt hyperplasia, intraepithelial lymphocytosis, and villous atrophy.

Clinical Features

- **Classic (GI):** Chronic diarrhea, failure to thrive (FTT), abdominal distension, anorexia, muscle wasting (buttocks/thighs).
- **Non-classic (Extra-intestinal):** Refractory iron-deficiency anemia, short stature, delayed puberty, chronic fatigue.
- **Specific signs:** Dermatitis herpetiformis (pruritic vesicular rash on extensor surfaces), dental enamel defects, aphthous stomatitis.
- **High-risk associations:** Type 1 Diabetes, Autoimmune Thyroiditis, Down syndrome, Turner syndrome, Williams syndrome, Selective IgA deficiency.

Diagnosis

- *Prerequisite:* Patient **must** be on a gluten-containing diet during all testing.
- **First-line Serology:** Total serum IgA + IgA anti-tTG antibody.
    - *Total IgA check:* Mandatory to rule out selective IgA deficiency (occurs in 2–3% of celiac patients).
    - *If IgA deficient:* Check IgG anti-tTG, IgG Deamidated Gliadin Peptide (DGP), or IgG Endomysial Antibody (EMA).
- **Histology (Traditional Gold Standard):** Upper GI endoscopy with multiple biopsies (1 from duodenal bulb, 4 from distal duodenum).
    - *Marsh Classification:* Type 1 (Increased Intraepithelial Lymphocytes [IELs] >25/100 enterocytes) → Type 2 (Crypt hyperplasia) → Type 3 (Villous atrophy).
- **ESPGHAN 2020 Update (No-Biopsy Pathway):**
    - Biopsy can be avoided if **ALL** the following are met:
        1. IgA anti-tTG is >10x the Upper Limit of Normal (ULN).
        2. Positive IgA-EMA on a *second, independent* blood draw.
    - *Update:* HLA-DQ2/DQ8 typing is *no longer* required for the no-biopsy diagnosis.

Management

- **Dietary:** Strict, lifelong Gluten-Free Diet (GFD).
- **Avoid (Mnemonic: BROW): B**arley, **R**ye, **O**ats (often cross-contaminated, though pure oats are tolerated by most), **W**heat.
- **Safe grains:** Rice, corn, potato, soybean, buckwheat, quinoa.
- **Nutritional Support:** Screen and supplement Iron, Calcium, Vitamin D, Folate, Vitamin B12.

- **Vaccinations:** Pneumococcal vaccine (due to risk of functional hyposplenism).
- **Referral:** Expert pediatric dietitian.

Monitoring

- Assess clinical symptoms and growth parameters at 3–6 months, then annually.
- Repeat IgA anti-tTG at 6–12 months to assess dietary compliance (levels should decline and normalize within 12 months on strict GFD).
- Screen for autoimmune comorbidities (T1DM, Thyroid) periodically.

Complications

- Refractory celiac disease (persistent villous atrophy despite strict GFD).
- Enteropathy-associated T-cell lymphoma (EATL) – rare in pediatrics, risk in adults.
- Osteopenia/osteoporosis.
- Infertility and adverse pregnancy outcomes (if untreated in adulthood).

Exam Summary

- **Must-write:** HLA-DQ2/DQ8; Tissue transglutaminase (tTG).
- **Screening:** Always check Total IgA alongside IgA anti-tTG to avoid false negatives from IgA deficiency.
- **No-Biopsy Criteria (ESPGHAN 2020):** tTG >10x ULN + positive EMA on second sample (HLA testing no longer needed).
- **Pathology:** Marsh criteria = Increased IELs + Crypt hyperplasia + Villous atrophy.
- **Trap:** Never start a gluten-free diet before confirming the diagnosis serologically/histologically.

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78. Peutz Jeghers syndrome diagnosis and complications

Subject: Gastroenterology / Hepatology

Basics & Genetics

- **Inheritance:** Autosomal dominant (high penetrance, variable expressivity)
- **Gene:** *STK11* (also known as *LKB1*) mutation on chromosome 19p13.3 (tumor suppressor gene)
- **Core Triad:** Hamartomatous GI polyps + Mucocutaneous pigmentation + Increased cancer risk

Clinical Features

- **Pigmentation:** Dark blue/brown/black macules on lips (crossing vermilion border), buccal mucosa, perianal area, and digits
- **Evolution:** Pigmentation appears in infancy, often fades after puberty (except buccal mucosa)
- **GI Symptoms:** Colicky abdominal pain, melena, hematochezia, fatigue (anemia)

Diagnosis

- **Clinical Criteria (WHO):** Requires at least **ONE** of the following:

  - ≥3 histologically confirmed PJS polyps
  - Any number of PJS polyps + positive family history of PJS
  - Characteristic mucocutaneous pigmentation + positive family history of PJS
  - Any number of PJS polyps + characteristic mucocutaneous pigmentation
- **Histopathology (Buzzword):** Hamartomatous polyps showing an **"arborizing network"** of smooth muscle bundles extending into the polyp core
- **Genetic Testing:** *STK11* mutation analysis (confirmatory; positive in 80–90% of clinical cases)
- **Imaging/Endoscopy:**
  - Video capsule endoscopy (VCE) or MR Enterography (MRE) to evaluate small bowel (most common site of polyps)
  - Upper GI endoscopy and Colonoscopy

Complications

- **Mechanical GI Complications:**
  - **Intussusception:** Small bowel-to-small bowel is classic; often transient/recurrent; leading cause of laparotomy in PJS children
  - **Obstruction:** Due to large polyps or intussusception
  - **Bleeding:** Chronic occult bleeding leading to refractory Iron Deficiency Anemia (IDA); overt GI hemorrhage
  - **Short Bowel Syndrome:** Iatrogenic complication from repeated surgical resections for intussusception
- **Malignancy Risk (Lifetime risk 85–90%):**
  - **GI Tract:** Colorectal (39%), pancreatic (11–36% - highly lethal), stomach (29%), small bowel (13%)
  - **Breast:** Highest overall cancer risk in females (54%)
  - **Female Gonadal:** Ovarian sex cord tumors with annular tubules (**SCTAT**), cervical adenoma malignum
  - **Male Gonadal:** Testicular large-cell calcifying Sertoli cell tumors (can secrete estrogen causing prepubertal gynecomastia/advanced bone age)
  - **Other:** Lung cancer (15%)

Management & Surveillance

- **Acute Management:** Endoscopic polypectomy via Double-Balloon Enteroscopy (DBE) for bleeding/obstruction
- **Surgical Strategy:** Intraoperative enteroscopy with a **"clean sweep"** (removal of all polyps >1–1.5 cm) to minimize future intussusceptions and preserve bowel length
- **Surveillance Protocol (Current Guidelines):**
  - **Baseline GI:** Upper endoscopy, colonoscopy, and VCE/MRE starting at age 8–10 years (earlier if symptomatic)

- **Breast:** Clinical exam starting at 20 years; annual MRI/Mammogram starting at age 25–30
- **Pancreatic:** MRCP or Endoscopic Ultrasound (EUS) starting at age 25–30
- **Pelvic/Testicular:** Annual clinical exam/ultrasound starting in childhood to monitor for gonadal tumors

Exam Summary

- **Must-write Gene:** *STK11* (LKB1) on chromosome 19p.
- **Diagnostic Triad:** Mucocutaneous pigmentation (fades except buccal) + Hamartomatous polyps + Family history.
- **Histology Trap:** Polyps are hamartomas with "arborizing smooth muscle", NOT adenomas (though adenomatous change can occur later).
- **Top Pediatric Complication:** Small bowel intussusception requiring "clean sweep" surgery.
- **Top Adult Complication:** Extremely high lifetime risk of malignancies (Breast, GI, Pancreas, SCTAT).

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79. IBD in children

Subject: Gastroenterology / Hepatology

Basics

- **Definition:** Chronic, relapsing, immune-mediated intestinal inflammation.
- **Subtypes:** Crohn Disease (CD), Ulcerative Colitis (UC), IBD-unclassified (IBD-U).
- **VEO-IBD:** Very Early Onset IBD (<6 years); high suspicion for monogenic immune defects (e.g., IL-10 receptor mutations).

Etiology & Pathogenesis

- **Genetics:** *NOD2/CARD15* mutations strongly associated with CD.
- **Immunology:** Dysregulated mucosal immune response to gut microbiota (CD: Th1/Th17 driven; UC: Th2 driven).
- **Environment:** Altered microbiome, Western diet, NSAID use, smoking (worsens CD, protective in UC).

Clinical Features

- **Gastrointestinal:**
  - **CD:** Insidious onset, right lower quadrant pain, non-bloody diarrhea, perianal disease (tags, fistulas, fissures).
  - **UC:** Acute/subacute onset, bloody diarrhea, tenesmus, left lower quadrant pain.
- **Systemic (Pediatric Hallmarks):**
  - Unexplained weight loss.
  - Growth failure and delayed puberty (often predates GI symptoms in CD).

- **Extraintestinal Manifestations (EIMs):**
    - *Joints:* Peripheral arthritis, sacroiliitis.
    - *Skin:* Erythema nodosum (parallels bowel activity), Pyoderma gangrenosum.
    - *Eyes:* Uveitis, episcleritis.
    - *Liver:* Primary Sclerosing Cholangitis (PSC) – highly associated with UC.

Diagnosis

- **Initial Labs:** Microcytic anemia, thrombocytosis, elevated ESR/CRP, hypoalbuminemia.
- **Fecal Markers:** Fecal calprotectin (>250 µg/g indicates active mucosal inflammation; excellent screening tool).
- **Serology (Differentiating):** ASCA positive in CD; pANCA positive in UC (low sensitivity, high specificity).
- **Endoscopy (Gold Standard):** Upper GI endoscopy + Ileocolonoscopy with biopsies.
    - **CD:** Skip lesions, cobblestone mucosa, aphthous ulcers, rectal sparing, transmural inflammation, non-caseating granulomas.
    - **UC:** Continuous inflammation starting from rectum, loss of vascular pattern, friability, mucosal/submucosal inflammation, crypt abscesses.
- **Imaging:** Magnetic Resonance Enterography (MRE) is the modality of choice for small bowel evaluation (strictures, fistulas) without radiation exposure.

Management

- **Goals:** "Treat-to-target" (clinical remission + endoscopic mucosal healing) and optimization of growth/puberty.
- **Nutrition (ECCO/ESPGHAN Update):**
    - Exclusive Enteral Nutrition (EEN) for 6–8 weeks is the **first-line induction therapy** for pediatric luminal CD (spares steroids, heals mucosa).
- **Medical Therapy – Induction:**
    - *CD:* EEN or systemic corticosteroids (if EEN fails/refused).
    - *UC:* 5-Aminosalicylates (Mesalamine) for mild/moderate; Systemic steroids for severe.
- **Medical Therapy – Maintenance:**
    - *Immunomodulators:* Azathioprine, 6-Mercaptopurine, Methotrexate (CD).
    - *Biologics (Anti-TNF):* Infliximab, Adalimumab.
    - *Current Paradigm Shift:* "Top-down" therapy (early use of biologics) is now recommended for high-risk pediatric CD (extensive disease, severe growth failure, perianal fistulizing disease).
- **Surgical Therapy:**
    - *UC:* Total proctocolectomy with ileal pouch-anal anastomosis (IPAA) is curative.

- *CD:* Bowel resection for complications (strictures, refractory fistulas); not curative (disease recurs at anastomosis).

Complications

- **CD:** Strictures/obstruction, fistulas, intra-abdominal abscesses, severe osteopenia/osteoporosis, nephrolithiasis (oxalate stones).
- **UC:** Toxic megacolon, severe hemorrhage, colorectal carcinoma (risk increases with disease duration >8–10 years and PSC overlap).

Prognosis & Prevention

- **Prognosis:** Lifelong condition; pediatric-onset disease tends to be more extensive and aggressive than adult-onset.
- **Monitoring:** Annual colonoscopic surveillance for dysplasia begins 8–10 years after symptom onset.
- **Prevention:** No primary prevention; secondary prevention of flares via strict medication adherence and avoiding NSAIDs.

Exam Summary

- Growth failure and delayed puberty are classic presenting signs of pediatric CD, often preceding GI symptoms.
- Fecal calprotectin is the best non-invasive screening test to differentiate IBD from functional bowel disorders (IBS).
- **CD buzzwords:** Skip lesions, transmural, non-caseating granulomas, ASCA+, perianal disease.
- **UC buzzwords:** Continuous, rectum involved, mucosal crypt abscesses, pANCA+, bloody diarrhea, PSC risk.
- Exclusive Enteral Nutrition (EEN) is the first-line induction agent for pediatric CD to induce mucosal healing and spare steroids.

Nutrition

80. Micronutrients in children

Subject: Nutrition

Basics

- **Definition:** Essential vitamins and trace minerals required in minute quantities (<100 mg/day) for vital physiological functions, growth, and immune response.
- **Hidden Hunger:** Global phenomenon of micronutrient deficiency without overt clinical caloric deficit; severely impacts neurodevelopment and immunity.
- **Classification:**
  - *Trace Minerals:* Iron, Zinc, Iodine, Copper, Selenium.
  - *Fat-Soluble Vitamins:* A, D, E, K.

- *Water-Soluble Vitamins:* B-complex, C.

High-Yield Micronutrients: Clinical & Management Profiles

1. Iron (Fe)

- **Function:** Hemoglobin synthesis, myelination, neurotransmitter function.
- **Clinical Features:** Pallor, pica, koilonychia, irritability, breath-holding spells, cognitive decline.
- **Diagnosis:** Low Hb, Low MCV/MCH, Low Serum Ferritin (earliest & most sensitive marker), High TIBC, High sTfR (soluble transferrin receptor).
- **Management (Therapeutic):** Elemental iron 3–6 mg/kg/day for 3 months.
- **Prevention (Anemia Mukt Bharat - AMB Guidelines):**
  - *6–59 months:* 20 mg elemental Fe + 100 mcg Folic Acid (FA) bi-weekly.
  - *5–9 years:* 45 mg elemental Fe + 400 mcg FA weekly.
  - *10–19 years:* 60 mg elemental Fe + 500 mcg FA weekly.

2. Vitamin A (Retinol)

- **Function:** Rhodopsin synthesis (vision), epithelial integrity, immune regulation.
- **Clinical Features (WHO Staging):** Night blindness (XN - earliest symptom) → Conjunctival xerosis (X1A) → Bitot spots (X1B) → Corneal xerosis (X2) → Corneal ulceration <1/3 (X3A) → Keratomalacia >1/3 (X3B) → Corneal scar (XS).
- **Management (Therapeutic):** Day 1, Day 2, and Day 14.
  - <6 months: 50,000 IU
  - 6–11 months: 100,000 IU
  - 12 months: 200,000 IU
- **Prevention (National Prophylaxis Program):** Total 9 doses.
  - 1st dose: 100,000 IU at 9 months (with MR vaccine).
  - Subsequent: 200,000 IU every 6 months up to 5 years.
  - *Measles adjunct:* Given to all severe measles cases to prevent blindness/mortality.

3. Vitamin D & Calcium

- **Function:** Intestinal calcium/phosphorus absorption, bone mineralization.
- **Clinical Features (Rickets):** Craniotabes (earliest sign), frontal bossing, delayed fontanelle closure, rachitic rosary (non-tender), Harrison sulcus, widening of wrists, genu varum/valgum.
- **Diagnosis:** Normal/Low Ca, Low PO4, High ALP, High PTH, Low 25(OH)D (<20 ng/mL).
- **X-Ray (Wrist):** Cupping, splaying, fraying of metaphyses.
- **Management (Therapeutic):**
  - Daily: 2000 IU (<1 yr) or 3000–6000 IU (1–12 yrs) for 3 months.

- *Alternative (Stoss therapy):* 300,000–600,000 IU single dose (oral/IM) — *Caution: Risk of hypercalcemia*.
- *Mandatory:* Co-administer elemental Calcium (30–75 mg/kg/day).

- **Prevention (AAP/IAP 2021 Update):** 400 IU/day for all breastfed/partially breastfed infants from birth to 1 year.

4. Zinc

- **Function:** Metalloenzyme cofactor, gut mucosal repair, immunity.
- **Clinical Features:** Acrodermatitis enteropathica (classic triad: periorificial/acral dermatitis, alopecia, chronic diarrhea), poor wound healing, growth restriction.
- **Management (WHO Diarrhea Guidelines):**
  - <6 months: 10 mg/day for 14 days.
  - 6 months: 20 mg/day for 14 days.
- **Other Uses:** Maintenance therapy in Wilson disease (blocks enteral copper absorption).

5. Iodine

- **Function:** Thyroid hormone synthesis (T3/T4).
- **Clinical Features:** Endemic goiter, Neonatal hypothyroidism.
- **Neurological Cretinism:** Severe intellectual disability, deaf-mutism, spastic diplegia.
- **Prevention:** Universal Salt Iodization (USI) — target ≥15 ppm at the consumer level.

6. Vitamin C (Ascorbic Acid)

- **Function:** Collagen synthesis (proline/lysine hydroxylation), antioxidant, enhances iron absorption.
- **Clinical Features (Scurvy):** Bleeding gums, perifollicular petechiae, corkscrew hairs, pseudoparalysis (frog-leg posture), scorbutic rosary (sharp, tender - unlike rickets).
- **X-Ray Findings:** Frankel line (dense zone of provisional calcification), Wimberger ring (calcified epiphysis periphery), Pelkan spur (metaphyseal healing).

7. B-Complex Vitamins (Classic Presentations)

- **B1 (Thiamine):** Beriberi. Dry = peripheral neuropathy; Wet = high-output heart failure.
- **B3 (Niacin):** Pellagra. Triad = Dermatitis (Casal necklace), Diarrhea, Dementia.
- **B9 (Folate) & B12 (Cobalamin):** Megaloblastic anemia. B12 deficiency includes neurological symptoms (subacute combined degeneration); Folate deficiency does not.

Complications of Untreated Deficiencies

- **Irreversible Neurological Damage:** Severe iron deficiency in infancy, Iodine deficiency (cretinism), B12 deficiency.
- **Permanent Blindness:** Untreated Vitamin A deficiency (keratomalacia).

- **Increased Mortality:** Zinc and Vitamin A deficiency dramatically increase mortality from diarrhea and measles.

Exam Summary: Must-Write Buzzwords & Dosages

- **Zinc in Diarrhea:** 10 mg/day (<6 mo) or 20 mg/day (>6 mo) for exactly 14 days.
- **Vitamin A Prophylaxis:** 9 doses total; starts at 9 months (1 lakh IU), then 2 lakh IU every 6 months.
- **IAP Vit D Prophylaxis:** 400 IU/day from birth to 1 year for all infants.
- **AMB Iron Prophylaxis (6-59 mo):** 20 mg elemental Fe + 100 mcg FA bi-weekly.
- **Ferritin:** First marker to fall in Iron Deficiency Anemia.
- **Rosary D/D:** Rachitic rosary is rounded and non-tender; Scorbutic rosary is sharp (step-off) and exquisitely tender.

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81. Micronutrient deficiencies in Nepal

Subject: Nutrition

Epidemiology & Context

- **Burden:** High prevalence of "hidden hunger" in Nepal despite reductions in severe acute malnutrition.
- **Latest Data (NDHS 2022):** 43% of children (6–59 months) are anemic; stunting (linked to chronic zinc/micronutrient deficiency) is at 25%.
- **The "Big Four":** Iron, Vitamin A, Iodine, and Zinc.

Etiology & Risk Factors (Nepal Context)

- **Dietary:** Cereal-heavy diets (phytates inhibit iron/zinc absorption), low consumption of animal-source foods (Vitamin B12, heme iron).
- **Geographic:** Himalayan/hilly terrain with iodine-depleted soil (historically high endemic goiter).
- **Infectious:** High burden of soil-transmitted helminths (hookworm causing blood loss) and recurrent enteric infections (environmental enteropathy).
- **Socioeconomic:** Poverty, food insecurity, and poor maternal nutrition.

Key Deficiencies & Clinical Features

- **Iron Deficiency Anemia (IDA):**
    - *Pathophysiology:* Depleted iron stores → impaired heme synthesis → microcytic hypochromic anemia.
    - *Clinical:* Pallor, pica, fatigue, impaired cognitive/motor development, koilonychia (late).
- **Vitamin A Deficiency (VAD):**
    - *Pathophysiology:* Lack of retinol → impaired rhodopsin synthesis and epithelial cell keratinization.

- *Clinical:* Night blindness (earliest), Bitot's spots, corneal xerosis, keratomalacia, increased susceptibility to measles/diarrhea.

- **Iodine Deficiency Disorders (IDD):**
  - *Pathophysiology:* Insufficient substrate for thyroxine (T4) synthesis → elevated TSH → thyroid hypertrophy.
  - *Clinical:* Goiter, cretinism (severe mental retardation, deaf-mutism, spastic diplegia), neonatal hypothyroidism.
- **Zinc Deficiency:**
  - *Pathophysiology:* Metalloenzyme dysfunction → impaired cell growth and immunity.
  - *Clinical:* Stunting, recurrent diarrhea, acrodermatitis enteropathica-like rash, delayed wound healing, alopecia.

Diagnosis

- **Iron:** Hemoglobin <11 g/dL (children 6–59 mo); low serum ferritin (most sensitive early marker), high TIBC.
- **Vitamin A:** Serum retinol <20 mcg/dL; clinically via night blindness history.
- **Iodine:** Median urinary iodine concentration (UIC) <100 mcg/L (population level); neonatal TSH screening.
- **Zinc:** Serum zinc <65 mcg/dL (morning, fasting); often diagnosed clinically or presumptively in stunted/diarrheal children.

Management & National Prevention Programs (Nepal)

- **Iron & Anemia:**
  - *Baal Vita Program:* Multiple Micronutrient Powders (MNP) distributed to children 6–23 months (contains Iron, Zinc, Vit A, Folic acid, Vit C).
  - *Deworming:* Albendazole given biannually to children 12–59 months.
  - *Maternal:* Iron and Folic Acid (IFA) supplementation for pregnant/lactating women.
- **Vitamin A:**
  - *National Vitamin A Programme (NVAP):* Biannual mass distribution (Baisakh/April and Kartik/October).
  - *Dosing:* 100,000 IU (6–11 months); 200,000 IU (12–59 months).
  - *Therapeutic:* High-dose Vitamin A integrated into measles and severe acute malnutrition (SAM) management.
- **Iodine:**
  - *Universal Salt Iodization (USI):* Fortification of salt with potassium iodate ("Aayo Noon" brand with the two-child logo).
  - *Target:* >15 ppm iodine at the household level.
  - *Awareness:* February is celebrated as "Iodine Month" in Nepal.
- **Zinc:**

- *Diarrhea Protocol:* Zinc dispersible tablets (10 mg for <6 months; 20 mg for >6 months) daily for 10–14 days alongside ORS.

Complications of Unmanaged Deficiencies

- Irreversible cognitive deficits (Iron, Iodine).
- Permanent blindness (Vitamin A).
- Increased under-5 mortality due to impaired immunity (Zinc, Vitamin A).
- Intergenerational cycle of malnutrition (deficient mothers giving birth to low-birth-weight infants).

Prognosis

- Excellent if identified and supplemented early.
- *Caveat:* Cognitive deficits from severe early childhood iron or iodine deficiency are largely irreversible, highlighting the need for prevention.

Exam Summary: Must-Write Points

- **The "Big 4" in Nepal:** Iron, Vitamin A, Iodine, Zinc.
- **NDHS 2022 Data:** Anemia remains a massive public health issue (~43% in under-5s).
- **Key Interventions to list:** *NVAP* (Biannual Vit A), *Baal Vita* (MNP for 6–23 months), *USI* (Iodized salt/'Aayo Noon'), and *Zinc + ORS* for diarrhea.
- **Etiology Buzzwords:** Phytate-rich diets, Himalayan iodine-depleted soil, endemic helminthiasis.
- **Complications to flag:** Stunting (Zinc), Keratomalacia (Vit A), Cretinism (Iodine), Cognitive delay (Iron).

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82. Zinc supplementation in children

Subject: Nutrition

Basics & Physiology

- Essential trace element; cofactor for >300 metalloenzymes (e.g., alkaline phosphatase, RNA polymerase).
- Crucial for cellular immunity, growth, wound healing, and intestinal ion transport.
- Absorbed in the duodenum/jejunum; bound to metallothionein.
- Excreted primarily via feces.

Etiology of Deficiency

- **Nutritional:** Inadequate complementary feeding, exclusive breastfeeding >6 months, phytate-rich diets (binds intestinal zinc).
- **Genetic:** Acrodermatitis enteropathica (autosomal recessive mutation in *SLC39A4* gene impairing intestinal zinc transporter).

- **Losses:** Chronic diarrhea, nephrotic syndrome, burns.
- **Malabsorption:** Celiac disease, short bowel syndrome, cystic fibrosis.

Clinical Features (Deficiency)

- **Classic triad (Acrodermatitis enteropathica):** Periorificial/acral dermatitis, alopecia, diarrhea.
- **Growth:** Stunting, delayed puberty.
- **Immunity:** Recurrent infections, delayed wound healing.
- **Neurosensory:** Hypogeusia (decreased taste), anosmia, behavioral changes, night blindness.

Diagnosis

- **Serum Zinc:** Normal is 70–120 µg/dL.
- *Pitfall:* Zinc is a negative acute-phase reactant; levels drop spuriously during acute infections/inflammation.
- **Alkaline Phosphatase:** Low levels serve as a surrogate marker for severe zinc deficiency.
- **Therapeutic Trial:** Clinical improvement upon supplementation is often the most practical diagnostic tool.

Indications & Dosing (High-Yield)

- **1. Acute & Persistent Diarrhea (WHO/IAP Guidelines):**
    - **Mechanism:** Promotes enterocyte regeneration, restores brush border enzymes, enhances water/electrolyte absorption.
    - **Dose (<6 months):** 10 mg elemental zinc/day for 14 days.
    - **Dose (>6 months):** 20 mg elemental zinc/day for 14 days.
    - *Note:* Must complete the full 14-day course to replenish body stores and prevent episodes for the next 2–3 months.
- **2. Severe Acute Malnutrition (SAM):**
    - **Dose:** 2 mg/kg/day.
    - *Update (WHO/IAP):* Do not give additional zinc if the child is receiving standard therapeutic foods (F-75, F-100, RUTF), as these are already fortified. Add only if using non-fortified local diets.
- **3. Acrodermatitis Enteropathica:**
    - **Dose:** 3 mg/kg/day of elemental zinc (lifelong).
- **4. Wilson Disease (Maintenance):**
    - **Mechanism:** Induces intestinal metallothionein, which traps dietary copper and prevents its absorption.
    - **Drug of choice:** Zinc acetate.
- **5. Respiratory Infections:**

- Used as an adjunct in severe pneumonia in developing nations (reduces mortality and duration of stay), though routine universal use is debated. Dose: 10–20 mg/day.

Formulations

- Available as Zinc sulfate, Zinc acetate, Zinc gluconate.
- *Note:* 20 mg elemental zinc = 88 mg zinc sulfate.
- Best absorbed on an empty stomach, but given with food if GI upset occurs.

Adverse Effects & Toxicity

- **GI Upset:** Metallic taste, nausea, vomiting, epigastric pain.
- **Copper Deficiency:** High-dose prolonged zinc competes with copper for absorption, leading to microcytic anemia and neutropenia.
- **Immune Suppression:** Paradoxical impairment of macrophage and neutrophil function at toxic doses.

Exam Summary

- **Diarrhea dose:** 10 mg/day (<6 mo) and 20 mg/day (>6 mo) for exactly 14 days (WHO/IAP).
- **SAM pitfall:** Do NOT add extra zinc if the child is already on F-75/F-100/RUTF.
- **Acrodermatitis enteropathica:** *SLC39A4* mutation; triad of acral dermatitis, alopecia, and diarrhea.
- **Wilson disease:** Zinc acetate is used for maintenance to block copper absorption.
- **Interaction:** Prolonged high-dose zinc causes copper deficiency (anemia/neutropenia).

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83. Biochemical changes in kwashiorkor and marasmus

Subject: Nutrition

Basics & Definitions

- **Marasmus:** Non-edematous Severe Acute Malnutrition (SAM) driven primarily by severe chronic energy (calorie) deficiency.
- **Kwashiorkor:** Edematous SAM driven by protein deficiency, oxidative stress, and microbiome alterations.
- **Marasmic-Kwashiorkor:** Features of both (severe wasting + edema).

Pathophysiology (Metabolic Mechanisms)

- **Marasmus (Reductive Adaptation):** Body successfully adapts to starvation. Downregulation of Basal Metabolic Rate (BMR), active lipolysis, and muscle breakdown to supply amino acids to the liver for essential protein synthesis.
- **Kwashiorkor (Dysadaptation):** Failure of metabolic adaptation. Severe oxidative stress, glutathione depletion, and failure to mobilize muscle proteins lead to an acute drop in visceral proteins and antioxidant defenses.

Core Biochemical Changes (Comparative)

1. Proteins & Amino Acids

- **Kwashiorkor:**
  - Severe hypoalbuminemia (<2.5 g/dL).
  - Decreased transport proteins: Transferrin, ceruloplasmin, retinol-binding protein.
  - Amino acid imbalance: Decreased essential amino acids (especially branched-chain: valine, leucine, isoleucine); elevated ratio of non-essential to essential amino acids.
- **Marasmus:**
  - Serum albumin and transport proteins remain normal or are only mildly decreased (due to successful adaptation/muscle breakdown).

2. Lipids & Lipoproteins

- **Kwashiorkor:**
  - Decreased synthesis of Apolipoprotein B-100 → inability to export triglycerides from the liver → **Fatty liver (Steatosis)**.
  - Low serum cholesterol and triglycerides.
- **Marasmus:**
  - Increased free fatty acids (FFA) due to active lipolysis.
  - No fatty liver (apolipoprotein synthesis is maintained).

3. Carbohydrates

- **Both:**
  - Hypoglycemia due to depleted hepatic glycogen stores and impaired gluconeogenesis.
- **Kwashiorkor:** Severe impairment of gluconeogenic enzymes compared to marasmus.

4. Electrolytes & Minerals (Crucial WHO Concept)

- **Sodium (Both):** Increased *total body* sodium (intracellular accumulation due to Na+/K+ ATPase pump failure), but serum Na+ is often low (dilutional hyponatremia).
- **Potassium & Magnesium (Both):** Severe *total body* depletion. Intracellular K+ is lost and replaced by Na+. Serum levels may be low or falsely normal.
- **Calcium/Phosphate:** Often low (worsened during refeeding).

5. Endocrine Alterations

- **Insulin:** Low in both (allows lipolysis/proteolysis).
- **Cortisol:** Markedly elevated in Marasmus (drives adaptation); lower/inappropriately normal in Kwashiorkor (failure of adaptation).
- **Growth Hormone (GH):** Elevated in both, but Insulin-like Growth Factor 1 (IGF-1) is severely low due to hepatic **GH resistance**.
- **Thyroid:** "Euthyroid sick syndrome" – low T3, normal/high rT3, normal TSH (decreased BMR adaptation).

6. Enzymes, Antioxidants & Micronutrients

- **Kwashiorkor:** Severe depletion of glutathione, vitamin E, and superoxide dismutase (unopposed free radical damage).
- **Both:** Deficiencies in Zinc (low alkaline phosphatase), Copper, Vitamin A, and Vitamin D.
- **Iron:** High free iron in Kwashiorkor exacerbates oxidative stress via the Fenton reaction (transferrin is low, leaving iron unbound).

Clinical Correlates of Biochemistry

- **Edema (Kwashiorkor):** Hypoalbuminemia (decreased oncotic pressure) + increased capillary permeability (leukotrienes/oxidative damage) + sodium retention.
- **Flaky Paint Dermatitis/Hair Changes:** Due to Zinc, Copper, and essential amino acid deficiencies.
- **Hepatomegaly:** Triglyceride accumulation (fatty liver) due to apolipoprotein deficiency.

Diagnosis (WHO SAM Criteria)

- Weight-for-height/length (WFH) < -3 Z-scores.
- Mid-Upper Arm Circumference (MUAC) < 115 mm (in children 6–59 months).
- Presence of bilateral pitting edema.

Management Principles (Biochemical Focus - WHO 10 Steps)

- **Step 1 (Hypoglycemia):** 10% Dextrose (50 ml bolus) or immediate oral sucrose.
- **Step 4 (Electrolytes):** Add extra K+ (3-4 mEq/kg/day) and Mg2+ (0.4-0.6 mEq/kg/day). *Strictly avoid IV Sodium* (worsens edema/heart failure).
- **Step 6 (Micronutrients):** Give Vitamin A, Zinc, Copper, Folic acid. *Do not give Iron* in the initial stabilization phase (free iron worsens oxidative damage and promotes bacterial growth).

Complications

- **Refeeding Syndrome:** Rapid carbohydrate feeding → insulin surge → massive intracellular shift of Phosphate, Potassium, and Magnesium → severe hypophosphatemia, arrhythmias, seizures, and sudden death.

Exam Summary

- **Marasmus:** Reductive adaptation, elevated cortisol, active lipolysis, normal/mildly low albumin, no fatty liver.
- **Kwashiorkor:** Dysadaptation, severe oxidative stress, profound hypoalbuminemia, fatty liver (apolipoprotein deficiency).
- **Electrolyte Trap:** Both have high total body Na+ but low total body K+/Mg2+. Never give IV normal saline unless in severe shock.
- **Iron Trap:** Never give iron in the acute phase of SAM; it fuels oxidative stress and infections.
- **Refeeding Syndrome:** Driven by an insulin surge causing fatal hypophosphatemia and hypokalemia. Advance feeds slowly.

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84. Approach to a child with growth failure

Subject: Nutrition

Definition

- **Current Terminology:** "Growth faltering" is preferred over "Failure to Thrive" (FTT).
- Weight < 3rd or 5th percentile for age and sex on appropriate charts (WHO for <2 years; CDC/IAP for >2 years).
- Weight crossing > 2 major percentile lines downward over 3–6 months.
- Weight-for-height < 5th percentile (wasting).

Etiology (Mechanistic Approach)

- **Inadequate Caloric Intake (Most Common; >80%):** Poverty, neglect, incorrect formula preparation, poor breastfeeding technique, cleft lip/palate, severe GERD, neurodisability (cerebral palsy).
- **Inadequate Absorption:** Celiac disease, Cystic Fibrosis (CF), Cow's Milk Protein Allergy (CMPA), chronic diarrhea, short bowel syndrome, biliary atresia.
- **Increased Metabolic Demand:** Congenital Heart Disease (CHD), Bronchopulmonary Dysplasia (BPD), hyperthyroidism, chronic infections (TB, HIV), malignancies.
- **Defective Utilization:** Inborn errors of metabolism, chromosomal anomalies (Turner syndrome, Down syndrome), skeletal dysplasias.

Pathophysiology

- **Sequential Growth Faltering:**
    - *Phase 1:* Weight drops (acute malnutrition/wasting).
    - *Phase 2:* Height drops (chronic malnutrition/stunting).
    - *Phase 3:* Head circumference drops (severe, prolonged malnutrition; loss of "brain sparing" effect).
- **Endocrine Shift:** Chronic undernutrition suppresses IGF-1 and causes growth hormone resistance, prioritizing immediate survival over linear growth.

Clinical Approach (History & Examination)

- **Dietary History:** 3-day diet record (gold standard for outpatient), formula preparation technique, breastfeeding frequency/latch, feeding behaviors (gagging, refusal).
- **Medical History:** Perinatal (SGA vs. AGA), recurrent infections, chronic cough, stool pattern (steatorrhea, blood).
- **Psychosocial History:** Maternal depression (Edinburgh Postnatal Depression Scale), financial distress, domestic violence.
- **Physical Examination:**
    - *Anthropometry:* Accurately measure and plot Weight, Length/Height, and Head Circumference.
    - *Dysmorphism:* Webbed neck (Turner), upslanting palpebral fissures (Down).

- *Systemic Clues:* Murmur/cyanosis (CHD), clubbing/barrel chest (CF), eczema (CMPA), hepatosplenomegaly (infections/metabolic).
- *Signs of neglect:* Diaper dermatitis, flat occiput, lack of eye contact.

Diagnosis & Investigations

- *Note:* Diagnosis is primarily clinical. Avoid shotgun testing; yield of broad lab panels in asymptomatic FTT is <1%.
- **Tier 1 (Screening - if no obvious cause on history/exam):**
  - CBC, ESR/CRP (chronic infection/anemia).
  - Urine routine & culture (UTI is a classic silent cause of FTT).
  - Stool routine, pH, reducing substances (malabsorption).
  - Serum electrolytes, BUN, Creatinine, LFTs (renal/hepatic function).
- **Tier 2 (Targeted - based on specific clues):**
  - *GI:* Tissue transglutaminase (tTG-IgA) + Total IgA (Celiac).
  - *Respiratory:* Sweat chloride test (CF).
  - *Endocrine:* TSH, free T4, IGF-1, Bone age (X-ray left wrist).
  - *Genetics:* Karyotype/Microarray (mandatory in any short female to rule out Turner Syndrome).
  - *Imaging:* Echocardiogram, Chest X-ray, Renal USG.

Management

- **Goal:** Achieve "Catch-up Growth" (requires 120–150% of the Recommended Dietary Allowance [RDA] for chronological age).
- **Catch-up Calorie Formula:**
  - *Calories required (kcal/kg/day)* = (RDA for age for Ideal Weight × Ideal Weight for Height) / Actual Weight.
- **Nutritional Rehabilitation:**
  - Increase caloric density: Concentrate infant formula (e.g., 24 to 30 kcal/oz) safely to avoid hyperosmolarity.
  - Add modular supplements: MCT oil, butter, cheese, glucose polymers.
  - Strict feeding schedules: Limit meals to 20–30 minutes, avoid grazing, limit juice/water intake before meals.
- **Micronutrient Support:** Empiric Iron (3-6 mg/kg/day), Zinc, and Vitamin D supplementation.
- **Multidisciplinary Team:** Dietitian, lactation consultant, speech-language pathologist (swallow study), social worker.
- **Indications for Hospitalization:** Severe malnutrition (marasmus/kwashiorkor), hypothermia/bradycardia, failed outpatient management, suspected abuse/extreme neglect.

Complications

- **Refeeding Syndrome:** Rapid feeding causes insulin spike → intracellular shift of electrolytes → severe *hypophosphatemia, hypokalemia, hypomagnesemia* (can lead to fatal arrhythmias).
- Long-term neurocognitive impairment and lower IQ.
- Permanent short stature (if intervention is delayed past epiphyseal fusion).
- Secondary immunodeficiency.

Prognosis & Prevention

- **Prognosis:** Reversibility of cognitive deficits depends on the timing of intervention. Highest plasticity and best outcomes occur if treated before 6 months of age.
- **Prevention:** Mandatory growth monitoring using WHO charts at all routine immunization and well-child visits. Early screening for maternal postpartum depression.

Exam Summary

- **Sequence of faltering:** Weight → Height → Head Circumference (loss of brain sparing = severe).
- **Most common cause:** Inadequate caloric intake (often non-organic/psychosocial).
- **Silent organic causes:** UTI, Celiac disease, mild CF, GERD.
- **Catch-up requirement:** 120–150% of expected RDA calories and protein.
- **Refeeding syndrome triad:** Hypophosphatemia, Hypokalemia, Hypomagnesemia (monitor closely during initial nutritional rehab).
- **Must-do test:** Karyotype in any unexplained growth failure in a female child (Turner syndrome).

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85. Management of severe acute malnutrition

Subject: Nutrition

Definition & Diagnostic Criteria (WHO/IAP)

- **Age 6–59 months:** Weight-for-height/length (WFH) < -3 SD
- **MUAC:** < 11.5 cm
- **Clinical:** Bilateral pitting edema of nutritional origin (Kwashiorkor)

Triage & Site of Care

- **Appetite Test:** Offer Ready-to-Use Therapeutic Food (RUTF); observe if child eats eagerly.
- **Community-Based Management (CMAM):** Alert, passes appetite test, no medical complications.
- **Facility-Based Management (NRC):** Fails appetite test, presence of edema (+++), or severe medical complications (shock, severe pneumonia, lethargy, intractable vomiting).

Stepwise Management (WHO 10 Steps)

Divided into **Stabilization Phase** (Days 1–7) and **Rehabilitation Phase** (Weeks 2–6).

1. Prevent/Treat Hypoglycemia (Blood glucose < 54 mg/dL)

- **Conscious:** 50 mL of 10% Dextrose or sucrose solution orally/NG.

- **Unconscious/Lethargic:** 10% Dextrose 5 mL/kg IV slowly.
- **Prevention:** Feed every 2 hours (day and night).

2. Prevent/Treat Hypothermia (Axillary temp < 35°C / 95°F)

- **Management:** Skin-to-skin contact (Kangaroo Mother Care), warm blankets, radiant warmer (use cautiously to avoid insensible water loss).
- **Prevention:** Avoid drafts, keep dry, feed frequently.

3. Treat Dehydration & Shock

- **Trap:** Standard ORS and standard IV boluses cause fatal heart failure in SAM.
- **Dehydration:** Use **ReSoMal** (Oral Rehydration Solution for Malnutrition) – lower sodium (45 mEq/L), higher potassium (40 mEq/L). Dose: 5 mL/kg every 30 mins for 2 hours, then 5–10 mL/kg/hr.
- **Shock:** Lethargic + cold extremities + weak/fast pulse.
- **Shock Fluids:** IV Ringer's Lactate with 5% Dextrose, **15 mL/kg over 1 hour** (Do NOT give 20 mL/kg). Reassess; if improving, repeat 15 mL/kg over 1 hour. If no improvement, assume septic shock.

4. Correct Electrolyte Imbalances

- **Pathophysiology:** Excess total body sodium (even if serum Na is low) and severe total body potassium/magnesium deficit.
- **Action:** Restrict dietary sodium.
- **Supplement:** Potassium (3–4 mEq/kg/day) and Magnesium (0.4–0.6 mEq/kg/day).

5. Treat Infection (Empiric Antibiotics for ALL SAM)

- **Uncomplicated (Outpatient):** Oral Amoxicillin (15 mg/kg 8-hourly for 5 days).
- **Complicated (Inpatient):** IV Ampicillin (50 mg/kg 6-hourly) + IV Gentamicin (7.5 mg/kg once daily) for 7 days.
- **Non-responders/Severe sepsis:** Upgrade to IV Ceftriaxone.
- **Parasites:** Mebendazole/Albendazole (on Day 7, once stabilized).

6. Correct Micronutrient Deficiencies

- **Vitamin A:** Give on Days 1, 2, and 14 (Age <6 mo: 50k IU; 6-12 mo: 100k IU; >12 mo: 200k IU).
- **Folic Acid:** 5 mg on Day 1, then 1 mg/day.
- **Zinc & Copper:** Add to feeds (if not using pre-fortified F-75/F-100).
- **Rule: NO IRON** during the stabilization phase (free iron promotes bacterial growth and free radical damage).

7. Cautious Feeding (Stabilization Phase)

- **Formula: F-75 diet** (75 kcal/100 mL, 0.9g protein/100 mL).
- **Goal:** Maintain basal metabolism, prevent overloading liver/kidneys.
- **Volume:** 130 mL/kg/day (100 mL/kg/day if severe edema).

- **Frequency:** Small, frequent feeds (every 2–3 hours).

8. Catch-up Growth (Rehabilitation Phase)

- **Timing:** Starts when appetite returns and edema resolves (usually Day 4–7).
- **Formula:** Transition to **F-100 diet** (100 kcal/100 mL, 2.9g protein/100 mL) or **RUTF** (Ready-to-Use Therapeutic Food).
- **Goal:** 150–220 kcal/kg/day; 4–6 g/kg/day protein.
- **Iron:** Start Iron (3 mg/kg/day) ONLY in this phase, once child is gaining weight.

9. Sensory Stimulation

- Tender loving care, structured play therapy for 15–30 mins/day, maternal involvement.

10. Discharge & Follow-up

- **Discharge Criteria:** Weight gain >8g/kg/day for 3 consecutive days, edema resolved, passing appetite test, MUAC > 11.5 cm or WFH > -2 SD.
- **Follow-up:** Weekly for 1st month, then fortnightly.

Complications (Refeeding Syndrome)

- **Mechanism:** Rapid feeding causes insulin surge → intracellular shift of electrolytes.
- **Hallmarks:** Severe hypophosphatemia, hypokalemia, hypomagnesemia.
- **Clinical:** Heart failure, arrhythmias, respiratory failure, seizures.
- **Prevention:** Start feeds low and slow (F-75).

Exam Summary

- **Shock in SAM:** 15 mL/kg RL+5%D over 1 hour (never 20 mL/kg).
- **Dehydration fluid:** ReSoMal (Low Na, High K).
- **Iron rule:** Strictly contraindicated in stabilization phase; start only in rehabilitation.
- **Diets:** F-75 for stabilization (prevents refeeding syndrome); F-100/RUTF for catch-up growth.
- **Criteria for NRC admission:** Failed appetite test, severe edema, or medical complications.

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86. Nutritional rehabilitation after severe acute malnutrition

Subject: Nutrition

Definition & Criteria

- **SAM criteria (WHO/IAP):** Weight-for-height/length (WFH) < -3 SD, OR Mid-Upper Arm Circumference (MUAC) < 11.5 cm (in children 6–59 months), OR bilateral pitting pedal edema.
- **Rehabilitation Phase (Phase 2):** Encompasses steps 8–10 of the WHO 10-step SAM management protocol (Catch-up growth, Sensory stimulation, Follow-up).

Prerequisites for Rehabilitation

- Appetite has returned (passes appetite test).

- Bilateral pitting edema has resolved/resolving.
- Acute infections are controlled.
- Usually begins around Day 8–14 of admission.

Nutritional Targets (Rehabilitation Phase)

- **Calories:** 150–220 kcal/kg/day (to support rapid catch-up growth).
- **Protein:** 4–6 g/kg/day.
- **Fluid:** 150–200 mL/kg/day.

Dietary Management

- **Facility-based (Inpatient):** F-100 therapeutic milk (100 kcal and 2.9 g protein per 100 mL).
- **Community-based (CMAM):** Ready-to-Use Therapeutic Food (RUTF).
- **RUTF composition:** Lipid-based paste (peanuts, oil, sugar, milk powder, micronutrients). Provides ~540 kcal/100 g.
- **Advantage of RUTF:** No water required for preparation (prevents waterborne bacterial contamination), high energy density, long shelf-life.
- **Transition feeding:** Gradual shift from F-75 (Stabilization) to F-100/RUTF over 2–3 days to prevent osmotic diarrhea and volume overload.

Micronutrient Supplementation

- **Iron:** 3 mg/kg/day. *Exam Trap:* NEVER give iron during the stabilization phase (promotes bacterial growth and free radical damage). Start ONLY in the rehabilitation phase.
- **Zinc:** 2 mg/kg/day (continue for 14 days if diarrhea was present).
- **Folic Acid:** 5 mg on Day 1, then 1 mg/day.
- **Vitamin A:** High dose on Day 1, 2, and 14 (if clinical eye signs present) OR single dose if no signs (as per national immunization schedule).
- **Potassium & Magnesium:** Continue dietary inclusion (RUTF/F-100 are pre-fortified).

Monitoring Catch-up Growth

- **Metric:** Weight gain in g/kg/day = [(Current wt - Previous wt) / Previous wt] × 1000 / number of days.
- **Poor:** < 5 g/kg/day (requires full reassessment for hidden infection/TB/HIV).
- **Moderate:** 5–10 g/kg/day.
- **Good:** > 10 g/kg/day.

Complications of Rehabilitation

- **Refeeding Syndrome:** Sudden shift from fat to carbohydrate metabolism causes massive cellular uptake of electrolytes.
- **Hallmarks:** Hypophosphatemia (classic), hypokalemia, hypomagnesemia.
- **Clinical signs:** Edema, heart failure, arrhythmias, muscle weakness, seizures.

- **Prevention:** Start feeds slowly (F-75 first), avoid early high-protein/high-calorie loads.

Discharge Criteria (WHO/IAP)

- WFH/WFL ≥ -2 SD OR MUAC ≥ 12.5 cm for at least 2 consecutive weeks.
- No edema for at least 2 weeks.
- Clinically well and alert.
- Adequate weight gain demonstrated on CMAM/home diet.
- Mother/caregiver educated on continued feeding and vaccination.

Follow-up & Prevention

- **Schedule:** Weekly for 1st month, fortnightly for 2nd month, monthly thereafter up to 6 months.
- **Sensory stimulation:** Play therapy, structured physical activity, and maternal affection are critical for neurocognitive recovery.
- **Prevention:** Exclusive breastfeeding for 6 months, timely and adequate complementary feeding, routine immunization, WASH (Water, Sanitation, and Hygiene) practices.

Exam Summary: Absolute Must-Write Points

- Rehabilitation starts only after appetite returns and edema resolves.
- Energy goal: 150–220 kcal/kg/day; Protein goal: 4–6 g/kg/day.
- Diet: F-100 (inpatient) or RUTF (outpatient/CMAM).
- Iron (3 mg/kg/day) is added **only** in the rehabilitation phase, never in stabilization.
- Target weight gain is > 10 g/kg/day; watch strictly for Refeeding Syndrome (Hypophosphatemia).
- Discharge criteria: WFH ≥ -2 SD or MUAC ≥ 12.5 cm.

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87. Golden thousand days concept

Subject: Nutrition

Definition

- **Timeframe:** Period from conception to a child's second birthday.
- **Calculation:** 270 days (pregnancy) + 365 days (first year) + 365 days (second year) = 1000 days.
- **Concept:** Represents a critical, non-replicable window of opportunity for physical, neurological, and metabolic development.

Significance & Pathophysiology

- **Neurodevelopment:** 80% of brain growth, myelination, and synaptogenesis occur during this period.
- **Growth Velocity:** Highest rate of linear growth; primary window to prevent stunting.
- **Immune Maturation:** Critical phase for establishing gut microbiome and immune tolerance.

- **Metabolic Programming (DOHaD):** Barker's Hypothesis / Developmental Origins of Health and Disease; early nutritional insults cause epigenetic modifications, predisposing to adult Non-Communicable Diseases (NCDs).

Consequences of Deprivation

- **Short-term:** Low birth weight (LBW), severe acute malnutrition (SAM), increased susceptibility to infections, increased infant mortality.
- **Long-term:** Irreversible stunting, reduced cognitive potential (lower IQ), poor school performance.
- **Adult-onset:** Increased risk of obesity, type 2 diabetes, and hypertension (Thrifty Phenotype).

Phase-Wise Interventions (WHO/IAP Guidelines)

Phase 1: Pregnancy (Conception to Birth - 270 Days)

- **Maternal Nutrition:** Adequate caloric and protein intake to ensure optimal gestational weight gain.
- **Supplementation:** Folic acid (periconceptional), Iron-Folic Acid (IFA) for 180 days, Calcium (1g/day).
- **Infection Control:** Deworming (albendazole in 2nd trimester), maternal immunization (Td/TT), malaria prophylaxis (endemic areas).
- **Delivery:** Institutional delivery, delayed cord clamping (1–3 minutes) to prevent infant anemia.

Phase 2: Early Infancy (0 to 6 Months - 180 Days)

- **Early Initiation:** Breastfeeding within 1 hour of birth; feeding of colostrum.
- **Exclusive Breastfeeding (EBF):** No prelacteal feeds, no water; only breast milk (and prescribed vitamins/medications).
- **Neonatal Care:** Kangaroo Mother Care (KMC) for LBW/preterm infants, routine immunization.

Phase 3: Late Infancy & Toddlerhood (6 to 24 Months - 550 Days)

- **Complementary Feeding:** Timely initiation at exactly 6 months (180 days).
- **Dietary Diversity:** Minimum Acceptable Diet (MAD) using 4 out of 7 WHO food groups.
- **Continued Breastfeeding:** Sustained on-demand breastfeeding up to 2 years and beyond.
- **Supplementation:** Vitamin A (every 6 months), IFA drops (biweekly under NIPI).
- **WASH Interventions:** Safe Water, Sanitation, and Hygiene to prevent Environmental Enteric Dysfunction (EED) and recurrent diarrhea.

National Programs & Policies (India)

- **POSHAN Abhiyaan (National Nutrition Mission):** Aims to reduce stunting (2% per annum), undernutrition (2%), anemia (3%), and LBW (2%).
- **MAA Program (Mothers' Absolute Affection):** Promotes optimal breastfeeding practices.
- **Anemia Mukt Bharat (AMB):** 6x6x6 strategy targeting anemia across the life cycle, focusing heavily on pregnant women and infants.

Exam Summary

- **Must-write math:** 270 (pregnancy) + 365 (year 1) + 365 (year 2) = 1000 days.
- **Core buzzwords:** DOHaD (Barker's hypothesis), Epigenetic programming, Irreversible stunting, Neurogenesis.
- **Triad of action:** Maternal nutrition/ANC → Exclusive Breastfeeding (0-6m) → Adequate Complementary Feeding (6-24m).
- **Ultimate goal:** Prevent irreversible cognitive deficits and adult-onset metabolic syndrome.

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88. Feeding guidelines in emergencies

Subject: Nutrition

Definition & Context

- **IYCF-E:** Infant and Young Child Feeding in Emergencies; targeted interventions to protect infant nutrition and survival during humanitarian crises (natural disasters, conflicts).
- **Vulnerability:** Children <2 years are at the highest risk of mortality in emergencies due to diarrhea, pneumonia, and acute malnutrition.
- **Core Guideline:** WHO/UNICEF Operational Guidance on IYCF-E (v3.0).

Core Principles

- **Uphold the Code:** Strict adherence to the *International Code of Marketing of Breast-milk Substitutes*.
- **No Untargeted BMS:** General distribution of Breast-milk Substitutes (formula), bottles, and teats is absolutely prohibited.
- **Integration:** Combine feeding support with WASH (Water, Sanitation, and Hygiene) and maternal psychosocial support.

Assessment & Triage

- **Rapid Assessment:** Evaluate pre-emergency feeding practices, displaced population demographics, and resource availability (safe water, fuel).
- **Screening:** Universal MUAC (Mid-Upper Arm Circumference) and bilateral pitting edema checks for all children 6–59 months.
- **Identify High-Risk:** Unaccompanied infants, non-breastfed infants, severely malnourished mothers, and infants with SAM (Severe Acute Malnutrition).

Feeding Guidelines by Age/Status

- **Infants <6 months (Breastfed):**
    - Initiate breastfeeding within 1 hour of birth.
    - Ensure strict Exclusive Breastfeeding (EBF).
    - Counter common myths: Maternal stress/malnutrition does *not* stop milk production (it only temporarily affects let-down reflex).
- **Children 6–23 months:**
    - Continue breastfeeding for up to 2 years and beyond.

    - **Complementary Feeding (CF):** Must be safe, age-appropriate, and nutrient-dense.
    - Use fortified rations: Lipid-based Nutrient Supplements (LNS), Micronutrient Powders (MNPs), or fortified blended foods (e.g., Super Cereal Plus).
- **Non-Breastfed Infants (<6 months):**
    - *Hierarchy of alternative feeding (in order of preference):*
        1. Relactation (if mother/caregiver is present).
        2. Wet nursing (requires culturally acceptable, HIV-screened/safe protocols).
        3. Donor Human Milk (from safe, regulated milk banks if available).
        4. Targeted Breast-milk Substitute (BMS) as a last resort.

Management of Breast-milk Substitutes (Targeted BMS)

- **Indication:** Only for orphans, maternal absence/death, maternal HIV (if safe AFASS criteria met), or established non-breastfed status pre-emergency.
- **Prescription-only:** Distributed discreetly within the healthcare setting, not in general rations.
- **Method:** Feed via **cup** only. *Bottles and teats are strictly banned* due to high contamination risk.
- **Prerequisites for BMS:** Must supply adequate formula for 6 months (approx. 20 kg per infant), plus safe water, fuel, and equipment for safe preparation.

Maternal Support Interventions

- **"Feed the Mother":** Prioritize pregnant and lactating women (PLW) for additional food rations and hydration.
- **Safe Spaces:** Establish "Baby-Friendly Tents" or safe corners for private breastfeeding, counseling, and peer support.
- **Psychosocial Support:** Skin-to-skin contact and counseling to restore maternal confidence and let-down reflex.

Complications of Poor IYCF-E

- Infectious outbreaks (Cholera, Shigella, Rotavirus) due to contaminated formula/water.
- Rapid progression to Severe Acute Malnutrition (SAM) and Moderate Acute Malnutrition (MAM).
- Increased infant mortality (non-breastfed infants in emergencies are up to 6–10 times more likely to die).

Exam Summary: Must-Write Points

- **Absolute Ban:** Untargeted distribution of formula, bottles, and pacifiers is strictly prohibited under WHO/UNICEF guidelines.
- **Myth Busting:** Maternal stress/mild malnutrition does not dry up breastmilk; frequent suckling and psychological support restore let-down.
- **Non-Breastfed Cascade:** Relactation → Wet nursing → Donor milk → Targeted BMS (cup feeding only).

- **Integration:** IYCF-E must always be coupled with maternal nutritional support and WASH interventions.

Hematology / Oncology

89. Approach to severe anemia in children

Subject: Hematology / Oncology

Definition

- **Severe Anemia:** Hemoglobin (Hb) < 7.0 g/dL (WHO criteria for children 6 months – 5 years).
- **Life-threatening / Very Severe Anemia:** Hb < 4.0–5.0 g/dL or any anemia with hemodynamic instability/heart failure.

Etiology (By Reticulocyte Count)

- **Low/Inadequate Reticulocyte Count (Decreased Production):**
  - *Nutritional (Most Common):* Iron, Vitamin B12, Folate deficiency.
  - *Marrow Failure:* Aplastic anemia, Diamond-Blackfan anemia, Transient Erythroblastopenia of Childhood (TEC).
  - *Marrow Infiltration:* Leukemia, neuroblastoma, myelofibrosis.
  - *Infection/Inflammation:* Parvovirus B19 (causes aplastic crisis), chronic disease/CKD.
- **High Reticulocyte Count (Increased Destruction or Loss):**
  - *Hemolysis (Intrinsic):* Hemoglobinopathies (Thalassemia major, Sickle cell), Enzymopathies (G6PD deficiency), Membranopathies (Hereditary spherocytosis).
  - *Hemolysis (Extrinsic):* Autoimmune hemolytic anemia (AIHA), Microangiopathic (HUS, DIC), Malaria.
  - *Blood Loss:* GI bleed (Meckel diverticulum, hookworm, cow's milk protein allergy), trauma.

Clinical Features

- **Compensatory Signs:** Severe pallor, resting tachycardia, tachypnea, bounding pulses, hyperdynamic precordium, systolic flow murmur.
- **Red Flags (Decompensation/Heart Failure):** Hepatomegaly, gallop rhythm (S3), basal crepitations, altered sensorium, feeding difficulty.
- **Etiological Clues:**
  - *Jaundice + Splenomegaly:* Hemolytic anemia.
  - *Petechiae + Bone Pain + Lymphadenopathy:* Leukemia / Marrow infiltration.
  - *Frontal Bossing + Maxillary Prominence:* Extramedullary hematopoiesis (Thalassemia).
  - *Pica + Koilonychia:* Severe iron deficiency.

Diagnostic Approach

- **Step 1: The Core Triad**
    - Complete Blood Count (CBC) + RBC Indices.
    - Reticulocyte Count (Corrected retic count or Reticulocyte Production Index - RPI).
    - Peripheral Blood Smear (PBS).
- **Step 2: Algorithm based on Reticulocyte Count**
    - *If High Retic (>2% or RPI >2):* Evaluate for Hemolysis or Bleed.
        - Test: Unconjugated bilirubin, LDH, Haptoglobin (low), Direct Coombs Test (DCT).
    - *If Low/Normal Retic (RPI <2):* Evaluate MCV.
- **Step 3: Algorithm based on MCV (Low Retic)**
    - *Microcytic (Low MCV):* Iron profile (Ferritin, Serum Iron, TIBC), Hb Electrophoresis/HPLC (Thalassemia trait).
    - *Macrocytic (High MCV):* Serum B12, RBC Folate, Bone marrow (if suspecting marrow failure).
    - *Normocytic (Normal MCV):* Renal function tests, Bone marrow aspiration/biopsy (leukemia, aplasia).
- **Specific Smear Clues (Buzzwords):**
    - *Target cells:* Thalassemia, Hemoglobinopathies.
    - *Schistocytes:* HUS, DIC, prosthetic valves.
    - *Spherocytes:* Hereditary spherocytosis, AIHA.
    - *Bite cells / Heinz bodies:* G6PD deficiency.
    - *Blasts:* Leukemia.

Management

- **Emergency Stabilization (ABCs):**
    - Provide supplemental oxygen.
    - Establish 2 large-bore IV lines.
- **Transfusion Indications (IAP/WHO Guidelines):**
    - Hb < 4 g/dL (irrespective of clinical condition).
    - Hb < 6 g/dL with signs of heart failure, respiratory distress, or altered sensorium.
    - Active, severe bleeding.
- **Transfusion Protocol (Packed RBCs):**
    - *Standard Dose:* 10–15 mL/kg infused over 3–4 hours.
    - *Severe Heart Failure Protocol:* Give in small aliquots of 2–5 mL/kg. Administer slowly.
    - *Diuretic Cover:* IV Furosemide (1 mg/kg) midway or post-transfusion to prevent Transfusion-Associated Circulatory Overload (TACO).

- **Definitive/Targeted Therapy:**
    - *Iron Deficiency:* Oral elemental iron 3–6 mg/kg/day for 3 months post-Hb normalization.
    - *AIHA:* IV Methylprednisolone or oral Prednisolone (2 mg/kg/day).
    - *Malaria:* IV Artesunate.
    - *Thalassemia Major:* Chronic regular transfusion regimen (target pre-transfusion Hb 9-10 g/dL) + Iron chelation.

Complications

- Anemic congestive heart failure (high-output failure).
- Transfusion reactions (febrile non-hemolytic, allergic, TRALI, TACO).
- Alloimmunization (in chronically transfused patients).
- Growth failure and cognitive impairment (if chronic and untreated).

Exam Summary

- **Must-Write Triad:** CBC, Reticulocyte Count, and Peripheral Smear form the mandatory first step in evaluating *any* anemia.
- **Branching Point:** Reticulocyte count differentiates production failure (low) from destruction/loss (high).
- **Emergency Trap:** In severe anemia with heart failure, transfuse PRBCs very slowly (2-5 mL/kg) with IV Furosemide to prevent fatal TACO.
- **Classic Clue:** Iron deficiency anemia is microcytic, hypochromic with *high* RDW; Thalassemia trait is microcytic, hypochromic with *normal* RDW.

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90. Bone marrow failure syndromes

Subject: Hematology / Oncology

Definition

- Inability of the bone marrow to produce adequate numbers of one or more hematopoietic lineages
- Results in peripheral cytopenias (anemia, leukopenia, thrombocytopenia) without primary peripheral destruction

Classification

- **Inherited Bone Marrow Failure Syndromes (IBMFS):**
    - Pancytopenia: Fanconi Anemia (FA), Dyskeratosis Congenita (DC)
    - Pure Red Cell Aplasia: Diamond-Blackfan Anemia (DBA)
    - Neutropenia: Shwachman-Diamond Syndrome (SDS), Severe Congenital Neutropenia (SCN)
    - Thrombocytopenia: Congenital Amegakaryocytic Thrombocytopenia (CAMT), Thrombocytopenia Absent Radius (TAR) syndrome

- **Acquired Aplastic Anemia (AAA):**
    - Idiopathic (70-80%, immune-mediated)
    - Secondary: Viral (Hepatitis-associated aplastic anemia, EBV, Parvovirus B19), Drugs (Chloramphenicol, NSAIDs, Anticonvulsants), Toxins (Benzene), Radiation

Pathophysiology

- **FA:** Defect in DNA cross-link repair (FANC gene complex)
- **DC:** Telomere biology disorder (DKC1, TERT, TERC genes) leading to premature cellular senescence
- **DBA & SDS:** Ribosomopathies (RPS19 in DBA; SBDS in SDS) disrupting ribosome biogenesis
- **Acquired AA:** Autoreactive cytotoxic T-cells (Th1/Tc1) secrete IFN-γ and TNF-α, destroying hematopoietic stem cells (HSCs)

Clinical Features

- **General:** Pallor, fatigue (anemia); mucosal bleeding, petechiae (thrombocytopenia); recurrent infections (neutropenia)
- **Syndrome-Specific Classic Associations:**
    - **FA:** Absent/hypoplastic thumbs, absent radii, microcephaly, short stature, café-au-lait macules, horseshoe kidney
    - **DC:** Classic triad (reticulated skin hyperpigmentation, nail dystrophy, oral leukoplakia)
    - **DBA:** Triphalangeal thumbs, webbed neck, cleft lip/palate, snub nose, pure RBC aplasia (presents in infancy)
    - **SDS:** Exocrine pancreatic insufficiency (steatorrhea), metaphyseal dysostosis, neutropenia
    - **TAR:** Absent radii with **present** thumbs, severe thrombocytopenia (improves with age)

Diagnosis

- **Initial Labs:**
    - CBC: Pancytopenia or single-lineage cytopenia
    - Reticulocyte count: Inappropriately low
    - Peripheral smear: Macrocytosis (common in IBMFS), elevated HbF, absence of blasts
- **Bone Marrow Aspirate & Biopsy:**
    - Profound hypocellularity (replaced by fat)
    - Absence of abnormal infiltrates, fibrosis, or malignant blasts
- **Specific Diagnostic Tests (Must-Know):**
    - **FA:** Chromosomal breakage test using Diepoxybutane (DEB) or Mitomycin C (MMC)
    - **DC:** Leukocyte telomere length testing (via Flow-FISH)
    - **DBA:** Elevated erythrocyte adenosine deaminase (eADA)

    - **AAA:** Flow cytometry for PNH clones (CD55/CD59 deficiency) to rule out Paroxysmal Nocturnal Hemoglobinuria

- **Genetics:** Next-Generation Sequencing (NGS) targeted IBMFS panel (current gold standard for typing)

Management

- **Supportive Care (All types):**
    - Transfusions: Leukoreduced, irradiated blood products (prevents alloimmunization and Transfusion-Associated Graft-vs-Host Disease)
    - Antimicrobial prophylaxis and prompt treatment of febrile neutropenia
    - Iron chelation therapy for transfusion-dependent patients
- **Targeted Medical Therapy:**
    - **FA:** Androgens (Oxymetholone, Danazol) to improve hemoglobin and platelets (temporary measure)
    - **DBA:** Corticosteroids (first-line); ~80% respond initially
    - **SDS:** Pancreatic enzyme replacement, G-CSF for severe neutropenia
    - **Acquired Severe AA:** Immunosuppressive Therapy (IST)
        - *Update (Current Standard):* Horse Antithymocyte Globulin (ATG) + Cyclosporine A + **Eltrombopag** (TPO-receptor agonist)
- **Definitive Therapy:**
    - Hematopoietic Stem Cell Transplantation (HSCT)
    - *Critical Pitfall:* Patients with FA and DC require **Reduced-Intensity Conditioning (RIC)** regimens because standard conditioning causes fatal toxicity due to baseline DNA repair/telomere defects.

Complications & Prognosis

- **Malignancy Risk (High):**
    - Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML)
    - Solid tumors: Squamous cell carcinomas (head, neck, vulva) particularly in FA and DC
- **Endocrinopathies:** Secondary to iron overload (hypothyroidism, delayed puberty, diabetes)
- **Prognosis:** Fatal without treatment (HSCT or IST); excellent survival (>80-90%) with HLA-matched sibling donor HSCT.

Exam Summary

- **FA:** DNA repair defect, DEB test positive, absent thumbs/radii, high AML/SCC risk, requires RIC for HSCT.
- **DC:** Telomere defect, Flow-FISH diagnosis, triad of skin/nail/oral changes.
- **DBA:** Ribosomopathy, triphalangeal thumbs, elevated eADA, steroid-responsive pure red cell aplasia.

- **TAR:** Absent radii but thumbs are present (distinguishes from FA).
- **Acquired AA:** T-cell mediated destruction; frontline IST is Horse ATG + Cyclosporine + Eltrombopag.
- **Transfusions:** Must always be leukoreduced and irradiated in BMFS candidates for HSCT.

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91. Iron Deficiency anemia diagnosis and management

Subject: Hematology / Oncology

Definition

- Microcytic, hypochromic anemia resulting from inadequate total body iron to meet physiological demands for hemoglobin synthesis.

Etiology

- **Inadequate Intake:** Exclusive breastfeeding >6 months without supplementation, early introduction of cow's milk (<1 year), excessive cow's milk intake (>24 oz/day in toddlers).
- **Increased Demand:** Prematurity, low birth weight (LBW), rapid growth spurts (infancy, adolescence), cyanotic congenital heart disease.
- **Blood Loss:** Cow's milk protein allergy (occult intestinal bleeding), hookworm infestation, Meckel diverticulum, heavy menstruation.
- **Decreased Absorption:** Celiac disease, inflammatory bowel disease, concurrent use of antacids/calcium/tannins (tea).

Pathophysiology

- **Stage 1 (Storage Depletion):** Iron stores fall ⇒Serum ferritin ↓ (earliest marker).
- **Stage 2 (Transport Depletion):** Serum iron ↓, Total Iron Binding Capacity (TIBC) ↑, Transferrin saturation ↓.
- **Stage 3 (Functional Depletion):** Hemoglobin ↓, Free Erythrocyte Protoporphyrin (FEP) ↑, microcytosis (MCV ↓).

Clinical Features

- **General:** Pallor (palmar creases, conjunctiva), fatigue, irritability, poor feeding, tachycardia, flow murmur.
- **Specific to Iron:** Pica (pagophagia - craving ice, dirt), breath-holding spells, restless leg syndrome.
- **Epithelial Changes (Severe/Chronic):** Koilonychia (spoon nails), angular stomatitis, glossitis, esophageal web (Plummer-Vinson syndrome).
- **Neurological:** Poor cognitive, motor, and socio-emotional development (can be irreversible if prolonged in infancy).

Diagnosis

- **CBC & Indices:**
    - ↓Hb, ↓MCV, ↓MCH, ↓MCHC.

- ↑ Red Cell Distribution Width (RDW) > 14.5% (earliest CBC change).

- **Peripheral Smear:** Microcytic hypochromic RBCs, anisopoikilocytosis, pencil/cigar cells.
- **Iron Profile (Confirmatory):**
  - **Serum Ferritin:** <12–15 µg/L (Most sensitive/specific early marker; acute phase reactant, falsely normal in infection).
  - **Serum Iron:** Decreased.
  - **TIBC:** Increased.
  - **Transferrin Saturation:** <16%.
- **Advanced Biomarkers:**
  - **Soluble Transferrin Receptor (sTfR):** Elevated (Differentiates IDA from Anemia of Chronic Disease where sTfR is normal).
- **Thalassemia Trait Differentiation (Mentzer Index):** MCV / RBC count.
  - 13 indicates IDA.
  - < 13 indicates Thalassemia trait.

Management

- **Dietary Modification:**
  - Discontinue cow's milk if <1 year; limit to <500 mL/day (16-24 oz) if >1 year.
  - Increase iron-rich foods (meat, fortified cereals, green leafy vegetables).
  - Enhance absorption: Co-administer Vitamin C (citrus juices).
  - Inhibit absorption: Avoid tea, coffee, and calcium supplements with meals.
- **Oral Iron Therapy (First line):**
  - **Dose:** 3–6 mg/kg/day of *elemental* iron in 1–2 divided doses.
  - **Formulation:** Ferrous sulfate, ferrous gluconate, or ferrous ascorbate (better GI tolerance).
  - **Administration:** Give between meals (empty stomach) for max absorption.
  - **Duration:** Continue for **2 to 3 months after Hb normalizes** to replenish iron stores.
- **Parenteral Iron (IV):**
  - **Indications:** Severe non-compliance, malabsorption (Celiac), severe intolerance to oral iron, active IBD, chronic kidney disease.
  - **Formulations:** Iron sucrose, Ferric carboxymaltose (preferred, single-dose infusion).
- **Blood Transfusion:**
  - **Indications:** Hb <4 g/dL, or Hb <5 g/dL with impending heart failure, extreme lethargy, or concurrent severe infection.
  - **Dose:** PRBCs 3–5 mL/kg given slowly to prevent fluid overload.

Timeline of Response to Oral Iron

- **12–24 hours:** Improved appetite, decreased irritability (replacement of intracellular enzymes).
- **36–48 hours:** Bone marrow erythroid hyperplasia.
- **48–72 hours:** Reticulocytosis begins.
- **5–7 days:** Reticulocyte count peaks (Proof of compliance and correct diagnosis).
- **1–2 weeks:** Hemoglobin begins to rise (expected ↑ 1–2 g/dL per month).
- **1–3 months:** Iron stores (ferritin) repleted.

Prevention (AAP/IAP Guidelines)

- **Delayed Cord Clamping:** 30–60 seconds at birth increases iron stores for the first 6 months.
- **Term Exclusively Breastfed Infants:** 1 mg/kg/day elemental iron starting at 4 months until iron-rich solid foods are introduced.
- **Preterm/LBW Infants:** 2–4 mg/kg/day starting at 2 weeks to 1 month of age, continued through the first year.

Exam Summary: Must-Write Points

- **Earliest lab change:** Decreased serum ferritin; earliest CBC change: Increased RDW.
- **Mentzer Index (>13):** Crucial for differentiating IDA from Thalassemia trait.
- **Dose:** 3-6 mg/kg/day elemental iron; must continue 2-3 months *post-Hb normalization* to replete stores.
- **Response marker:** Reticulocytosis peaking at 5-7 days confirms diagnosis and compliance.
- **Cow's milk rule:** None <1 year; limit to <24 oz/day in toddlers. Occult blood loss + poor iron bioavailability.

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92. Vitamin B12 deficiency anemia diagnosis and management

Subject: Hematology / Oncology

Basics

- Megaloblastic anemia caused by cobalamin (Vitamin B12) deficiency.
- Leads to defective DNA synthesis with nuclear-cytoplasmic asynchrony (RNA/protein synthesis continues, cell size increases).
- Essential for two key enzymes: Methionine synthase (folate pathway) and Methylmalonyl-CoA mutase (myelin synthesis).

Etiology

- **Dietary:** Exclusively breastfed infants of strict vegan mothers (most common infant presentation), strict vegan diet in older children.
- **Gastric:** Congenital pernicious anemia (Intrinsic Factor [IF] deficiency), autoimmune pernicious anemia (older kids).
- **Intestinal Malabsorption:** Terminal ileum resection, Crohn disease, Celiac disease, *Diphyllobothrium latum* (fish tapeworm) infection.

- **Genetic/Metabolic:** Imerslund-Gräsbeck syndrome (cubilin receptor defect in ileum with proteinuria), Transcobalamin II deficiency (presents early, normal serum B12).

Clinical Features

- **General:** Insidious onset of severe pallor, extreme lethargy, anorexia, failure to thrive.
- **Gastrointestinal:** Beefy red, smooth, sore tongue (glossitis), diarrhea.
- **Dermatological:** Knuckle and palmar crease hyperpigmentation, vitiligo (if autoimmune).
- **Neurological (Hallmark):** Developmental regression/delay, marked apathy, hypotonia, paresthesias, sensory ataxia.
- **Advanced Neuro:** Subacute combined degeneration of the spinal cord (posterior and lateral columns), absent deep tendon reflexes, extensor plantars.
- *Trap:* Neurological manifestations can occur even in the absence of significant anemia.

Diagnosis

- **CBC & Indices:** Macrocytic anemia (MCV > 100 fL), inappropriately low reticulocyte count. Pancytopenia in severe/prolonged cases.
- **Peripheral Smear:** Macro-ovalocytes, hypersegmented neutrophils (≥5 lobes in >5% of neutrophils, or any cell with ≥6 lobes).
- **Biochemistry:**
    - Serum Vitamin B12: Low (<150 pg/mL).
    - Hemolysis markers: Elevated LDH and indirect bilirubin (due to intramedullary destruction/ineffective erythropoiesis).
- **Metabolites (Highly Specific):**
    - Elevated Methylmalonic Acid (MMA) *and* Homocysteine.
    - *Differentiation:* In Folate deficiency, ONLY Homocysteine is elevated; MMA is normal.
- **Bone Marrow (Rarely needed):** Hypercellular, megaloblastic erythroid hyperplasia, giant metamyelocytes.

Management

- **Drug of Choice:** Cyanocobalamin or Hydroxocobalamin (longer half-life).
- **Route:** Intramuscular (IM) or deep subcutaneous preferred for severe anemia, neurological symptoms, or malabsorption. High-dose oral is acceptable for strict dietary deficiency.
- **Standard Pediatric IM Regimen:**
    - 1,000 mcg/day IM for 2–7 days (to replenish tissue stores), *followed by*
    - 100–1,000 mcg IM weekly for 1 month, *followed by*
    - 100–1,000 mcg IM monthly for life (if irreversible etiology like pernicious anemia).
- **Oral Alternative:** 1,000–2,000 mcg/day (effective via 1% passive diffusion independent of Intrinsic Factor).

- **Blood Transfusion:** Strictly reserved for hemodynamic instability or heart failure. Give PRBCs slowly (2–3 mL/kg aliquots) with diuretics to avoid fatal volume overload.

Monitoring & Complications

- **Treatment Complication (Red Flag):** Severe hypokalemia can occur within 48 hours of starting therapy due to massive intracellular potassium shift during rapid hematopoiesis. Monitor electrolytes and supplement K+ if needed.
- **Response Timeline:**
    - Bone marrow becomes normoblastic in 48 hours.
    - Reticulocyte crisis (peak) occurs at 5–7 days.
    - Hemoglobin normalizes in 4–6 weeks.
- **Prognosis:** Hematologic and GI symptoms resolve rapidly. Neurological deficits may be permanent if treatment is delayed >6 months.

Exam Summary: Must-Write Points

- *Classic presentation:* Exclusively breastfed infant of a vegan mother presenting with pallor, hyperpigmented knuckles, and developmental regression.
- *Peripheral smear:* Macro-ovalocytes + Hypersegmented neutrophils.
- *Diagnostic clincher:* Elevated MMA + Elevated Homocysteine (distinguishes from folate deficiency).
- *Fatal pitfall:* Watch for and aggressively manage hypokalemia during the first few days of B12 replacement.
- *Blood transfusion:* Avoid unless absolutely necessary; high risk of volume overload in chronic severe anemia.

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93. Thrombocytopenia differential diagnosis

Subject: Hematology / Oncology

Definition

- **Thrombocytopenia:** Platelet count < 150,000/μL.
- **Severity:** Mild (100–150k), Moderate (50–100k), Severe (<50k). Spontaneous bleeding risk peaks at <20,000/μL.

Differential Diagnosis (Pathophysiological Classification)

- **1. Pseudothrombocytopenia (Spurious)**
    - EDTA-induced platelet clumping (Verify with peripheral smear or heparin/citrate vial).
- **2. Increased Destruction (Immune)**
    - **Primary ITP:** Most common childhood cause (post-viral).
    - **Secondary ITP:** SLE, Evans syndrome (ALPS), HIV, Hepatitis C.

- **Neonatal:** Neonatal Alloimmune Thrombocytopenia (NAIT - maternal anti-HPA-1a), Maternal ITP.
- **Drug-induced:** Heparin (HIT), Valproate, Linezolid, Penicillins.

- **3. Increased Destruction / Consumption (Non-Immune)**
  - **Microangiopathic Hemolytic Anemias (MAHA):** Hemolytic Uremic Syndrome (HUS), Thrombotic Thrombocytopenic Purpura (TTP).
  - **Consumptive:** Disseminated Intravascular Coagulation (DIC), Sepsis.
  - **Vascular:** Kasabach-Merritt phenomenon (giant kaposiform hemangioendothelioma).
- **4. Decreased Production (Bone Marrow Failure)**
  - **Infiltration:** Acute Leukemia (ALL, AML), Neuroblastoma, Lymphoma.
  - **Aplastic/Hypoplastic:** Severe Aplastic Anemia, Parvovirus B19.
  - **Inherited Bone Marrow Failure Syndromes (IBMFS):** Fanconi Anemia, Dyskeratosis Congenita.
  - **Congenital Platelet Disorders:**
    - *TAR Syndrome:* Thrombocytopenia with Absent Radii (Thumbs are PRESENT).
    - *Wiskott-Aldrich Syndrome (WAS):* X-linked, Microthrombocytopenia, Eczema, Immunodeficiency.
    - *Bernard-Soulier Syndrome:* Giant platelets, GP Ib-IX-V defect.
    - *Congenital Amegakaryocytic Thrombocytopenia (CAMT):* MPL gene mutation.
  - **Nutritional:** Severe Vitamin B12 / Folate deficiency.
- **5. Sequestration**
  - **Hypersplenism:** Portal hypertension (Extrahepatic portal venous obstruction), Gaucher disease, Malaria, Thalassemia major.

Clinical Features & Diagnostic Clues

- **Bleeding Pattern:** Mucocutaneous (petechiae, purpura, ecchymoses, epistaxis, menorrhagia).
- **Red Flag:** "Wet purpura" (blood blisters on oral mucosa) strongly predicts impending intracranial hemorrhage (ICH).
- **Physical Exam Clues:**
  - *Hepatosplenomegaly / Lymphadenopathy:* Suggests Leukemia, Lymphoma, or Infection (Not typical ITP).
  - *Skeletal anomalies:* Radius absent/Thumb present (TAR); Thumb absent/abnormal (Fanconi).
  - *Eczema + Recurrent infections:* WAS.
  - *Massive spleen:* Hypersplenism, Gaucher, Malaria.

Diagnostic Approach

- **Step 1: Peripheral Blood Smear (PBS) - Absolute Mandatory First Step**

  - Rule out clumping (Pseudothrombocytopenia).
  - *Schistocytes:* HUS, TTP, DIC.
  - *Blasts:* Leukemia.
  - *Platelet Size:* Giant (Bernard-Soulier, ITP recovery), Micro (WAS).
- **Step 2: CBC Indices**
  - *Mean Platelet Volume (MPV):* High in destructive causes (ITP); Low in WAS; Normal/Low in production defects.
  - *Pancytopenia:* Points to Aplastic anemia, Leukemia, or severe B12 deficiency.
- **Step 3: Bone Marrow Aspiration & Biopsy (Indications)**
  - Abnormal WBC count or differential (blasts).
  - Unexplained anemia (non-bleeding related).
  - Unexplained hepatosplenomegaly or lymphadenopathy.
  - Failure to respond to standard ITP therapy (IVIG/Steroids).
  - *Update (ASH 2019 / IAP):* Bone marrow is NO LONGER strictly required before starting corticosteroids in classic, typical childhood ITP.
- **Step 4: Targeted Investigations**
  - PT/aPTT/Fibrinogen/D-dimer (DIC).
  - BUN/Creatinine, Urinalysis (HUS).
  - ANA, dsDNA, Direct Coombs Test (SLE, Evans syndrome).

Management Principles

- **General:** Avoid NSAIDs/Aspirin, intramuscular injections, and contact sports.
- **Platelet Transfusions:**
  - *Indications:* Active life-threatening bleeding (ICH), count <10k with high fever/sepsis, or prior to invasive procedures.
  - *Contraindications:* TTP, HIT (fuels thrombosis).
  - *Relative Contraindications:* ITP, HUS (transfused platelets are rapidly destroyed; use only in life-threatening hemorrhage).
- **Disease-Specific (Brief):**
  - *ITP:* Observation (if no mucosal bleeding), IVIG (1 g/kg), or short-course Corticosteroids.
  - *HUS:* Supportive care, dialysis, Eculizumab (for atypical HUS).
  - *Leukemia:* Induction chemotherapy.

Complications

- Intracranial Hemorrhage (ICH): Incidence <1% in ITP, but highest mortality.
- Severe GI or pulmonary hemorrhage.

- Treatment-related: Steroid toxicity, IVIG-induced aseptic meningitis.

Exam Summary (Must-Write Points)

- Always rule out pseudothrombocytopenia via peripheral smear first.
- Differentiate TAR (thumbs present) vs. Fanconi anemia (thumbs absent/hypoplastic).
- Wiskott-Aldrich triad: Microthrombocytopenia, Eczema, Immunodeficiency.
- Bone marrow is indicated in thrombocytopenia if there is hepatosplenomegaly, lymphadenopathy, or abnormalities in other cell lines.
- Platelet transfusions are contraindicated in TTP and HIT, and generally avoided in ITP/HUS unless life-threatening bleeding occurs.

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94. Immune thrombocytopenic purpura

Subject: Hematology / Oncology

Definition & Classification

- **Definition:** Acquired immune-mediated isolated thrombocytopenia (platelet count <100,000/microL) with normal WBC and Hb, in the absence of other causes.
- **Current Terminology (International Working Group):**
  - *Newly diagnosed:* <3 months duration
  - *Persistent:* 3–12 months duration
  - *Chronic:* >12 months duration

Etiology & Pathophysiology

- **Trigger:** Often preceded by a viral illness (URTI, gastroenteritis, Varicella) or live vaccination (MMR) 1–4 weeks prior.
- **Antibody Production:** Autoreactive IgG antibodies target platelet surface glycoproteins (GP IIb/IIIa and GP Ib/IX).
- **Destruction:** Opsonized platelets are phagocytosed by tissue macrophages, primarily in the spleen.
- **Impaired Production:** Autoantibodies also target megakaryocytes, causing relative thrombopoietin (TPO) unresponsiveness and decreased platelet production.

Clinical Features

- **Classic Presentation:** Previously healthy child (peak age 2–5 years) with abrupt onset of bruising.
- **Skin (Dry Purpura):** Petechiae, purpura, and ecchymoses over bony prominences.
- **Mucosal (Wet Purpura):** Epistaxis, gingival bleeding, hematuria, menorrhagia (indicates higher risk of severe hemorrhage).
- **Physical Exam:** Well-appearing child. No hepatosplenomegaly (HSM), no lymphadenopathy, no pallor (unless significant bleeding has occurred).

- **Red Flags (Suggest Alternative Diagnoses like Leukemia/Aplastic Anemia):** Fever, bone pain, HSM, lymphadenopathy, dysmorphic features.

Diagnosis

- **Nature:** Diagnosis of exclusion.
- **CBC:** Isolated thrombocytopenia. WBC count and differential are normal. Hemoglobin normal (or appropriately low if active bleeding).
- **Peripheral Smear:** Large platelets (megathrombocytes); normal RBC and WBC morphology; no blasts.
- **Coagulation Profile:** PT and aPTT are strictly normal.
- **Bone Marrow Aspiration (BMA):** Shows normal or increased megakaryocytes.
    - *ASH 2019 Update:* BMA is **not** routinely required in classic ITP, even before starting corticosteroids.
    - *Indications for BMA:* Atypical clinical features (HSM, bone pain), abnormal WBC/RBC on smear, failure to respond to initial IVIG therapy, or before splenectomy.

Management (ASH 2019 & IAP Guidelines)

- *Core Principle:* Treat the bleeding, not the platelet count.
- **1. Observation (First-line for most):**
    - Indicated for children with no bleeding or mild bleeding (skin manifestations only), regardless of the absolute platelet count.
    - Counseling: Restrict contact sports, avoid NSAIDs/aspirin.
- **2. Pharmacological Therapy (First-line options):**
    - *Indication:* Significant mucosal bleeding (wet purpura) or severe thrombocytopenia with high bleeding risk.
    - **Corticosteroids:** Prednisolone (2–4 mg/kg/day for 1–2 weeks, then taper) OR Dexamethasone pulse (0.6 mg/kg/day for 4 days).
    - **IVIG:** 0.8–1 g/kg as a single dose. Rapidly blocks Fc receptors on splenic macrophages. Preferred if rapid rise in platelets is needed.
    - **Anti-D Immune Globulin:** 50–75 mcg/kg IV.
        - *Prerequisites:* Patient must be Rh-positive, have an intact spleen, and a negative Direct Antiglobulin Test (DAT).
        - *Black Box Warning:* Fatal intravascular hemolysis (monitor urine color/Hb closely).
- **3. Emergency Management (Life-threatening bleed / ICH):**
    - Platelet transfusion (2–3 times normal dose).
    - IV Methylprednisolone (30 mg/kg/day) + IVIG (1 g/kg/day).
    - Consider emergency splenectomy or Romiplostim.

Chronic / Refractory ITP Management

- **TPO Receptor Agonists (TPO-RAs):** Eltrombopag (oral) or Romiplostim (subcutaneous). *Update:* Now preferred second-line agents over Rituximab.
- **Rituximab:** Anti-CD20 monoclonal antibody. Good response but risk of prolonged hypogammaglobulinemia.
- **Splenectomy:** Curative in 70-80%, but delayed as much as possible (ideally >5 years of age) due to risk of Overwhelming Post-Splenectomy Infection (OPSI). Requires prior vaccination (Pneumococcus, Meningococcus, Hib).

Complications & Prognosis

- **Complications:** Intracranial hemorrhage (ICH) is the most feared but extremely rare (<1%). Severe epistaxis causing anemia.
- **Prognosis:** Excellent. 80–90% of childhood ITP resolves spontaneously within 6 months.
- **Risk factors for chronicity:** Older age (>10 years), insidious onset, lack of preceding viral illness, presence of other autoimmune markers.

Exam Summary

- **Classic Triad:** Healthy child + sudden petechiae/purpura + isolated thrombocytopenia.
- **Smear Finding:** Large platelets with normal WBC/RBCs.
- **Guideline Trap:** Do NOT treat based solely on platelet count; treat based on bleeding severity (Observation is standard for dry purpura).
- **Anti-D Rule:** Only works if Rh-positive and spleen is intact; watch out for severe hemolysis.
- **Bone Marrow Rule:** Not mandatory for typical ITP; required if atypical features (HSM, bone pain, blasts) are present.

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95. Acute lymphoblastic leukemia

Subject: Hematology / Oncology

Definition & Basics

- Clonal malignant proliferation of lymphoid progenitor cells in bone marrow (>20% blasts)
- Most common childhood cancer (~25% of all pediatric malignancies)
- Peak age: 2–5 years; Male > Female predominance

Etiology & Risk Factors

- **Genetic syndromes:** Down syndrome (10–20x increased risk), Bloom syndrome, Ataxia-telangiectasia, Li-Fraumeni syndrome
- **Environmental:** In utero or early childhood exposure to ionizing radiation
- **Infections:** Postulated delayed infection hypothesis (Greaves) leading to aberrant immune response

Classification (WHO 2022 Updates)

- **B-lymphoblastic leukemia (B-ALL):** ~80–85% of cases; classified heavily by genetic abnormalities (e.g., hyperdiploidy, hypodiploidy, Ph-chromosome positive, Ph-like)

- **T-lymphoblastic leukemia (T-ALL):** ~15–20% of cases; associated with older age, male sex, high WBC, and mediastinal mass

Clinical Features

- **Marrow Failure:**
    - Anemia: Pallor, lethargy, tachycardia
    - Thrombocytopenia: Petechiae, purpura, mucosal bleeding
    - Neutropenia: Fever, recurrent or atypical infections
- **Tissue Infiltration:**
    - Bone/Joint pain: Limp, refusal to walk (often misdiagnosed as JIA or osteomyelitis)
    - Organomegaly: Hepatosplenomegaly, painless lymphadenopathy
- **T-ALL specific:** Anterior mediastinal mass causing SVC syndrome or respiratory distress (stridor, wheeze)
- **Sanctuary Sites (Extramedullary):**
    - CNS: Headache, vomiting, cranial nerve palsies (CN VII most common)
    - Testes: Painless, unilateral (or bilateral) testicular enlargement

Diagnosis & Investigations

- **CBC & Smear:** Cytopenias, circulating lymphoblasts (blasts may be absent in "aleukemic leukemia")
- **Bone Marrow Aspiration (Gold Standard):** ≥20% lymphoblasts replaces normal architecture
- **Flow Cytometry (Lineage assignment):**
    - *B-ALL:* TdT+, CD19+, CD22+, CD79a+, CD10+ (CALLA)
    - *T-ALL:* TdT+, CD2+, CD3+, CD5+, CD7+
- **Cytogenetics/Molecular (Crucial for prognosis):**
    - *Favorable:* Hyperdiploidy (51–65 chromosomes), t(12;21) [ETV6-RUNX1]
    - *Unfavorable:* Hypodiploidy (<44), t(9;22) [Philadelphia/BCR-ABL1], t(4;11) [KMT2A/MLL rearrangement - common in infants]
- **CSF Analysis:** Cytospin to evaluate CNS status (CNS 1: no blasts; CNS 2: <5 WBCs + blasts; CNS 3: ≥5 WBCs + blasts or cranial nerve palsy)
- **Baseline Workup:** Uric acid, electrolytes (Ca, PO4, K), LDH, LFT, RFT, Echo (pre-anthracycline), Chest X-ray (rule out mediastinal mass)

Risk Stratification (NCI/Rome Criteria)

- **Standard Risk:** Age 1 to <10 years AND WBC < 50,000/microL
- **High Risk:** Age <1 year OR ≥10 years OR WBC ≥ 50,000/microL
- *Note:* Minimal Residual Disease (MRD) response now supersedes initial NCI criteria for final treatment stratification.

Management (Phases of Chemotherapy)

- **1. Remission Induction (4 weeks):**
    - *Drugs:* Vincristine, Corticosteroid (Dexamethasone/Prednisolone), PEG-Asparaginase. Add Anthracycline (Daunorubicin) for high-risk.
    - *Goal:* Eradicate >99% of initial burden; achieve morphological remission (<5% blasts) and MRD negative (<0.01%).
- **2. Consolidation/Intensification:** High-dose Methotrexate, Cytarabine, Mercaptopurine (6-MP) to eradicate residual drug-resistant cells.
- **3. Maintenance (2–3 years):** Daily oral 6-MP, weekly oral Methotrexate, intermittent pulses of Vincristine/Steroid.
- **CNS-Directed Therapy:** Given throughout all phases via Intrathecal Methotrexate (± Cytarabine and Hydrocortisone as "triple intrathecal therapy"). Cranial irradiation reserved for severe CNS disease/relapse.

Targeted & Advanced Therapies (Recent Updates)

- **Ph+ ALL:** Add Tyrosine Kinase Inhibitors (Imatinib or Dasatinib) to frontline chemotherapy.
- **Relapsed/Refractory B-ALL:**
    - *Blinatumomab:* BiTE antibody (CD19 and CD3)
    - *Inotuzumab ozogamicin:* Anti-CD22 antibody-drug conjugate
    - *CAR-T Cell Therapy (Tisagenlecleucel):* Chimeric antigen receptor T-cells targeting CD19 (revolutionary for refractory cases)
- **HSCT:** Indicated for very high-risk first remission (e.g., severe hypodiploidy, infant ALL with KMT2A) or 2nd/subsequent remissions.

Supportive Care & Complications

- **Tumor Lysis Syndrome (TLS):** Hyperuricemia, hyperkalemia, hyperphosphatemia, *hypo*calcemia.
    - *Prevention/Treatment:* Hyperhydration, Allopurinol (low risk) or Rasburicase (high risk/established TLS).
- **Infection Prophylaxis:** Cotrimoxazole (PCP prophylaxis) starting post-induction; antifungal prophylaxis in select high-risk blocks.
- **Drug Toxicity:**
    - *Vincristine:* Peripheral neuropathy, foot drop, constipation.
    - *Asparaginase:* Pancreatitis, thrombosis (sagittal sinus), anaphylaxis.
    - *Steroids:* Avascular necrosis (AVN), hyperglycemia, mood changes.

Prognosis

- Overall 5-year survival in children is now >90%.
- **End-of-Induction MRD:** The single most powerful independent prognostic factor. MRD ≥0.01% indicates need for treatment intensification.

- Infants (<1 year) have the worst prognosis (frequent KMT2A rearrangements, CD10 negative).

Exam Summary: Must-Write Points

- Most common pediatric cancer; peak age 2-5 years; Down syndrome is a major risk factor.
- Diagnosis requires ≥20% blasts in bone marrow; flow cytometry differentiates B-ALL (CD19+, CD10+) vs T-ALL (CD3+, mediastinal mass).
- Good prognosis: t(12;21), hyperdiploidy. Poor prognosis: t(9;22), t(4;11), hypodiploidy.
- Minimal Residual Disease (MRD) at the end of induction (<0.01%) is the ultimate prognosticator.
- Modern relapsed ALL management relies on immunotherapy: Blinatumomab (CD19/CD3) and CAR-T cells.

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96. Non Hodgkin lymphoma

Subject: Hematology / Oncology

Basics

- Malignant proliferation of lymphoid cells (B, T, or NK cells)
- Accounts for ~7% of childhood cancers
- Unlike adults, pediatric NHL is almost exclusively high-grade, diffuse, and rapidly growing
- Extranodal involvement is highly characteristic in children

Etiology & Risk Factors

- **Immunodeficiency:** Primary (Wiskott-Aldrich, Ataxia-Telangiectasia, Severe Combined Immunodeficiency) or Acquired (HIV/AIDS)
- **Post-transplant:** Post-Transplant Lymphoproliferative Disorder (PTLD)
- **Viral infections:** Epstein-Barr Virus (EBV) heavily associated with endemic Burkitt lymphoma; HIV

Classification & Genetics (WHO)

- **Mature B-cell (Burkitt Lymphoma):** Most common (~40%); t(8;14) translocation; *c-myc* oncogene; "Starry sky" appearance on histology
- **Lymphoblastic Lymphoma (LL):** ~30%; predominantly T-cell precursor; genetically overlaps with T-ALL
- **Diffuse Large B-Cell Lymphoma (DLBCL):** ~15%; CD20 positive
- **Anaplastic Large Cell Lymphoma (ALCL):** ~10%; mature T-cell; t(2;5) translocation; ALK (Anaplastic Lymphoma Kinase) positive; CD30 positive

Clinical Features

- **Burkitt Lymphoma:**
    - *Endemic (African):* Jaw/facial bone tumors

    - *Sporadic:* Abdominal mass (ileocecal), mimics intussusception or appendicitis, massive ascites

- **Lymphoblastic Lymphoma:** Anterior mediastinal mass, SVC syndrome, pleural effusion, airway compromise, cervical lymphadenopathy
- **Anaplastic Large Cell Lymphoma:** Painless peripheral lymphadenopathy, systemic "B symptoms" (fever, weight loss, night sweats), skin/bone lesions

Diagnosis

- **Blood:** CBC (cytopenias if marrow involved), extremely high LDH (marker of tumor burden/turnover), hyperuricemia
- **Tissue (Gold Standard):** Excisional biopsy or large core needle biopsy (FNA is inadequate for architecture)
- **Pathology:** Flow cytometry, immunohistochemistry (IHC), cytogenetics/FISH
- **Staging Imaging:** Whole-body PET-CT (preferred) or CT neck/chest/abdomen/pelvis
- **Dissemination check:** Bone marrow aspiration/biopsy and CSF cytology (mandatory to rule out Stage IV/leukemic conversion)

Staging (St. Jude / Murphy System)

- **Stage I:** Single tumor/nodal area (excluding mediastinum/abdomen)
- **Stage II:** Single tumor with regional nodes, or two tumors on the *same side* of diaphragm, or primary GI tract tumor (completely resected)
- **Stage III:** Tumors on *both sides* of diaphragm, any primary intrathoracic (mediastinal) tumor, extensive unresectable intra-abdominal disease, or paraspinal/epidural tumors
- **Stage IV:** Any of the above WITH initial involvement of Bone Marrow (<25% blasts) and/or CNS

Management

- **General Principle:** Systemic chemotherapy is the mainstay; radiation is rarely used (unlike Hodgkin lymphoma)
- **Mature B-cell (Burkitt/DLBCL):** Short-duration, intensive, pulse-dose multi-agent chemotherapy (COPADM: Cyclophosphamide, Vincristine, Prednisolone, Doxorubicin, Methotrexate)
    - *Update (AAP/Current standard):* Addition of **Rituximab** (anti-CD20) significantly improves survival in high-risk mature B-cell NHL
- **Lymphoblastic Lymphoma:** Prolonged, leukemia-like regimen (Induction, Consolidation, Maintenance) lasting ~2 years
- **ALCL:** Chemotherapy (APO: Doxorubicin, Prednisone, Vincristine); *Targeted:* **Brentuximab vedotin** (anti-CD30) or **Crizotinib** (ALK inhibitor) for relapsed/refractory disease
- **Surgery:** Limited to diagnostic biopsy or management of acute emergencies (e.g., bowel resection for intussusception)

Oncologic Emergencies & Complications

- **Tumor Lysis Syndrome (TLS):** Extremely high risk in Burkitt Lymphoma

- *Prevention/Treatment:* Hyperhydration (no potassium in IV fluids), Allopurinol (low risk) or **Rasburicase** (high risk/elevated uric acid), monitor electrolytes q4-6h

- **Superior Vena Cava (SVC) Syndrome:** High risk in Lymphoblastic Lymphoma
  - *Management:* Secure airway, avoid sedation/general anesthesia; empiric steroids or emergent radiation *only* if life-threatening and biopsy impossible
- **Spinal Cord Compression:** Requires urgent dexamethasone and local therapy

Prognosis

- Overall survival >80-90% with modern risk-adapted chemotherapy
- Poor prognostic factors: High LDH (>2x normal), CNS involvement, poor early response to therapy

Exam Summary

- **Buzzwords:** Burkitt = t(8;14), c-myc, jaw/abdomen, starry sky; Lymphoblastic = T-cell, mediastinal mass; ALCL = t(2;5), ALK+, CD30+.
- **Emergencies:** Prophylaxis for Tumor Lysis Syndrome (Rasburicase + hydration) is a mandatory step before initiating chemo for Burkitt.
- **Staging:** Murphy staging is standard; BM or CNS involvement automatically makes it Stage IV.
- **Treatment Trap:** Do NOT use radiation routinely for pediatric NHL; it is a systemic disease requiring intensive chemotherapy.

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97. Tumor lysis syndrome

Subject: Hematology / Oncology

Basics

- **Definition:** Oncologic emergency caused by massive, rapid destruction of malignant cells releasing intracellular contents into the systemic circulation.
- **Timing:** Typically occurs 48–72 hours after initiation of cytotoxic chemotherapy, but can occur spontaneously before treatment.

Etiology & Risk Factors

- **High-Risk Malignancies:** Burkitt lymphoma, T-cell Acute Lymphoblastic Leukemia (ALL) with hyperleukocytosis (WBC > 100,000/mm^3), Acute Myeloid Leukemia (AML), bulky advanced-stage lymphomas.
- **Patient Factors:** Pre-existing renal dysfunction, baseline hyperuricemia, dehydration, oliguria, acidic urine.

Pathophysiology

- **Hyperkalemia:** Massive release of intracellular potassium.
- **Hyperphosphatemia:** Release of intracellular phosphate (malignant cells have up to 4x normal phosphate).

- **Secondary Hypocalcemia:** Excess phosphate binds to serum calcium, precipitating as calcium phosphate crystals in tissues and renal tubules.
- **Hyperuricemia:** Breakdown of cellular nucleic acids (purines) → hypoxanthine → xanthine → uric acid (via xanthine oxidase). Uric acid precipitates in acidic renal tubules.
- **Acute Kidney Injury (AKI):** Dual mechanism of obstructive nephropathy (uric acid crystals + calcium phosphate precipitation).

Clinical Features

- **Hyperkalemia:** Muscle weakness, paresthesias, arrhythmias, ECG changes (tall peaked T waves, wide QRS).
- **Hypocalcemia:** Tetany, Chvostek/Trousseau signs, muscle cramps, seizures, prolonged QT interval.
- **Hyperuricemia/AKI:** Oliguria, anuria, hematuria, flank pain, lethargy, edema, hypertension.

Diagnosis (Cairo-Bishop Criteria)

1. Laboratory TLS (LTLS)

- Requires ≥2 of the following metabolic abnormalities occurring within 3 days before or 7 days after therapy initiation (or a 25% change from baseline):
    - **Uric Acid:** ≥8 mg/dL
    - **Potassium:** ≥6.0 mEq/L
    - **Phosphorus:** ≥6.5 mg/dL (children) or ≥4.5 mg/dL (adults)
    - **Calcium:** $\le$ 7.0 mg/dL

2. Clinical TLS (CTLS)

- Requires Laboratory TLS **PLUS** ≥1 of the following:
    - **Renal:** AKI (Serum creatinine ≥1.5x upper limit of normal for age)
    - **Cardiac:** Arrhythmia / sudden death
    - **Neurologic:** Seizures

Prevention (Risk-Stratified Approach)

- **Aggressive Hydration (Cornerstone):** 2–3 L/m^2/day (without potassium) to maintain urine output ≥100 mL/m^2/hr (or ≥3 mL/kg/hr in infants).
- **Urine Alkalinization:** *Previously* routine; *Now* discouraged if hyperphosphatemia is present (increases risk of calcium-phosphate precipitation).
- **Low/Intermediate Risk:** Allopurinol (xanthine oxidase inhibitor) 10 mg/kg/day + Hydration. *Note: Allopurinol prevents new uric acid formation but does not clear existing uric acid; it also increases xanthine levels which can precipitate.*
- **High Risk:** Rasburicase (recombinant urate oxidase) 0.2 mg/kg IV.
    - *Mechanism:* Clears existing uric acid by converting it to highly soluble allantoin.
    - *Contraindication:* G6PD deficiency (causes severe hemolysis/methemoglobinemia).

Management of Established TLS

- **Hyperuricemia:** Rasburicase is treatment of choice. Send uric acid blood samples on ice (rasburicase continues to degrade uric acid ex vivo at room temperature, causing falsely low results).
- **Hyperkalemia:**
    - Mild/Moderate: Stop all K+ fluids, give loop diuretics, sodium polystyrene sulfonate (Kayexalate).
    - Severe/ECG changes: IV Calcium gluconate (cardioprotective), IV Insulin + Dextrose, nebulized Salbutamol, Sodium bicarbonate.
- **Hyperphosphatemia:** Phosphate binders (sevelamer, aluminum hydroxide), dietary restriction.
- **Hypocalcemia: DO NOT TREAT** asymptomatic hypocalcemia (treating increases calcium-phosphate precipitation). Give IV Calcium gluconate *only* for symptomatic hypocalcemia (tetany/seizures) or severe hyperkalemia.
- **Renal Replacement Therapy (Dialysis):**
    - *Indications:* Refractory hyperkalemia, fluid overload/pulmonary edema, refractory oliguria/anuria, severe symptomatic hypocalcemia, calcium-phosphate product > 70.

Prognosis & Complications

- **Complications:** Permanent renal damage, fatal ventricular arrhythmias, status epilepticus.
- **Prognosis:** Excellent if anticipated and prevented. Mortality significantly increases once Clinical TLS and AKI develop requiring dialysis.

Exam Summary (Must-Write Points)

- **Hallmark tetrad:** Hyperkalemia, Hyperphosphatemia, Hyperuricemia, Hypocalcemia.
- **Diagnosis:** Cairo-Bishop Criteria (Lab TLS = 2+ metabolic derangements; Clinical TLS = Lab TLS + AKI/arrhythmia/seizure).
- **Prevention:** Hyperhydration is the most critical intervention.
- **Drug choice:** Allopurinol for prevention (blocks formation); Rasburicase for high-risk/treatment (clears existing).
- **Trap:** Never treat asymptomatic hypocalcemia in TLS; it worsens metastatic calcium-phosphate precipitation in kidneys.
- **Contraindication:** Rasburicase is strictly contraindicated in G6PD deficiency.

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98. Thalassemia antenatal diagnosis and management

Subject: Hematology / Oncology

Basics & Indications

- **Inheritance:** Autosomal recessive quantitative globin chain defect.
- **Risk:** 25% chance of Thalassemia Major/Intermedia if both parents are carriers.

- **Target Conditions:** Beta-thalassemia major (severe anemia) and Alpha-thalassemia major (Hb Barts / Hydrops fetalis).
- **Indication for Antenatal Diagnosis (AND):** Both partners confirmed as carriers of beta or alpha thalassemia mutations.

Step 1: Parental Screening

- **Timing:** Ideally pre-conceptional or first trimester (first antenatal visit).
- **Approach:** Screen mother first; if positive, screen father immediately.
- **Primary Screen (CBC):** MCV < 80 fL, MCH < 27 pg.
- **Mentzer Index:** MCV / RBC count < 13 strongly suggests thalassemia trait (differentiates from Iron Deficiency).
- **Confirmatory (Hb HPLC):** HbA2 > 3.5% diagnostic for Beta-thalassemia trait.
- **Molecular Diagnosis:** Essential to identify specific parental genetic mutations (via ARMS-PCR or Sanger sequencing) *before* fetal testing.

Step 2: Antenatal Diagnosis (AND)

- **Prerequisite:** Parental mutations must be known. Maternal contamination must be ruled out (using VNTR markers).
- **Non-Invasive Prenatal Testing (NIPT):**
    - Uses cell-free fetal DNA (cffDNA) from maternal blood.
    - Can be done from 10 weeks gestation.
    - Useful for detecting paternal mutations or using relative haplotype dosage (RHDO).
- **Invasive Testing (Gold Standard):**
    - **Chorionic Villus Sampling (CVS):** 11–14 weeks gestation. *Procedure of choice* (allows early diagnosis and safer termination).
    - **Amniocentesis:** 15–18 weeks gestation. Done if late presentation or CVS contraindicated.
    - **Cordocentesis (PUBS):** 18–21 weeks gestation. Fetal blood sampling (rarely used now due to advanced DNA techniques, reserved for late presenters).
- **Fetal Tissue Analysis:** ARMS-PCR (common known mutations), Gap-PCR (alpha-thalassemia deletions), or Next-Generation Sequencing (NGS).

Step 3: Management & Counseling

- **Counseling Style:** Strict non-directive genetic counseling.
- **If Fetus is Normal / Carrier (Trait):**
    - Reassure parents.
    - Continue routine obstetric care.
- **If Fetus has Beta-Thalassemia Major:**

    - Discuss prognosis, lifelong transfusion needs, chelation therapy, and curative HSCT (Bone Marrow Transplant).
    - **Termination:** Offer Medical Termination of Pregnancy (MTP). *Update:* Under Indian MTP Amendment Act 2021, termination for severe fetal anomalies is legally permitted up to 24 weeks (and beyond 24 weeks with Medical Board approval).
    - **Continuation:** If parents opt to continue, prepare for postnatal management (baseline screening, arranged blood supply, HLA-typing of parents/siblings for future HSCT).
- **If Fetus has Alpha-Thalassemia Major (Hb Barts):**
    - High risk of fetal hydrops and maternal "Mirror Syndrome" (severe preeclampsia-like state).
    - Termination is generally recommended.
    - **In-Utero Therapy:** If continuation desired, serial Intrauterine Transfusions (IUT) can prevent hydrops, followed by lifelong postnatal transfusions/HSCT.

Prevention & Future Planning

- **Pre-implantation Genetic Testing (PGT-M):** IVF with testing of the embryo at the 8-cell stage; implants only unaffected/carrier embryos.
- **HLA Matching (Savior Sibling):** PGT-M can be combined with HLA-typing to conceive a child who is an exact bone marrow match for an affected older sibling.
- **Cascade Screening:** Mandatory screening of extended family members of identified carriers.

Exam Summary: Must-Write Points

- **Screening triad:** MCV < 80, Mentzer Index < 13, Hb HPLC showing HbA2 > 3.5%.
- **Prerequisite for AND:** Exact parental genetic mutations must be mapped first.
- **Gold Standard AND:** CVS at 11–14 weeks followed by PCR-based fetal DNA analysis.
- **Legal limit:** MTP permitted up to 24 weeks in India for severe fetal anomalies.
- **Alpha-thalassemia trap:** Hb Barts causes hydrops fetalis and maternal mirror syndrome; in-utero transfusion (IUT) is the only fetal salvage therapy.

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99. Iron chelation therapy

Subject: Hematology / Oncology

Definition & Goals

- Pharmacological removal of toxic non-transferrin-bound iron (NTBI) and labile plasma iron (LPI) to prevent end-organ hemosiderosis.
- **Goal:** Maintain safe body iron burden (Serum ferritin 500–1000 ng/mL; Liver Iron Concentration [LIC] 3–7 mg Fe/g dry weight).

Indications to Initiate

- **Transfusion threshold:** After 10–20 packed RBC transfusions.

- **Biochemical threshold:** Serum ferritin consistently >1,000 ng/mL.
- **Tissue threshold:** LIC >3 mg Fe/g dry weight (by MRI or biopsy).
- **Age:** Usually initiated >2 years of age (allows early bone growth without chelation toxicity).

Pharmacological Agents

1. Deferasirox (DFX)

- **Status:** Current 1st-line agent for most patients >2 years.
- **Route/Dosing:** Oral, once daily. Film-coated tablets (14–28 mg/kg/day) have replaced dispersible tablets (20–40 mg/kg/day) due to better GI tolerability.
- **Mechanism:** Tridentate (2 molecules bind 1 iron atom); primarily fecal excretion.
- **Key Toxicities:** Renal (↑ creatinine, Fanconi syndrome), hepatic (↑ transaminases), severe GI upset, cytopenias.
- **Monitoring:** Monthly Serum Creatinine, Urine protein/creatinine ratio, and LFTs.

2. Deferoxamine (DFO)

- **Route/Dosing:** Subcutaneous infusion via pump (8–12 hours/night, 5–7 nights/week) or IV. Dose: 20–40 mg/kg/day (max 50 mg/kg/day).
- **Mechanism:** Hexadentate (1 molecule binds 1 iron atom); urinary and fecal excretion.
- **Key Toxicities:**
    - Infectious: Increased risk of ***Yersinia enterocolitica*** and *Mucormycosis* (acts as a siderophore for these organisms; must stop DFO during fever).
    - Neurosensory: High-frequency sensorineural hearing loss, retinal toxicity.
    - Skeletal: Metaphyseal dysplasia, growth retardation (if therapeutic index > 0.025).
- **Monitoring:** Annual audiometry, ophthalmology evaluation, and growth velocity tracking.

3. Deferiprone (DFP)

- **Route/Dosing:** Oral, TID. Dose: 75–100 mg/kg/day.
- **Mechanism:** Bidentate (3 molecules bind 1 iron atom); urinary excretion. Highly lipophilic, easily crosses cell membranes.
- **Best for: Cardiac iron clearance** (superior to others for preventing/treating myocardial siderosis).
- **Key Toxicities: Agranulocytosis** (5%), erosive arthropathy, GI symptoms.
- **Monitoring:** Absolute Neutrophil Count (ANC) **weekly**; stop immediately if ANC <1,500/mm^3.

Combination Therapy

- **Indication:** Severe iron overload, myocardial siderosis (Cardiac MRI T2* < 10 ms), or failure of monotherapy.
- **Regimen:** DFO (subcutaneous) + DFP (oral).
- **Mechanism:** "Shuttle effect" — DFP enters cells, removes intracellular iron, and transfers it to DFO in the plasma for excretion.

Monitoring Efficacy

- **Serum Ferritin:** Every 3 months (useful for trends, but behaves as an acute-phase reactant).
- *MRI T2 (Gold Standard):**
    - **Liver MRI:** Annually to assess LIC. Normal > 6.3 ms.
    - **Cardiac MRI:** Annually starting at age 8–10 years. Normal > 20 ms. High risk of heart failure if < 10 ms.

Complications of Inadequate Chelation

- **Cardiac:** Dilated cardiomyopathy, arrhythmias (leading cause of mortality in thalassemia).
- **Endocrine:** Hypogonadotropic hypogonadism (most common), diabetes mellitus, hypothyroidism, hypoparathyroidism.
- **Hepatic:** Hepatic fibrosis progressing to cirrhosis and hepatocellular carcinoma.

Exam Summary

- **Start chelation:** Ferritin >1000 ng/mL or after 10–20 transfusions (usually age >2).
- **Deferasirox (DFX):** 1st line, oral once daily, watch renal/liver function.
- **Deferoxamine (DFO):** SC pump, causes *Yersinia* sepsis, deafness, retinal damage, bone dysplasia.
- **Deferiprone (DFP):** Best for cardiac iron, requires strict weekly CBC due to agranulocytosis risk.
- **Gold Standard Monitoring:** MRI T2* of liver and heart.

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100. Hematopoietic stem cell transplantation

Subject: Hematology / Oncology

Definition & Basics

- Infusion of multipotent hematopoietic stem cells (HSCs) to re-establish hematopoietic and immune function
- **Stem cell sources:** Bone marrow (BM), Peripheral blood stem cells (PBSC), Umbilical cord blood (UCB)
- **PBSC mobilization:** Requires G-CSF ± Plerixafor to push stem cells (CD34+ cells) into peripheral circulation

Types of HSCT

- **Allogeneic:** From related or unrelated donor; carries Graft-versus-Host Disease (GVHD) risk but offers Graft-versus-Tumor (GVT) effect
- **Autologous:** Patient's own cells; no GVHD risk, no GVT effect; used primarily for dose-escalation of chemotherapy in solid tumors
- **Syngeneic:** From identical twin; no GVHD, but higher relapse risk in malignancies due to lack of GVT effect

Indications (Pediatric)

- **Malignant (Allogeneic):** High-risk/relapsed ALL, AML, Juvenile Myelomonocytic Leukemia (JMML), CML, Myelodysplastic syndrome (MDS)
- **Malignant (Autologous):** High-risk Neuroblastoma, Medulloblastoma, Relapsed Hodgkin/Non-Hodgkin Lymphoma, Ewing sarcoma
- **Non-Malignant (Allogeneic):**
    - *Bone marrow failure:* Severe Aplastic Anemia, Fanconi anemia, Diamond-Blackfan anemia
    - *Hemoglobinopathies:* Thalassemia major, Severe Sickle Cell Disease
    - *Immunodeficiencies:* SCID (medical emergency), Wiskott-Aldrich syndrome, Chronic Granulomatous Disease (CGD)
    - *Metabolic disorders:* Hurler syndrome (MPS I), Krabbe disease, Adrenoleukodystrophy (must be done before severe neurodegeneration)

Donor Selection & HLA Typing

- **Target:** High-resolution typing for HLA-A, -B, -C, -DRB1, and -DQB1 (10/10 match is ideal)
- **Hierarchy of Donors:**
    1. Matched Sibling Donor (MSD) – First choice
    2. Matched Unrelated Donor (MUD)
    3. Haploidentical Donor (Half-matched, usually a parent) – *Rapidly increasing use due to newer protocols*
    4. Umbilical Cord Blood (UCB) – Tolerates greater HLA mismatch, but slower engraftment

Conditioning Regimens

- **Goals:** Eradicate underlying disease, create physical space in marrow, suppress host immunity to prevent graft rejection
- **Myeloablative Conditioning (MAC):** Irreversible cytopenia requiring stem cell rescue (e.g., Busulfan/Cyclophosphamide or Total Body Irradiation [TBI]/Etoposide)
- **Reduced-Intensity Conditioning (RIC):** Lower dose chemo; relies heavily on donor T-cell mediated GVT effect to clear residual disease
- **Non-myeloablative (NMA):** Purely immunosuppressive; minimal cytoreduction

Procedure & Timeline

- **Day minus (e.g., Day -7 to -1):** Conditioning phase
- **Day 0:** Stem cell infusion via central venous catheter (not irradiated, not filtered)
- **Day plus (Day +1 to +14/21):** Aplasia phase; highest risk of severe infection and bleeding
- **Engraftment:** Absolute Neutrophil Count (ANC) >500/mm^3 for 3 consecutive days and Platelets >20,000/mm^3 for 3 consecutive days without transfusion

Complications: Early (<100 Days)

- **Mucositis:** Severe GI mucosal breakdown; requires aggressive pain management and TPN
- **Sinusoidal Obstruction Syndrome (SOS) / VOD:**
    - *Features:* Tender hepatomegaly, weight gain, ascites, jaundice (usually within first 21 days)
    - *Treatment:* Fluid restriction, Defibrotide (endothelial stabilizer)
- **Infections:**
    - *Pre-engraftment:* Gram-negative/positive bacteria, *Candida*, HSV
    - *Post-engraftment (Cellular immunodeficiency):* CMV, Adenovirus, *Pneumocystis jirovecii*, *Aspergillus*
- **Acute GVHD:** Donor immunocompetent T-cells attack host tissue (Skin: maculopapular rash; Liver: elevated bilirubin/ALP; Gut: profound secretory diarrhea)

Complications: Late (>100 Days)

- **Chronic GVHD:** Scleroderma-like skin changes, bronchiolitis obliterans, sicca syndrome (dry eyes/mouth), malabsorption
- **Endocrine:** Hypothyroidism, growth failure, delayed puberty, primary gonadal failure/infertility
- **Other:** Cataracts (especially post-TBI), Iron overload (from transfusions), Secondary malignancies (e.g., PTLD driven by EBV)

GVHD Prophylaxis & Management

- **Prophylaxis:** Calcineurin inhibitors (Cyclosporine/Tacrolimus) + short-course Methotrexate or Mycophenolate Mofetil (MMF)
- **Update (Haploidentical HSCT):** Post-Transplant Cyclophosphamide (PTCy) given on Day +3 and +4 selectively destroys alloreactive T-cells (standard of care for haplo-HSCT)
- **Treatment (Acute GVHD):** Systemic corticosteroids (Methylprednisolone 2 mg/kg/day)
- **Treatment (Steroid-refractory GVHD):** Ruxolitinib (JAK1/2 inhibitor) – *Current FDA/IAP approved first-line for steroid-refractory cases*

Exam Summary

- **Autologous** = Solid tumors (Neuroblastoma); **Allogeneic** = Leukemias, marrow failure, PID, metabolic errors.
- **SCID** is a pediatric emergency requiring urgent allogeneic HSCT; conditioning is often omitted or reduced.
- **SOS/VOD classic triad:** Jaundice, tender hepatomegaly, unexplained weight gain/fluid retention; treat with **Defibrotide**.
- **Graft-vs-Tumor (GVT) effect** is crucial for curing leukemias but is inseparable from **GVHD** risk.
- **PTCy (Post-Transplant Cyclophosphamide)** has revolutionized haploidentical transplants, making parents viable donors for almost all children.

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101. Histiocytosis syndrome

Subject: Hematology / Oncology

Classification (Histiocyte Society 2016 Update)

- **Group L:** Langerhans-related (Langerhans Cell Histiocytosis [LCH], Erdheim-Chester disease).
- **Group C:** Cutaneous/mucocutaneous non-LCH (e.g., Juvenile xanthogranuloma).
- **Group M:** Malignant histiocytoses.
- **Group R:** Rosai-Dorfman disease.
- **Group H:** Hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS).
- *Note:* In pediatric exams, "Histiocytosis syndrome" predominantly refers to **Langerhans Cell Histiocytosis (LCH)**.

Langerhans Cell Histiocytosis (LCH)

Pathogenesis & Genetics

- Clonal neoplastic proliferation of aberrant epidermal dendritic cells (Langerhans cells).
- Driven by hyperactivation of the MAPK/ERK signaling pathway.
- **Genetics:** BRAF V600E mutation present in 50–60% of cases; MAP2K1 mutations in 15–20%.

Clinical Features (By System)

- **Bone (80%):** Painful, localized swelling; classic punched-out lytic lesions (skull, femur, pelvis). Causes "vertebra plana" (collapse of vertebral body).
- **Skin (30-50%):** Refractory seborrheic dermatitis-like rash (scalp, diaper area, retroauricular); petechial eruptions.
- **Ear/Nose/Throat:** Chronic purulent otitis media unresponsive to antibiotics; mastoid involvement; gingival hypertrophy/teeth loss ("floating teeth" on X-ray).
- **Endocrine (25%):** Central Diabetes Insipidus (DI) due to posterior pituitary infiltration. Anterior pituitary deficits (growth hormone deficiency) may follow.
- **High-Risk Organs (Liver, Spleen, Bone Marrow):** Hepatosplenomegaly, jaundice, pancytopenia. Indicates severe, life-threatening disease.
- **Historical Eponyms (Now obsolete but exam-tested):**
    - *Eosinophilic Granuloma:* Localized bone disease.
    - *Hand-Schüller-Christian Disease:* Triad of lytic skull lesions, exophthalmos, and DI.
    - *Letterer-Siwe Disease:* Acute, disseminated multisystem disease in infants.

Diagnosis

- **Biopsy (Gold Standard):** Shows histiocytes mixed with eosinophils and multinucleated giant cells.
- **Immunohistochemistry (IHC): CD1a (+), Langerin / CD207 (+), S-100 (+)**.

- **Electron Microscopy: Birbeck granules** (classic "tennis-racket" shaped cytoplasmic organelles).
- **Imaging:**
    - Skeletal survey: Well-demarcated lytic lesions without sclerotic margins.
    - MRI Brain: Thickening of the pituitary stalk.
- **Molecular Testing:** Test all biopsy samples for BRAF V600E mutation.

Management (Based on LCH-IV Protocol)

- **Single-System Disease (Bone/Skin):**
    - Observation (some spontaneously regress).
    - Local curettage or intralesional corticosteroids.
    - Topical nitrogen mustard or steroids for isolated skin disease.
- **Multisystem Low-Risk (No risk organ involvement):**
    - Standard first-line: **Vinblastine + Prednisolone** for 12 months.
- **Multisystem High-Risk (Liver, Spleen, or Bone Marrow involvement):**
    - Intensive therapy: **Vinblastine + Prednisolone + 6-Mercaptopurine**.
- **Refractory / Relapsed LCH:**
    - *Update:* Targeted therapy is now standard for mutation-positive refractory cases.
    - **Vemurafenib / Dabrafenib** (BRAF V600E inhibitors).
    - **Trametinib** (MEK inhibitor for MAP2K1 mutations).

Complications & Prognosis

- **Neurodegenerative LCH:** Progressive ataxia, dysarthria, and cognitive decline (can occur years after diagnosis; MRI shows cerebellar/basal ganglia hyperintensities).
- **Pulmonary:** Cystic lung disease leading to pneumothorax (strongly linked to smoking/passive smoke).
- **Prognosis:** Excellent (>99% survival) for low-risk disease; High-risk disease has ~80% survival but high morbidity.

Hemophagocytic Lymphohistiocytosis (HLH) - Group H

Basics & Pathophysiology

- Hyperinflammatory syndrome caused by severe impairment of NK-cell and cytotoxic T-cell function.
- Results in failure to clear antigens/triggering pathogens ⇒unchecked macrophage activation ⇒extreme "Cytokine Storm" (IFN-γ, IL-6, TNF-α).
- Can be Primary (Familial, e.g., Perforin gene mutations) or Secondary (triggered by EBV, rheumatologic disease [MAS], or malignancy).

Diagnosis (HLH-2004 Criteria) *Must meet genetic diagnosis OR 5 out of 8 clinical criteria:*

1. Fever (≥38.5°C).
2. Splenomegaly.
3. Cytopenias (affecting ≥2 lineages).
4. Hypertriglyceridemia (fasting ≥265 mg/dL) and/or Hypofibrinogenemia ($\le$ 1.5 g/L).
5. Hemophagocytosis in bone marrow, spleen, or lymph nodes.
6. Low or absent NK-cell activity.
7. **Ferritin ≥500 mcg/L** (often >10,000 in practice).
8. Soluble CD25 (soluble IL-2 receptor) elevated.

Management

- **HLH-94 Protocol:** Dexamethasone + Etoposide (to suppress hyperinflammation).
- CNS disease: Intrathecal Methotrexate.
- Refractory/Primary HLH: Emapalumab (anti-IFN-γ monoclonal antibody - *Recent FDA approval*).
- **Definitive Cure:** Hematopoietic Stem Cell Transplant (HSCT) for all familial cases or relapsing secondary cases.

Exam Summary

- **LCH Markers:** CD1a (+), Langerin/CD207 (+), S-100 (+).
- **LCH EM finding:** Birbeck granules (tennis-racket).
- **LCH Mutation:** BRAF V600E (>50%); treat refractory cases with Vemurafenib.
- **High-Risk LCH Organs:** Liver, Spleen, Bone Marrow (dictates aggressive chemotherapy).
- **Classic LCH Triad:** Lytic skull lesions, Exophthalmos, Diabetes Insipidus.
- **HLH Hallmark:** Cytokine storm, Ferritin >500, Hemophagocytosis, defective NK cells; requires Etoposide/Dexamethasone ⇒HSCT.

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102. Types of graft versus host disease clinical manifestations and management

Subject: Hematology / Oncology

Definition

- Systemic inflammatory condition occurring after allogeneic hematopoietic stem cell transplantation (HSCT) or solid organ transplant.
- Immunocompetent donor T-cells recognize recipient human leukocyte antigens (HLA) as foreign, leading to tissue destruction.

Pathophysiology (3-Step Model)

- **Phase 1 (Afferent):** Conditioning regimen (chemo/radiation) causes host tissue damage, releasing pro-inflammatory cytokines (TNF-α, IL-1) and activating host antigen-presenting cells (APCs).
- **Phase 2 (Induction):** Donor T-cells interact with host APCs, leading to T-cell activation, proliferation, and differentiation (Th1/Th17).
- **Phase 3 (Effector):** Target organ destruction via cellular (Cytotoxic T-cells, NK cells) and soluble mediators (FasL, perforin, granzyme).

Types & Classification (NIH Consensus Criteria) *Previously based strictly on a 100-day cutoff; currently based on clinical manifestations.*

- **Classic Acute GVHD:** Occurs ≤100 days post-HSCT; typical acute features.
- **Late-Onset Acute GVHD:** Occurs >100 days post-HSCT; features of acute GVHD only.
- **Classic Chronic GVHD:** Can occur at any time; autoimmune/fibrotic features only.
- **Overlap Syndrome:** Features of both acute and chronic GVHD present simultaneously.

Clinical Manifestations 1. Acute GVHD (Target Organs: Skin, Liver, GI)

- **Skin (Earliest & Most Common):** Pruritic maculopapular rash starting on palms, soles, nape of neck, and ears. Can progress to generalized erythroderma or toxic epidermal necrolysis (TEN)-like blistering.
- **Gastrointestinal:** Profuse, watery, green, secretory diarrhea (>500 mL/day); severe crampy abdominal pain; nausea/vomiting (upper GI GVHD); GI bleeding.
- **Liver:** Cholestatic jaundice (conjugated hyperbilirubinemia), elevated alkaline phosphatase (ALP).

2. Chronic GVHD (Resembles Autoimmune/Collagen Vascular Diseases)

- **Skin/Nails:** Scleroderma-like thickening, poikiloderma, lichen planus-like lesions, nail dystrophy.
- **Eyes/Mouth:** Sicca syndrome (dry eyes/mouth), oral lichenoid mucosal striations, ulcers.
- **Lungs (High-Yield):** Bronchiolitis obliterans (hallmark of chronic GVHD; presents with wheezing, air trapping, fixed airflow obstruction).
- **GI/Liver:** Esophageal webs/strictures, chronic cholestasis, wasting syndrome.
- **Immune:** Functional asplenia, cytopenias, profound immunodeficiency.

Diagnosis & Evaluation

- **Clinical:** Diagnosis is primarily clinical based on typical organ involvement.
- **Biopsy (Confirmatory):**
    - *Skin/GI:* Epithelial apoptosis (classic buzzword: "apoptotic bodies in crypts/basal layer"), lymphocytic infiltration.
    - *Liver:* Bile duct epithelial damage, endothelitis.
- **Staging/Grading:** MAGIC criteria or modified Glucksberg criteria (Grades I–IV) based on the extent of skin, liver, and GI involvement.

Prevention (Prophylaxis)

- **Standard Regimen:** Calcineurin inhibitor (CNI: Cyclosporine or Tacrolimus) + short-course Methotrexate.
- **Major Update (Current Standard for Haploidentical/Mismatched):** Post-transplantation Cyclophosphamide (PTCy) given on days +3 and +4 to selectively deplete alloreactive T-cells.
- **Alternative:** In vivo T-cell depletion (Anti-thymocyte globulin [ATG] or Alemtuzumab) or ex vivo CD34+ selection.

Management of Acute GVHD

- **Grade I (Skin only <50%):** High-potency topical corticosteroids.
- **Grade II–IV (First-Line):** Systemic Methylprednisolone (1–2 mg/kg/day).
- **Steroid-Refractory Acute GVHD (SR-aGVHD):**
    - *First-line for SR-aGVHD (FDA Approved/Update):* **Ruxolitinib** (JAK1/2 inhibitor).
    - *Alternatives/Adjuncts:* Extracorporeal photopheresis (ECP), Infliximab, Vedolizumab (gut-specific), Basiliximab.

Management of Chronic GVHD

- **First-Line:** Systemic corticosteroids (Prednisone 1 mg/kg/day) often combined with a CNI (Tacrolimus/Cyclosporine).
- **Refractory Chronic GVHD (Recent Approvals):**
    - **Ruxolitinib** (JAK1/2 inhibitor).
    - **Ibrutinib** (BTK inhibitor).
    - **Belumosudil** (ROCK2 inhibitor – targets fibrosis pathway).
- **Supportive Care:** Antimicrobial prophylaxis (PCP, fungal, encapsulated organisms), artificial tears, physical therapy, nutritional support.

Complications & Prognosis

- **Infections:** Leading cause of death (CMV reactivation, invasive Aspergillosis, encapsulated bacteria due to functional asplenia).
- **Organ Failure:** Severe GI bleeding, liver failure, respiratory failure (from bronchiolitis obliterans).
- **Graft-vs-Leukemia (GVL) Effect:** Mild GVHD is associated with a lower risk of primary malignancy relapse (beneficial side effect of alloreactivity).

Exam Summary (Must-Write Points)

- **NIH Criteria Shift:** Classification is now based on clinical features (maculopapular/diarrhea vs. fibrotic/sclerodermatous), not strictly the 100-day mark.
- **Acute Triad:** Skin rash (palms/soles) + Cholestatic jaundice + Secretory diarrhea.
- **Chronic Hallmark:** Bronchiolitis obliterans and scleroderma-like skin changes.
- **Prophylaxis Revolution:** Post-transplant Cyclophosphamide (PTCy) is the game-changer for mismatched transplants.

- **Refractory Rx:** Ruxolitinib (JAK inhibitor) is the undisputed modern standard for steroid-refractory acute and chronic GVHD.

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103. Oncological emergencies in children

Subject: Hematology / Oncology

Here is a comprehensive, high-yield, and structured guide to Oncological Emergencies in Children, designed for MD Pediatrics examinations.

Classification

- **Metabolic:** Tumor Lysis Syndrome (TLS), Hypercalcemia, SIADH
- **Hematologic:** Febrile Neutropenia (FN), Hyperleukocytosis, Disseminated Intravascular Coagulation (DIC)
- **Structural:** Superior Mediastinal Syndrome (SMS) / Superior Vena Cava (SVC) Syndrome, Spinal Cord Compression, Raised Intracranial Pressure (ICP)

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1. Tumor Lysis Syndrome (TLS)

- **Pathophysiology:** Massive lysis of malignant cells releasing intracellular contents (K^+, PO_4^{3-}, nucleic acids) overwhelming renal excretion.
- **High-Risk Malignancies:** Burkitt lymphoma, T-cell ALL, tumors with high bulky disease or high LDH.
- **Clinical Features:** Arrhythmias (hyperkalemia), tetany/seizures (hypocalcemia), oliguria/anuria (uric acid or calcium phosphate nephropathy).
- **Diagnosis (Cairo-Bishop Criteria):**
    - *Laboratory TLS (≥2 within 3 days before or 7 days after chemo):* Uric acid ≥8 mg/dL, K^+ ≥6 mEq/L, PO_4^{3-} ≥6.5 mg/dL (children), Ca^{2+} ≤7 mg/dL (or 25% change from baseline).
    - *Clinical TLS:* Lab TLS + ↑Creatinine (≥1.5x ULN), arrhythmias, or seizures.
- **Management:**
    - **Hyperhydration:** 3 L/m^2/day (without potassium) to maintain urine output >100 mL/m^2/hr.
    - **Uric Acid Reduction:**
        - *Allopurinol:* Xanthine oxidase inhibitor (prevents new uric acid formation).
        - *Rasburicase:* Recombinant urate oxidase (degrades existing uric acid to soluble allantoin). *Contraindicated in G6PD deficiency.*
    - **Electrolyte Correction:** Calcium gluconate for symptomatic hypocalcemia; insulin-glucose/kayexalate for hyperkalemia.
    - **Renal Replacement:** Hemodialysis if refractory hyperkalemia, fluid overload, or severe uremia.

- **Update (Current Guidelines):** *Previously:* Urine alkalinization with sodium bicarbonate was routine. *Now:* **Not recommended** (promotes calcium phosphate precipitation in renal tubules).

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2. Febrile Neutropenia (FN)

- **Definition:** Single oral temp ≥38.3°C (101°F) OR ≥38.0°C (100.4°F) for >1 hour **PLUS** Absolute Neutrophil Count (ANC) <500/mm^3 (or expected to drop <500 within 48h).
- **Diagnosis:** Prompt blood cultures (from central line and peripheral vein), CBC, CRP, urinalysis, CXR (if respiratory symptoms).
- **Management (Golden Hour Protocol):**
    - Initiate broad-spectrum empiric IV antibiotics **within 60 minutes** of presentation.
    - *First-line:* Antipseudomonal beta-lactam (Cefepime, Ceftazidime, or Piperacillin-Tazobactam).
    - *Additions:* Add Vancomycin ONLY if hemodynamic instability, suspected catheter infection, severe mucositis, or known MRSA colonization.
    - *Antifungal:* Add empiric IV Caspofungin or Liposomal Amphotericin B if fever persists >4–7 days despite broad-spectrum antibiotics.

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3. Hyperleukocytosis & Leukostasis

- **Definition:** Peripheral WBC count >100,000/mm^3.
- **Etiology:** AML (more symptomatic at lower counts due to large myeloblasts), ALL, CML.
- **Pathophysiology:** Increased blood viscosity → microvascular sludging → tissue hypoxia/infarction.
- **Clinical Features:**
    - *CNS:* Altered sensorium, headache, stroke, intracranial hemorrhage.
    - *Pulmonary:* Dyspnea, hypoxia, diffuse interstitial infiltrates.
    - *GU:* Priapism.
- **Management:**
    - Hyperhydration and TLS prophylaxis (mandatory).
    - Cytoreduction: Hydroxyurea or low-dose induction chemotherapy.
    - Leukapheresis or Exchange Transfusion (if symptomatic or WBC >200k in AML/ >400k in ALL).
- **Exam Trap: Do NOT transfuse PRBCs** initially (increases viscosity and worsens leukostasis) unless Hb <6 g/dL. Keep platelets >20,000/mm^3 to prevent fatal ICH.

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4. Superior Mediastinal / SVC Syndrome

- **Definition:**

- *SVC Syndrome:* Compression of SVC → impaired venous return.
- *Superior Mediastinal Syndrome (SMS):* SVCS + tracheal/airway compression (life-threatening).

- **Etiology:** Anterior mediastinal masses (T-ALL, Non-Hodgkin Lymphoma, Hodgkin Lymphoma).
- **Clinical Features:** Orthopnea, stridor, facial plethora, neck vein distension, "Stokes collar" (edema of neck/face).
- **Diagnosis:** CXR (mediastinal widening), Echocardiogram (rule out pericardial effusion).
- **Management:**
  - Keep head of bed elevated; provide supplemental O_2.
  - **Absolute Contraindication:** Avoid sedation, general anesthesia, or supine positioning (risk of total airway collapse).
  - If tissue diagnosis is impossible due to anesthetic risk: Empiric therapy with systemic steroids (Dexamethasone) or emergent local radiotherapy.

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5. Spinal Cord Compression

- **Etiology:** Neuroblastoma (dumbbell tumor), Ewing sarcoma, Osteosarcoma, metastatic Medulloblastoma.
- **Clinical Features:**
  - *Early:* Localized back pain (characteristically worse on lying down/at night).
  - *Late:* Motor weakness, sensory level loss, bowel/bladder dysfunction (autonomic).
- **Diagnosis:** Urgent MRI of the **entire spine** (skip lesions are common).
- **Management:**
  - Immediate high-dose IV Dexamethasone (reduces peritumoral edema).
  - Definitive: Emergent neurosurgical decompression (laminectomy) OR emergent radiotherapy (for highly radiosensitive tumors like lymphomas).

Exam Summary: Must-Write Buzzwords

- **TLS Triad:** Hyperkalemia, Hyperuricemia, Hyperphosphatemia with Hypocalcemia.
- **TLS Update:** Rasburicase is preferred for high-risk TLS; *do not alkalinize urine*.
- **Febrile Neutropenia:** Golden Hour (antibiotics <60 mins); Piperacillin-Tazobactam or Cefepime.
- **Hyperleukocytosis:** Avoid PRBC transfusions to prevent fatal hyperviscosity.
- **Mediastinal Mass:** Never sedate/anesthetize a child with SMS/stridor; treat empirically if airway compromise is imminent.
- **Spinal Cord Compression:** Back pain worse at night/supine is a massive red flag; give IV Dexamethasone stat before MRI.

Genetics

104. Down syndrome genetic counseling and recurrence risk

Subject: Genetics

Definition & Genetics

- **Down Syndrome (DS):** Trisomy 21, the most common chromosomal disorder causing intellectual disability.
- **Genetic Mechanisms:**
    - **Nondisjunction (95%):** Meiotic error (usually maternal meiosis I).
    - **Robertsonian Translocation (3–4%):** Attachment of the long arm of chromosome 21 to another acrocentric chromosome (usually 14, occasionally 13, 15, 21, or 22).
    - **Mosaicism (1–2%):** Post-zygotic mitotic nondisjunction (mixture of 46 and 47,+21 cell lines).

Prerequisites for Counseling

- **Mandatory Step:** Karyotype of the *affected child* is an absolute prerequisite.
- **Clinical Pitfall:** Never counsel on recurrence risk based solely on clinical phenotype; mechanism dictates risk.
- **Parental Testing:** Parental karyotyping is *only* indicated if the child has a translocation.

Recurrence Risk (The Core)

- **1. Nondisjunction (Free Trisomy 21)**
    - **Risk:** Empiric risk of **1%** OR the maternal age-specific risk, whichever is higher.
    - **Parental Karyotype:** Not indicated (parents are normal).
- **2. Robertsonian Translocation**
    - **Action:** Must perform parental karyotyping to check for balanced carrier status.
    - **De Novo (Parents normal):** Recurrence risk is **~1%** (due to theoretical gonadal mosaicism).
    - **Inherited t(14;21), t(13;21), or t(15;21):**
        - **Maternal carrier: 10–15%** recurrence risk.
        - **Paternal carrier: 1–3%** recurrence risk (lower due to selection against unbalanced sperm).
    - **Inherited t(21;21):**
        - **Risk: 100%** recurrence risk for viable pregnancies.
        - **Outcome:** All viable offspring will have Down syndrome; other conceptions result in spontaneous abortion (monosomy 21 is lethal).
- **3. Mosaicism**

- **Risk:** Approximately **1%** (background population risk).
- **Phenotype:** Highly variable; does not correlate strictly with percentage of mosaicism in blood.

Principles of Genetic Counseling

- **Approach:** Non-directive, empathetic, and culturally sensitive.
- **Communication:** Explain the natural history, spectrum of intellectual disability, and life expectancy (now >60 years).
- **Comorbidities:** Discuss screening for congenital heart disease (AVSD most common), hypothyroidism, celiac disease, leukemia (TMD, AML, ALL), and early-onset Alzheimer's.
- **Future Pregnancies:** Offer prenatal screening and diagnostic options to all couples with a previous DS child.

Prenatal Screening & Diagnosis (Future Pregnancies)

- **First Trimester (11–13+6 weeks):**
  - Combined test: Nuchal translucency (NT) + maternal serum PAPP-A (↓) + free β-hCG (↑).
- **Second Trimester (15–20 weeks):**
  - Quadruple screen: AFP (↓), Unconjugated Estriol (↓), hCG (↑), Inhibin A (↑).
- **NIPT (Cell-Free DNA):**
  - **Current AAP/ACOG Guideline:** Can be offered as a primary screening test from 10 weeks gestation; highest sensitivity (>99%) and specificity for Trisomy 21.
- **Definitive Diagnosis:**
  - Chorionic Villus Sampling (CVS) at 10–13 weeks.
  - Amniocentesis at 15–20 weeks.
  - *Note:* NIPT is a screening test; positive results require confirmation via CVS or amniocentesis.

Exam Summary: High-Yield Must-Write Points

- **Child's karyotype is mandatory** before providing any recurrence risk counseling.
- **Nondisjunction (95%):** Recurrence risk is ~1%; parental karyotype is unnecessary.
- **Translocation t(14;21):** Risk is 10–15% if mother is carrier, 1–3% if father is carrier.
- **Translocation t(21;21):** 100% recurrence risk of Down syndrome in viable offspring.
- **NIPT:** Current gold-standard screening modality for future pregnancies, starting at 10 weeks.

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105. Prenatal diagnosis in Down syndrome

Subject: Genetics

Basics

- **Definition:** Antenatal detection of Trisomy 21 (most common chromosomal aneuploidy; 1:700 live births)
- **Goal:** Early detection to allow informed parental decision-making and optimal perinatal management
- **Current Recommendation (ACOG/IAP):** Offer aneuploidy screening to **ALL** pregnant women, regardless of maternal age

Indications for Targeted Testing

- Advanced maternal age (≥35 years at delivery)
- Previous pregnancy with chromosomal abnormality
- Parent carrying a balanced Robertsonian translocation
- Abnormal maternal serum screening
- Structural anomalies or soft markers on fetal ultrasound

First Trimester Screening (11 to 13+6 weeks)

- **Combined Test:** Highest detection rate for 1st trimester (~85-90%)
- **Ultrasound:** Increased Nuchal Translucency (NT) ≥ 3 mm
- **Maternal Serum:**
    - Pregnancy-Associated Plasma Protein A (PAPP-A): **Decreased**
    - Free β-hCG: **Increased**
- *Note:* Absence of fetal nasal bone on USG further increases risk

Second Trimester Screening (15 to 20 weeks)

- **Quadruple Test:** Detection rate ~80%
- **Maternal Serum Markers:**
    - Alpha-fetoprotein (AFP): **Decreased**
    - Unconjugated Estriol (uE3): **Decreased**
    - Human Chorionic Gonadotropin (hCG): **Increased**
    - Inhibin-A: **Increased**
- *Mnemonic:* In Down syndrome, **HI**gh = **H**CG and **I**nhibin-A

Non-Invasive Prenatal Testing (NIPT)

- **Mechanism:** Analyzes cell-free fetal DNA (cffDNA) in maternal plasma
- **Timing:** Can be done from **10 weeks** gestation onwards
- **Efficacy:** Highest sensitivity (>99%) and specificity for Trisomy 21
- **Update (ACOG/ACMG):** NIPT is the most sensitive screening option and should be offered to all pregnant women
- **Pitfall:** It is a *screening* test, not diagnostic; a positive NIPT *must* be confirmed with invasive diagnostic testing

Ultrasound Soft Markers (18 to 22 weeks)

- **Head/Neck:** Absent/hypoplastic nasal bone, increased nuchal fold thickness (≥6 mm)
- **Cardiac:** Echogenic Intracardiac Focus (EICF)
- **GI:** Echogenic bowel
- **Limbs:** Short femur/humerus, clinodactyly of 5th digit, wide "sandal gap" between 1st and 2nd toes
- **Major Structural Anomalies:** Atrioventricular (AV) canal defect, Duodenal atresia ("double-bubble" sign)

Definitive Diagnosis (Invasive Testing)

- **Indication:** High-risk screening result or major USG anomaly
- **Chorionic Villus Sampling (CVS):** Done at **10-13 weeks**. Transabdominal or transcervical. Fetal loss risk ~0.5-1%.
- **Amniocentesis:** Done at **15-20 weeks**. Transabdominal aspiration of amniotic fluid. Fetal loss risk ~0.1-0.5%.
- **Fetal Tissue Analysis:**
    - **FISH (Fluorescence In Situ Hybridization):** Rapid result (24-48 hrs) for chromosomes 13, 18, 21, X, Y
    - **QF-PCR:** Rapid, detects aneuploidies via DNA amplification
    - **Karyotyping:** Gold standard confirmation (takes 1-2 weeks)
    - **Chromosomal Microarray (CMA):** Recommended if USG shows structural anomalies

Management & Counseling

- **Approach:** Non-directive genetic counseling (provide facts, allow parents to decide)
- **Continuation:** Plan delivery in a tertiary center with pediatric cardiology and NICU support
- **Termination:** Advise regarding legal limits.
    - *Update (India MTP Amendment Act 2021):* Termination allowed up to 24 weeks; beyond 24 weeks permitted only for substantial fetal anomalies approved by a Medical Board.

Exam Summary

- **Screening Rule:** Offer to ALL pregnant women; age >35 is high risk.
- **1st Trimester:** Combined test (NT + PAPP-A [Low] + β-hCG [High]) at 11-13+6 weeks.
- **2nd Trimester:** Quadruple test at 15-20 weeks; **HI**gh = **H**CG & **I**nhibin-A; Low = AFP & Estriol.
- **NIPT:** cffDNA >10 weeks; highest sensitivity (>99%), but requires invasive confirmation if positive.
- **Diagnosis:** CVS (10-13 wks) or Amniocentesis (15-20 wks) → FISH (rapid) → Karyotype/Microarray (gold standard).

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106. Multifactorial inheritance

Subject: Genetics

Definition

- Inheritance determined by the interaction of multiple genes (polygenic) and environmental factors.
- Does not follow classic Mendelian inheritance ratios.

Pathophysiology (Threshold Model)

- **Liability:** The combined total of genetic and environmental factors predisposing to a disease; follows a normal distribution (bell-shaped curve) in the population.
- **Threshold:** A specific point on the liability curve; individuals pushed past this threshold manifest the disease.
- **Sex-specific thresholds:** For some traits, the threshold differs by sex (e.g., Pyloric stenosis has a lower threshold/is more common in males; Developmental dysplasia of the hip [DDH] has a lower threshold in females).

Rules of Inheritance (Exam High-Yield)

- **Severity effect:** Recurrence risk increases with the severity of the defect in the proband (e.g., bilateral cleft lip carries a higher recurrence risk than unilateral).
- **Multiplicity effect:** Risk increases with the number of affected family members (unlike Mendelian inheritance, where the risk per pregnancy remains constant).
- **Carter Effect:** Recurrence risk is highest if the proband belongs to the *less commonly affected sex*. (e.g., A female with pyloric stenosis has a very high genetic liability to cross her higher threshold; thus, her relatives are at greater risk).
- **Degree of relationship:** Risk drops precipitously as the degree of relatedness decreases (e.g., 2–5% in 1st-degree relatives, dropping sharply in 2nd-degree relatives).
- **Consanguinity:** Increases the recurrence risk by shifting the overall family liability curve to the right.

Clinical Examples in Pediatrics

- **Congenital Malformations (Isolated):**
    - Neural tube defects (NTDs)
    - Cleft lip with/without cleft palate (CL/P)
    - Congenital heart defects (CHD)
    - Hypertrophic pyloric stenosis
    - Talipes equinovarus (Clubfoot)
    - Developmental dysplasia of the hip (DDH)
- **Pediatric/Adult-Onset Disorders:**
    - Asthma and atopy
    - Diabetes mellitus (Type 1 and 2)

- Autism spectrum disorder (ASD)
- Epilepsy

Diagnosis & Counseling

- **Rule out syndromes:** Must strictly exclude chromosomal (e.g., Trisomy 13) or single-gene syndromes before labeling a defect as isolated multifactorial.
- **Empirical Risk:** Genetic counseling relies on *empirical risk figures* derived from observed population data, rather than calculated Mendelian probabilities.
- **Baseline recurrence risk:** Generally quoted as 2–5% for a first-degree relative of an affected proband (for most structural birth defects).

Prevention & Management

- **Environmental modification:** Because genetics cannot be altered, prevention targets the environmental component of the liability threshold.
- **Classic intervention:** Periconceptional folic acid supplementation prevents NTDs.
  - *Standard risk:* 400 mcg/day.
  - *High risk (previous NTD):* 4 mg/day (starts 1 month before conception through the first trimester).
- **Lifestyle modifications:** Diet and exercise to prevent multifactorial conditions like Type 2 DM or hypertension in genetically susceptible children.

Exam Summary

- **Must-write concepts:** Liability curve, Threshold model, and Empirical risk.
- **Carter Effect:** Proband of the less frequently affected sex = higher recurrence risk for relatives.
- **Key differentiating rule:** Recurrence risk increases with disease severity and number of affected relatives (unlike Mendelian).
- **Classic trap:** Cleft palate alone vs. Cleft lip +/- palate are developmentally distinct; always exclude syndromic causes (e.g., Pierre Robin sequence) before counseling for multifactorial risk.

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107. Approach to child with dysmorphic facies

Subject: Genetics

Definitions & Concepts

- **Dysmorphology:** Study of abnormal form and structural birth defects.
- **Malformation:** Intrinsic developmental defect (e.g., cleft lip, neural tube defect).
- **Deformation:** Extrinsic mechanical force altering normal tissue (e.g., clubfoot from oligohydramnios).
- **Disruption:** Destruction of previously normal tissue (e.g., amniotic band syndrome).
- **Dysplasia:** Abnormal cellular organization/tissue function (e.g., achondroplasia).

- **Syndrome:** Multiple anomalies from a single pathogenic cause (e.g., Down syndrome).
- **Sequence:** Cascade of anomalies from a single initial defect (e.g., Pierre Robin sequence: micrognathia ⇒glossoptosis ⇒U-shaped cleft palate).
- **Association:** Non-random occurrence of anomalies without a defined genetic etiology (e.g., VACTERL).

History

- **Prenatal:** Maternal illness, teratogen exposure (alcohol, valproate, phenytoin), TORCH infections, oligohydramnios/polyhydramnios, decreased fetal movements.
- **Perinatal:** Gestational age, birth weight (symmetric vs. asymmetric IUGR), Apgar scores.
- **Developmental:** Delays in milestones, loss of acquired skills (regression).
- **Family:** 3-generation pedigree, consanguinity, recurrent miscarriages, stillbirths, advanced maternal/paternal age.

Clinical Examination

- **Growth Parameters:** Plot Height, Weight, and Occipitofrontal Circumference (OFC). Note microcephaly, macrocephaly, or disproportionate short stature.
- **Skull:** Shape (scaphocephaly, brachycephaly), fontanelle size, overriding sutures, hair whorls.
- **Eyes:**
    - Spacing: Hypertelorism (increased interpupillary distance) vs. Telecanthus (increased inner canthal distance only).
    - Fissures: Up-slanting (Down syndrome), down-slanting (Marfan, Treacher Collins).
    - Defects: Epicanthal folds, coloboma (CHARGE syndrome), cataracts, blue sclera.
- **Ears:** Low-set (upper border below a horizontal line drawn from the inner canthus), posteriorly rotated, preauricular tags/pits, abnormal folding.
- **Nose:** Depressed nasal bridge, anteverted nares, beaked nose (Rubinstein-Taybi).
- **Mouth/Jaw:** Micrognathia, retrognathia, macroglossia (Beckwith-Wiedemann, Pompe), cleft lip/palate, thin upper lip/smooth philtrum (Fetal Alcohol Syndrome).
- **Limbs/Skin:** Polydactyly, syndactyly, clinodactyly, single transverse palmar crease, hypopigmented macules, café-au-lait spots.
- **Systemic:** Check for congenital heart defects (murmurs), hepatosplenomegaly, ambiguous genitalia.

Diagnostic Algorithm (Investigations)

- *Current IAP/AAP Guideline:* **Chromosomal Microarray (CMA)** is the **first-line test** for a child with multiple congenital anomalies (MCA), developmental delay (DD), or autism spectrum disorder (ASD).
- **Karyotype / FISH:**
    - *Previously:* First-line for all dysmorphism.

- *Now:* Reserved for clinically obvious aneuploidies (e.g., Down, Turner, Patau) or history of recurrent miscarriages (to detect balanced translocations).

- **Targeted Gene Panel:** If a specific single-gene disorder or group is suspected (e.g., Noonan syndrome panel, skeletal dysplasia panel).
- **Methylation Studies:** Suspected imprinting disorders (Prader-Willi, Angelman).
- **Whole Exome Sequencing (WES) / Whole Genome Sequencing (WGS):** Indicated if CMA is negative and the phenotype remains undiagnosed.
- **Ancillary Testing:**
  - Echocardiography (standard for any syndromic child).
  - USG Abdomen (renal/hepatic anomalies).
  - Skeletal Survey (if disproportionate short stature/dysplasia suspected).
  - Neuroimaging (MRI Brain) for seizures or severe microcephaly.
  - Metabolic workup (TMS, GCMS) if coarse facies + organomegaly (e.g., Mucopolysaccharidosis).

Management & Counseling

- **Multidisciplinary Team (MDT):** Involve Clinical Geneticist, Pediatrician, specialized surgeons (plastic, cardiac), PT/OT, and speech therapist.
- **Anticipatory Guidance:** Screen for known complications of the suspected/confirmed syndrome (e.g., atlantoaxial subluxation in Down syndrome).
- **Genetic Counseling:**
  - Determine recurrence risk (e.g., 25% for Autosomal Recessive, 50% for Autosomal Dominant, ~1% for de novo mutations).
  - Offer prenatal diagnosis (CVS/Amniocentesis) for future pregnancies.
- **Psychosocial Support:** Connect family with support groups and early intervention programs.

Exam Summary

- Always differentiate Malformation (intrinsic) from Deformation (extrinsic) and Disruption (destructive).
- A 3-generation pedigree and detailed prenatal teratogen history are mandatory.
- **CMA (Chromosomal Microarray)** is the absolute first-line genetic test for unexplained dysmorphism + developmental delay.
- Use Karyotype *only* if classical aneuploidy (Trisomy 21, 18, 13, Turner) is clinically obvious.
- Look for classic buzzwords: Smooth philtrum (FAS), Beaked nose (Rubinstein-Taybi), Macroglossia (Beckwith-Wiedemann/Hypothyroidism).

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108. Duchenne muscular dystrophy

Subject: Genetics

Definition & Genetics

- Most common and severe childhood muscular dystrophy
- **Inheritance:** X-linked recessive (affects males; females are carriers)
- **Gene:** *DMD* gene on chromosome Xp21.2 (largest human gene)
- **Mutations:** Deletions (10%), point mutations (~25%)
- **Rule:** "Out-of-frame" mutations cause absent dystrophin (DMD); "in-frame" mutations cause truncated/partially functional dystrophin (milder Becker Muscular Dystrophy)

Pathophysiology

- Absence of dystrophin protein (normally anchors actin cytoskeleton to extracellular matrix via dystrophin-glycoprotein complex)
- Membrane instability during muscle contraction
- Massive calcium influx → protease activation → muscle fiber necrosis
- Degenerated muscle is replaced by fibrofatty tissue (pseudohypertrophy)

Clinical Features

- **Onset:** Typically presents at 2–3 years of age
- **Early Motor:** Delayed walking, frequent falls, toe walking, waddling (Trendelenburg) gait
- **Progression:** Proximal → distal; lower limbs → upper limbs
- **Classic Signs:**
    - **Gowers sign:** Patient uses hands to "climb up" their own legs to stand from supine (indicates proximal weakness)
    - **Pseudohypertrophy:** Enlarged, firm, rubbery calf muscles (also glutei/deltoids) due to fat/connective tissue infiltration
- **Loss of Ambulation:** Typically occurs by 10–12 years of age
- **Extra-muscular features:**
    - Mild, non-progressive intellectual disability (IQ usually ~1 standard deviation below mean)
    - Dilated cardiomyopathy (DCM)
    - Smooth muscle dysfunction (delayed gastric emptying, constipation)

Diagnosis

- **Creatine Phosphokinase (CPK):** First-line screening. Massively elevated (10,000–30,000+ U/L) even before clinical weakness
- **Genetic Testing (Diagnostic Algorithm):**
    - *Step 1:* MLPA (Multiplex Ligation-dependent Probe Amplification) to detect deletions/duplications
    - *Step 2:* Next-Generation Sequencing (NGS) to detect point mutations if MLPA is negative

- **Muscle Biopsy:** Rarely needed now. Used only if genetics are inconclusive. Shows absent dystrophin on immunostaining, necrosis, and fibrofatty replacement
- **EMG:** Myopathic pattern (small amplitude, short duration, polyphasic potentials) – *historical, rarely performed today*

Management: Pharmacological & Targeted

- **Corticosteroids (Gold Standard):**
  - *Indication:* Start in ambulatory phase (usually 4–5 years) when motor skills plateau or decline
  - *Drugs:* Prednisolone (0.75 mg/kg/day) or Deflazacort (0.9 mg/kg/day)
  - *Benefit:* Prolongs ambulation by 2–3 years, delays scoliosis, preserves respiratory/cardiac function
- **Mutation-Specific Therapies (Recent Updates):**
  - *Exon-skipping (converts out-of-frame to in-frame/Becker-like phenotype):* Eteplirsen (Exon 51), Golodirsen/Viltolarsen (Exon 53), Casimersen (Exon 45)
  - *Nonsense mutation read-through:* Ataluren
- **Gene Therapy (2023 FDA Update):** Delandistrogene moxeparvovec (micro-dystrophin gene transfer via AAV vector) approved for ambulatory children aged 4–5 years

Management: Multidisciplinary & Supportive

- **Physiotherapy:** Daily stretching to prevent contractures (Achilles, iliotibial band); avoid eccentric/high-resistance exercises
- **Orthopedics:** Ankle-foot orthoses (AFOs) for sleep; surgical release of contractures; spinal fusion for severe scoliosis
- **Cardiac:** Prophylactic ACE inhibitors/ARBs by age 10 (or earlier if echo shows dysfunction), followed by beta-blockers
- **Respiratory:** Annual PFTs. Nocturnal BiPAP for hypoventilation; mechanical inexsufflator (cough assist) for weak cough
- **Bone Health:** Vitamin D and calcium supplementation; bisphosphonates for symptomatic vertebral fractures (steroid-induced osteoporosis)

Complications

- Respiratory failure (leading cause of death)
- Dilated cardiomyopathy and arrhythmias
- Severe scoliosis (accelerates after loss of ambulation)
- Malignant hyperthermia-like reactions (avoid depolarizing muscle relaxants like succinylcholine and volatile anesthetics)

Prognosis

- Without intervention: Death in late teens/early 20s
- With steroids + BiPAP + cardiac care: Survival extended into 3rd or 4th decade

Prevention & Counseling

- **Genetic Counseling:** X-linked recessive risk (50% risk to sons, 50% risk of carrier status to daughters)
- **Carrier Screening:** CPK testing and genetic testing for female relatives
- **Prenatal Diagnosis:** CVS (10–12 weeks) or Amniocentesis (15–18 weeks) for known familial mutations

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Exam Summary: Must-Write Points

- X-linked recessive, *DMD* gene (Xp21.2), out-of-frame mutation causing absent dystrophin.
- Classic triad: Gowers sign, calf pseudohypertrophy, and proximal muscle weakness.
- Screening: CPK >10,000 U/L; Diagnosis: MLPA followed by NGS.
- Definitive management: Glucocorticoids (Prednisolone/Deflazacort) prolong ambulation.
- Avoid succinylcholine/inhalational anesthetics due to massive potassium release and rhabdomyolysis risk.

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109. Principles of genetic counseling

Subject: Genetics

Definition & Goals

- **Definition:** A communication process dealing with the medical, psychological, and familial implications of genetic contributions to disease.
- **Goals:** Comprehend medical facts/diagnosis, understand inheritance patterns, understand options for testing/management, make informed choices, and achieve psychosocial adaptation.

Core Principles (The "Must-Write" Core)

- **Non-directive counseling:** The counselor provides accurate, unbiased information but does not dictate the decision. *Key tenet: Facilitate patient choice, not counselor preference.*
- **Respect for Autonomy:** Upholding the individual's right to make informed, independent decisions regarding testing and reproduction.
- **Confidentiality:** Strict privacy of genetic information.
    - *Exception (Exam Trap):* "Duty to warn" at-risk relatives if a preventable/treatable condition is found and the patient refuses to disclose (weighing privacy vs. harm).
- **Informed Consent:** Full disclosure of test limitations, risks, benefits, and potential for incidental findings before testing.
- **Truth-telling:** Complete honesty regarding diagnosis, prognosis, and recurrence risks.

Indications

- **Maternal:** Advanced maternal age (>35 years), abnormal prenatal screen (NIPT, maternal serum markers, USG anomalies).

- **Fetal/Pediatric:** Congenital anomalies, intellectual disability, autism spectrum disorder, dysmorphic features.
- **Family History:** Known genetic disorder, carrier status, recurrent pregnancy loss (≥2 or 3), stillbirths of unknown etiology.
- **Consanguinity:** Increased risk for autosomal recessive conditions.

The Process (Stepwise Approach)

- **Information Gathering:** Construct a detailed **3-generation pedigree** (minimum requirement); review medical records and birth history.
- **Establishing Diagnosis:** Clinical evaluation, dysmorphology assessment, and targeted genetic testing (Karyotype, Chromosomal Microarray [CMA], Exome Sequencing [ES]).
- **Risk Assessment:** Calculating exact recurrence risks based on Mendelian laws, Bayes' theorem, or empiric data.
- **Communication:** Explaining the diagnosis, natural history, and recurrence risk in simple, culturally appropriate lay language.
- **Discussing Options:** Exploring reproductive options (Preimplantation Genetic Testing [PGT], prenatal diagnosis via CVS/amniocentesis, donor gametes, adoption).
- **Psychosocial Support:** Addressing emotional responses (guilt, blame, anxiety, grief); connecting with support groups.

Risk Assessment Rules (High-Yield)

- **Autosomal Dominant (AD):** 50% recurrence risk per pregnancy (if one parent affected). Note: Check for incomplete penetrance and variable expressivity.
- **Autosomal Recessive (AR):** 25% recurrence risk for carrier parents.
- **X-linked Recessive (XR):** 50% risk for sons to be affected, 50% risk for daughters to be carriers (if mother is a carrier).
- **Mitochondrial:** 100% transmission from affected mother to all children; 0% transmission from affected father.
- **De Novo Mutations:** Recurrence risk is typically <1% (due to gonadal mosaicism).

Ethical & Guideline Updates (AAP/ACMG)

- **Testing Minors (AAP/ACMG 2024 Update):** Predictive genetic testing for adult-onset conditions (e.g., Huntington disease, BRCA) is **strictly contraindicated** in minors unless a childhood medical intervention exists.
- **Incidental Findings:** ACMG recommends reporting specific actionable secondary findings (e.g., familial hypercholesterolemia, cancer syndromes) when doing Exome/Genome sequencing, unless the patient opts out.
- **Non-Paternity:** Often discovered incidentally; should not be disclosed unless directly relevant to the child's medical care or genetic risk.
- **Consanguinity Counseling:** Focus on the absolute increased risk of congenital anomalies (approx. 2-3% above the baseline population risk of 2-3% for first cousins).

Exam Summary

- **Buzzword:** Always use the term **"Non-directive counseling."**
- **First step:** Always draw a **3-generation pedigree**.
- **Major trap:** Do not offer predictive testing for adult-onset diseases in asymptomatic children.
- **Recurrence trap:** Always rule out gonadal mosaicism in apparent "de novo" dominant mutations before quoting a 0% recurrence risk (quote ~1%).
- **Counselor's role:** Provide information and options; the patient makes the final reproductive decision.

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110. Molecular diagnosis of genetic diseases

Subject: Genetics

Definition

- Analysis of human DNA, RNA, chromosomes, or proteins to detect heritable disease-related variations.
- Encompasses cytogenetics, molecular genetics, and biochemical genetics.

Clinical Indications

- **Preconception:** Carrier screening (e.g., Thalassemia, SMA).
- **Prenatal:** NIPT (cell-free fetal DNA), CVS, Amniocentesis for high-risk pregnancies.
- **Neonatal:** Newborn screening (NBS), ambiguous genitalia, severe early-onset encephalopathy.
- **Pediatric:** Global developmental delay (GDD), autism spectrum disorder (ASD), multiple congenital anomalies (MCA), dysmorphism.
- **Targeted:** Pharmacogenomics, predictive testing (e.g., familial cancer syndromes).

Cytogenetic Techniques (Chromosomal Level)

- **Karyotyping:**
  - Detects large structural abnormalities (>5–10 Mb) and aneuploidies.
  - *Indication:* Suspected Down syndrome, Turner syndrome, recurrent miscarriages.
- **FISH (Fluorescence In Situ Hybridization):**
  - Detects specific microdeletions/microduplications (100–500 kb).
  - *Indication:* DiGeorge syndrome (22q11.2), Williams syndrome (7q11.23), rapid aneuploidy screening.
- **CMA (Chromosomal Microarray):**
  - Detects submicroscopic Copy Number Variations (CNVs).
  - *Limitation:* Cannot detect balanced translocations or point mutations.
  - *Indication:* **First-line** test for unexplained GDD, ASD, and MCA.

Molecular Techniques (DNA/Gene Level)

- **PCR (Polymerase Chain Reaction):**
    - Amplifies specific DNA sequences.
    - *Indication:* Trinucleotide repeat disorders (Fragile X, Huntington), specific known point mutations.
- **Sanger Sequencing:**
    - Gold standard for reading exact nucleotide sequences of a single gene.
    - *Indication:* Small targeted regions, confirming NGS findings.
- **MLPA (Multiplex Ligation-dependent Probe Amplification):**
    - Detects intragenic deletions or duplications.
    - *Indication:* **First-line** for Duchenne Muscular Dystrophy (DMD) and Spinal Muscular Atrophy (SMA).
- **Methylation-Specific Testing:**
    - Detects epigenetic modifications.
    - *Indication:* Imprinting disorders (Prader-Willi, Angelman, Beckwith-Wiedemann syndromes).

Next-Generation Sequencing (NGS)

- **Targeted Gene Panels:**
    - Sequences multiple genes associated with a specific phenotype simultaneously.
    - *Indication:* High genetic heterogeneity (e.g., epilepsy panel, skeletal dysplasia panel, deafness panel).
- **WES (Whole Exome Sequencing):**
    - Sequences all protein-coding regions (~1–2% of the genome, but harbors ~85% of disease-causing mutations).
    - *Indication:* Complex, undiagnosed suspected genetic phenotypes.
- **WGS (Whole Genome Sequencing):**
    - Sequences the entire genome, including non-coding regions (introns, promoters).
    - *Indication:* When WES is negative, or looking for deep intronic variants.

Diagnostic Algorithm / Approach

- **Suspected Aneuploidy/Classic Trisomy:** ⇒Karyotype.
- **Unexplained GDD / ASD / MCA:** ⇒CMA (First-line).
- **Known specific gene defect (e.g., Deletion in DMD):** ⇒MLPA.
- **Known specific point mutation (e.g., Sickle Cell):** ⇒Targeted PCR / Sanger.
- **Specific phenotype, multiple possible genes:** ⇒NGS Targeted Panel.
- **Undiagnosed rare genetic disease:** ⇒WES / WGS (Ideally **"Trio testing"**: Proband + both biological parents).

Challenges & Limitations

- **VUS (Variant of Uncertain Significance):** A detected genetic change whose association with disease risk is currently unknown.
- **Incidental Findings:** Unintended discovery of pathogenic variants (e.g., BRCA in a child tested for GDD).
- Requires rigorous pre-test and post-test genetic counseling.

Recent Updates & Guidelines

- **ACMG/AAP 2023:** While CMA remains first-tier for GDD/MCA, **Rapid WES/WGS (rWGS)** is now strongly recommended as a first-tier test for critically ill infants in the NICU/PICU with suspected genetic etiology, significantly reducing time to diagnosis and altering management.

Exam Summary: Must-Write Points

- **CMA** is the first-line test for GDD, intellectual disability, autism, and multiple congenital anomalies.
- **MLPA** is the diagnostic test of choice for large gene deletions/duplications (DMD, SMA).
- **Methylation studies** are required for imprinting disorders (Prader-Willi/Angelman).
- **WES/WGS** is reserved for undiagnosed complex phenotypes; **Trio testing** increases diagnostic yield.
- **VUS** is a major clinical challenge requiring parental testing and functional correlation; do not base irreversible clinical decisions solely on a VUS.

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111. Pedigree of mitochondrial inheritance

Subject: Genetics

Definition & Basics

- Transmission of genetic disorders caused by mutations in mitochondrial DNA (mtDNA).
- Strictly **maternal inheritance** (sperm mitochondria are destroyed post-fertilization; only the oocyte contributes mtDNA to the zygote).
- mtDNA is circular, double-stranded, and codes for 13 proteins essential for oxidative phosphorylation (OXPHOS).

Pedigree Hallmarks

- **Affected Mother:** Transmits the mutation to **ALL** her offspring (both sons and daughters).
- **Affected Father:** Transmits the mutation to **NONE** of his offspring.
- **Sex ratio:** Both males and females are affected equally.
- **Vertical transmission:** Appears in every generation (similar to autosomal dominant), but distinguished by the absolute lack of paternal transmission.

Core Genetic Concepts (Must-Know)

- **Heteroplasmy:** Coexistence of both mutated and wild-type mtDNA within a single cell. Results in highly variable clinical severity (variable expressivity) even among siblings.

- **Homoplasmy:** All mtDNA copies in a cell are identical (either all normal or all mutant, e.g., LHON).
- **Threshold Effect:** Clinical symptoms manifest only when the mutant mtDNA load exceeds a critical percentage (usually 60–80%).
- **Replicative Segregation:** Random distribution of mitochondria to daughter cells during mitosis, causing phenotypic shifts over time.

Clinical Features (High-Energy Tissue Tropism)

- **Neurologic:** Encephalopathy, myoclonus, seizures, stroke-like episodes, ataxia.
- **Muscular:** Myopathy, hypotonia, exercise intolerance.
- **Ocular:** Progressive external ophthalmoplegia (PEO), optic atrophy, retinitis pigmentosa.
- **Systemic:** Sensorineural hearing loss, diabetes mellitus, cardiomyopathy, conduction blocks, lactic acidosis.

Classic Syndromes

- **MELAS:** Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes.
- **MERRF:** Myoclonic Epilepsy with Ragged Red Fibers.
- **LHON:** Leber Hereditary Optic Neuropathy (bilateral subacute vision loss, predominantly affects young males despite maternal inheritance).
- **Kearns-Sayre Syndrome:** PEO, pigmentary retinopathy, and cardiac conduction blocks.
- **NARP:** Neuropathy, Ataxia, and Retinitis Pigmentosa.

Diagnosis

- **Biomarkers:** Elevated serum and CSF lactate, high lactate-to-pyruvate ratio.
- **Muscle Biopsy:** Modified Gomori trichrome stain shows **"Ragged Red Fibers"** (subsarcolemmal accumulation of abnormal mitochondria).
- **Electron Microscopy:** "Parking lot" inclusions (paracrystalline arrays).
- **Genetic Testing:** mtDNA sequencing. *Trap:* Test affected tissue (e.g., skeletal muscle) if blood testing is negative, as mutant mtDNA may be cleared from rapidly dividing blood cells (tissue-specific heteroplasmy).

Management & Counseling

- **Supportive Care:** Multidisciplinary management of organ-specific complications (e.g., pacemakers for Kearns-Sayre, anticonvulsants for seizures).
- **Mitochondrial Cocktail:** Coenzyme Q10 (ubiquinone), riboflavin, L-carnitine, Vitamin C, and Vitamin E (aimed at optimizing electron transport chain and scavenging free radicals).
- **Drugs to Avoid:** Valproate (triggers fulminant hepatic failure in POLG mutations), aminoglycosides (triggers deafness in specific mtDNA mutations), linezolid, and propofol.
- **Prevention:** Mitochondrial replacement therapy ("Three-parent IVF" – replacing maternal mutant mitochondria with healthy donor mitochondria) is a cutting-edge preventative option (approved in specific regions like the UK).

Exam Summary

- **Pedigree key:** Mother passes to ALL children; Father passes to NO children.
- **Buzzwords:** Heteroplasmy, Threshold effect, Ragged Red Fibers.
- **Target organs:** High ATP-demand tissues (Brain, Muscle, Eye, Heart).
- **Avoid:** Valproic acid and mitochondrial-toxic antibiotics.

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112. Osteogenesis imperfecta X ray findings

Subject: Genetics

Basics

- **Definition:** Inherited connective tissue disorder characterized by extreme bone fragility and osteopenia.
- **Genetics:** Mostly Autosomal Dominant; mutations in *COL1A1* or *COL1A2* genes.
- **Pathophysiology:** Defective quantity (Type I - mild) or quality (Types II, III, IV - severe) of Type I collagen → abnormal osteoid formation → structurally weak bones.

Clinical Features

- **Bone fragility:** Recurrent low-impact fractures, progressive deformities.
- **Ocular:** Blue/grey sclerae (due to thin sclera revealing underlying choroid).
- **Dental:** Dentinogenesis imperfecta (opalescent, brittle teeth).
- **ENT:** Progressive hearing loss (conductive or mixed) appearing in 2nd–3rd decade.
- **Musculoskeletal:** Joint hypermobility, short stature, ligamentous laxity.

X-Ray Findings (Core Focus)

- **General:** Generalized severe osteopenia, thinned cortices, sparse trabeculae.
- **Skull:**
    - **Wormian bones:** Intrasutural accessory bones (typically >10, mosaic pattern).
    - Thin calvarium with delayed fontanelle closure.
    - Basilar invagination/platybasia (advanced cases).
- **Long Bones:**
    - Multiple fractures at various stages of healing.
    - **Bowing deformities:** "Saber shins" (anterior bowing of tibia), anterolateral bowing of femur.
    - **"Popcorn" calcifications:** Scalloped, radiolucent areas with sclerotic margins in metaphyses/epiphyses (especially knees in severe types).
    - **Hyperplastic callus:** Exuberant callus formation at fracture sites (can mimic osteosarcoma).
    - **"Ribbon-like" bones:** Extremely thin, crumpled long bones (classic for lethal Type II).

- **Spine:**
    - **"Codfish" vertebrae:** Biconcave vertebral bodies due to disc pressure on soft endplates.
    - Platyspondyly (flattened vertebrae) and compression fractures.
    - Severe kyphoscoliosis.
- **Chest & Pelvis:**
    - Rib fractures with "beaded" appearance; thin ribs (Type II).
    - Protrusio acetabuli (inward bulging of the acetabulum).

Other Diagnostics

- **DEXA Scan:** Significantly reduced bone mineral density (Z-score < -2.0).
- **Biochemical:** Serum calcium, phosphorus, and PTH are typically **normal** (differentiates from rickets/metabolic bone disease); elevated Alkaline Phosphatase post-fracture.
- **Definitive:** Molecular genetic testing for *COL1A1/COL1A2* (gold standard).

Management

- **Medical (First-line):** Intravenous Bisphosphonates.
    - *Update (Current Practice):* IV Zoledronic acid is increasingly preferred over IV Pamidronate due to shorter infusion times and equal efficacy.
    - *Mechanism:* Inhibits osteoclast-mediated bone resorption, increases cortical thickness.
- **Surgical:**
    - Intramedullary rodding (Fassier-Duval telescoping rods) to correct bowing and prevent fractures.
    - Spinal fusion for progressive severe scoliosis.
- **Supportive:** Physiotherapy (muscle strengthening, avoiding immobilization), audiology assessment, dental crowns for dentinogenesis imperfecta.
- **Contraindications:** Avoid prolonged casting/immobilization (worsens osteopenia).

Complications & Prognosis

- **Neurological:** Basilar invagination leading to brainstem compression/hydrocephalus (Red Flag: requires urgent neurosurgery).
- **Respiratory:** Cor pulmonale and respiratory failure secondary to severe kyphoscoliosis (leading cause of death in severe types).
- **Prognosis:**
    - Type I: Normal lifespan, ambulatory.
    - Type II: Perinatal lethal (pulmonary hypoplasia/severe fractures).
    - Type III: Severe, progressively deforming, often wheelchair-bound.

Prevention

- **Genetic Counseling:** Recurrence risk is 50% for affected individuals (AD).
- **Prenatal Diagnosis:** Level II Ultrasound at 18-20 weeks (detects severe bowing/fractures in Type II/III); Chorionic villus sampling (CVS) for targeted gene mutation if known.

Exam Summary

- **Classic Triad:** Fragile bones, blue sclerae, early deafness.
- **Must-Write X-Ray Buzzwords:** Wormian bones, Codfish vertebrae, Popcorn metaphyses, Ribbon-like bones, Hyperplastic callus.
- **Labs:** Calcium, Phosphorus, and PTH are **normal**.
- **Treatment of choice:** IV Bisphosphonates (Zoledronic acid/Pamidronate) + Telescoping intramedullary rods.

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113. Genetic testing in pediatric diseases

Subject: Genetics

Overview

- Analysis of human DNA, RNA, chromosomes, proteins, or metabolites to detect heritable disease-related genotypes, mutations, or karyotypes.
- Aims: Diagnosis, carrier screening, newborn screening (NBS), predictive testing, and pharmacogenomics.

Indications

- **Neonatal:** Abnormal NBS, ambiguous genitalia, severe hypotonia, unprovoked seizures, unexplained metabolic acidosis.
- **Childhood:** Developmental delay/intellectual disability (DD/ID), autism spectrum disorder (ASD), multiple congenital anomalies (MCA).
- **Physical:** Dysmorphism, abnormal growth (severe short stature/overgrowth), micro/macrocephaly.
- **Neurological:** Regression of milestones, neurodegeneration, unexplained deafness/blindness, myopathy.
- **Family History:** Known familial genetic disorder, recurrent miscarriages, consanguinity with affected sibling.

Testing Modalities & Yield

- **Karyotyping (G-Banding):**
    - *Resolution:* Detects large structural changes >5–10 Mb.
    - *Indications:* Suspected aneuploidies (Down, Turner, Klinefelter), large translocations, disorders of sex development (DSD).
- **FISH (Fluorescence In Situ Hybridization):**
    - *Resolution:* Submicroscopic deletions/duplications (100–500 kb).

  - *Indications:* Known specific microdeletion syndromes (e.g., 22q11.2/DiGeorge, Williams syndrome). *Limitation:* Must know the target locus beforehand.

- **CMA (Chromosomal Microarray):**
  - *Mechanism:* Detects Copy Number Variants (CNVs) across the genome.
  - *Update (ACMG/AAP):* **First-line test** for unexplained DD/ID, ASD, and MCA.
  - *Limitation:* Cannot detect balanced translocations or single nucleotide variants (SNVs).
- **Sanger Sequencing:**
  - *Mechanism:* Single gene sequencing.
  - *Indications:* Classic phenotype pointing to a single specific gene (e.g., *CFTR* for Cystic Fibrosis, *HBB* for Thalassemia).
- **Next-Generation Sequencing (NGS):**
  - *Targeted Panels:* For phenotypes with locus heterogeneity (e.g., Epilepsy panel, Skeletal dysplasia panel).
  - *Whole Exome Sequencing (WES):* Sequences all protein-coding regions (~1–2% of genome but contains ~85% of disease-causing mutations).
  - *Whole Genome Sequencing (WGS):* Sequences entire genome (including introns).
- **Specialized Molecular Tests:**
  - *Methylation Studies:* For imprinting disorders (Prader-Willi, Angelman, Beckwith-Wiedemann).
  - *PCR/Southern Blot:* For trinucleotide repeat expansions (Fragile X syndrome, Friedreich ataxia).

Diagnostic Algorithm

- **Recognizable Syndrome:** Specific test (e.g., Karyotype for Down syndrome, Single-gene for Achondroplasia).
- **Unexplained DD/ID, ASD, or MCA:**
  - *Step 1:* CMA + Fragile X testing (if male or suggestive family history).
  - *Step 2:* If negative, proceed to WES/WGS.
- **Critically Ill Neonate (NICU/PICU):**
  - *Update:* Rapid WES/WGS (rWGS) is now the emerging standard of care for undiagnosed critically ill infants to guide immediate life-saving management.

Ethics & Counseling

- **Pre-test Counseling:** Discuss yield, limitations, cost, and possibility of Variants of Uncertain Significance (VUS) or incidental findings.
- **Post-test Counseling:** Interpret results in the clinical context; discuss recurrence risk and family planning.
- **Predictive Testing in Minors (AAP/ACMG Guidelines):**

- *Actionable in childhood:* Testing is recommended (e.g., MEN2, Familial Adenomatous Polyposis).
- *Adult-onset disorders:* Testing is **strictly discouraged** until the child reaches the age of majority and can provide informed consent (e.g., Huntington disease, *BRCA* mutations).

Exam Summary

- **CMA** is the first-line test for unexplained developmental delay, intellectual disability, autism, and multiple congenital anomalies.
- **Karyotype** is reserved for suspected aneuploidies, balanced translocations, and ambiguous genitalia.
- **NGS Panels** are best for conditions with high locus heterogeneity (e.g., deafness, seizures).
- **Methylation studies** are mandatory to diagnose imprinting disorders (Prader-Willi/Angelman).
- **Ethical trap:** Never test an asymptomatic child for an adult-onset untreatable disease (e.g., Huntington's).

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114. Genetic basis of common pediatric diseases

Subject: Genetics

Classification of Genetic Disorders

- **Chromosomal Aneuploidies:** Numerical abnormalities (entire chromosome gained/lost)
- **Microdeletion/Microduplication:** Submicroscopic chromosomal imbalances
- **Mendelian (Single Gene):** Autosomal Dominant (AD), Autosomal Recessive (AR), X-Linked (XL)
- **Non-Mendelian:** Trinucleotide repeat expansions, Imprinting defects, Mitochondrial
- **Multifactorial:** Polygenic inheritance + environmental triggers

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Chromosomal Aneuploidies

- **Down Syndrome (Trisomy 21):**
  - *Mechanism:* Maternal meiotic nondisjunction (95%), Robertsonian translocation (4%), Mosaicism (1%)
  - *Key Gene Locus:* Down syndrome critical region (DSCR) on 21q22
  - *Clinical:* Up-slanting palpebral fissures, single palmar crease, AV septal defect
- **Turner Syndrome (45,X):**
  - *Mechanism:* Paternal X chromosome nondisjunction/loss (80%); high rate of mosaicism (45,X/46,XX)
  - *Key Gene Locus: SHOX* gene haploinsufficiency (Xp22.33) → short stature
  - *Clinical:* Webbed neck, streak ovaries, bicuspid aortic valve, coarctation of aorta

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Microdeletion Syndromes (Contiguous Gene Syndromes)

- **DiGeorge Syndrome (Velocardiofacial Syndrome):**
    - *Basis:* 22q11.2 microdeletion
    - *Key Gene: TBX1* (pharyngeal arch development defect)
    - *Clinical:* Conotruncal heart defects, hypocalcemia, thymic hypoplasia (CATCH-22)
- **Prader-Willi Syndrome (PWS) & Angelman Syndrome (AS):**
    - *Locus:* 15q11-q13 (Genomic Imprinting)
    - *PWS Basis:* Loss of *paternal* expression (Paternal deletion 75%, Maternal uniparental disomy 25%) → hyperphagia, obesity
    - *AS Basis:* Loss of *maternal UBE3A* gene expression → severe ID, "happy puppet" gait, seizures

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Mendelian (Single Gene) Disorders

Autosomal Dominant (AD)

- **Achondroplasia:**
    - *Basis: FGFR3* gene (4p16.3); gain-of-function mutation (G380R)
    - *Mechanism:* Constitutive activation inhibits chondrocyte proliferation
    - *Note:* 80% de novo mutations; associated with advanced paternal age
- **Marfan Syndrome:**
    - *Basis: FBN1* gene (15q21.1) encoding Fibrillin-1
    - *Mechanism:* Dominant negative effect → excessive TGF-β signaling
    - *Clinical:* Ectopia lentis (upward), aortic root dilation, arachnodactyly

Autosomal Recessive (AR)

- **Cystic Fibrosis (CF):**
    - *Basis: CFTR* gene (7q31.2); ΔF508 most common mutation
    - *Mechanism:* Class II defect (protein misfolding/degradation) → defective chloride/bicarbonate transport
- **Sickle Cell Disease (SCD):**
    - *Basis: HBB* gene (11p15.4)
    - *Mechanism:* Point mutation (Missense) → Glutamic acid replaced by Valine at 6th position of β-globin chain
- **Spinal Muscular Atrophy (SMA):**
    - *Basis: SMN1* gene deletion/mutation (5q13)
    - *Mechanism:* Loss of anterior horn cells; severity inversely proportional to *SMN2* copy number

X-Linked (XL)

- **Duchenne Muscular Dystrophy (DMD):**
    - *Basis: DMD* gene (Xp21.2) - largest human gene
    - *Mechanism:* Out-of-frame frameshift/nonsense mutation → completely absent dystrophin
    - *Contrast:* Becker MD (BMD) has in-frame mutation → truncated, partially functional dystrophin
- **Hemophilia A:**
    - *Basis: F8* gene (Xq28)
    - *Mechanism:* Intron 22 inversion (most common in severe cases) → Factor VIII deficiency

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Non-Mendelian & Dynamic Mutations

- **Fragile X Syndrome:**
    - *Basis: FMR1* gene (Xq27.3); Trinucleotide repeat expansion (CGG)
    - *Mechanism:* >200 repeats (full mutation) → promoter hypermethylation → gene silencing → absent FMRP protein
    - *Concept:* Demonstrates *Anticipation* (increasing severity/earlier onset in subsequent generations)

Multifactorial / Polygenic Disorders

- *Basis:* Interaction of multiple susceptibility genes + environmental triggers
- *Examples:* Congenital Heart Defects (CHD), Neural Tube Defects (NTDs), Cleft lip/palate, Type 1 Diabetes, Asthma
- *Risk:* Recurrence risk depends on number of affected relatives and severity (usually 2-5% for first-degree relatives)

Diagnostic Approach to Genetic Diseases

- **Chromosomal Microarray (CMA):** First-line test for global developmental delay (GDD), intellectual disability (ID), autism, or multiple congenital anomalies (AAP 2023 update). Detects microdeletions/duplications.
- **Karyotype:** Indicated for suspected aneuploidy (Down, Turner) or structural balanced translocations.
- **Targeted Mutation Panel / PCR:** For known single-gene AR/AD disorders (e.g., ΔF508 in CF).
- **MLPA (Multiplex Ligation-dependent Probe Amplification):** Test of choice for large deletions/duplications (e.g., SMA, DMD).
- **Next-Generation Sequencing (NGS):**
    - *Clinical Exome Sequencing (WES):* For suspected genetic disorders with negative CMA/phenotype-specific panels.

Cutting-Edge Management (Therapeutics)

- *Gene Replacement Therapy:* **Onasemnogene abeparvovec (Zolgensma)** (AAV9 vector delivering functional *SMN1*) for SMA.
- *Antisense Oligonucleotides (ASO):* **Nusinersen** (modifies *SMN2* splicing) for SMA; **Eteplirsen** (exon 51 skipping) for DMD.
- *Small Molecule Modulators:* **Elexacaftor/Tezacaftor/Ivacaftor** (Trikafta) for CF patients with at least one ΔF508 allele.
- *CRISPR-Cas9:* **Exa-cel (Casgevy)** recently FDA-approved (2023) for Sickle Cell Disease and Transfusion-Dependent Thalassemia.

Genetic Counseling & Prevention

- **Autosomal Recessive:** 25% recurrence risk; carrier screening essential.
- **Autosomal Dominant:** 50% recurrence risk; evaluate parents for mild/variable expression.
- **Prenatal Diagnosis:** Chorionic Villus Sampling (10-13 weeks) or Amniocentesis (15-20 weeks).
- **Non-Invasive Prenatal Testing (NIPT):** Cell-free fetal DNA in maternal blood (from 10 weeks) for highly sensitive aneuploidy screening.

Exam Summary (Must-Write Points)

- **CMA is the first-line investigation** for unexplained developmental delay, autism, and multiple congenital anomalies.
- **Down Syndrome** is primarily caused by maternal meiotic nondisjunction (95%), while **Turner Syndrome** is predominantly due to paternal X loss.
- **Microdeletions:** DiGeorge (22q11.2, *TBX1*), Prader-Willi/Angelman (15q11-q13 imprinting).
- **Mutational mechanisms:** Achondroplasia is a *gain-of-function* (*FGFR3*), Marfan is *dominant negative* (*FBN1*), and Fragile X is *gene silencing via hypermethylation* (*FMR1*).
- **Modern Therapeutics:** Explicitly mention ASOs (Nusinersen for SMA), Gene therapy (Zolgensma for SMA), and CRISPR (Exa-cel for Sickle Cell) for high-scoring answers.

Public Health / Social Pediatrics

115. Trends in child health indicators in Nepal

Subject: Public Health / Social Pediatrics

Context & Data Source

- **Primary Source:** Nepal Demographic and Health Survey (NDHS) 2022.
- **Overall Trend:** Significant progress in survival and chronic malnutrition; however, neonatal mortality and acute malnutrition remain stagnant.

- **Goal:** Alignment with Sustainable Development Goals (SDG) 2030 targets.

Mortality Trends (per 1,000 live births)

- **Under-5 Mortality Rate (U5MR):** ↓ Declined from 39 (2016) to **33** (2022). *SDG 2030 target: ≤25*.
- **Infant Mortality Rate (IMR):** ↓ Declined from 32 (2016) to **28** (2022).
- **Neonatal Mortality Rate (NMR):** ↔ Stagnant at **21** (2022), same as 2016. *SDG 2030 target: ≤12*.
- **Proportional Mortality:** Neonatal deaths now account for **~64%** of all under-5 deaths (shifting burden from post-neonatal to neonatal period).

Nutritional Trends

- **Stunting (Chronic malnutrition):** ↓ Improved significantly from 36% (2016) to **25%** (2022). *SDG target: 15%*.
- **Wasting (Acute malnutrition):** ↔ Stagnant at **8%** (2022) vs 10% (2016). *SDG target: 4%*.
- **Underweight:** ↓ Declined from 27% (2016) to **19%** (2022).
- **Anemia (6–59 months):** ↓ Improved from 53% (2016) to **43%** (2022), but remains a severe public health problem.
- **Exclusive Breastfeeding (<6 months):** ↓ **Declined** from 66% (2016) to **56%** (2022). *Major red flag for child health*.

Immunization Trends

- **Fully Immunized:** ↑ Increased to **80%** (2022) for basic antigens.
- **Zero-Dose Children: 4%** of children (12–23 months) received no vaccinations.
- **Coverage Disparity:** Lowest coverage in Madhesh Province; highest in Bagmati.

Maternal & Perinatal Service Utilization

- **Institutional Delivery:** ↑ Massive increase from 57% (2016) to **79%** (2022).
- **Skilled Birth Attendant (SBA):** ↑ Increased to **80%** (2022).
- *Paradox:* Despite high institutional delivery, NMR remains stagnant, indicating gaps in the *quality* of intrapartum and immediate newborn care.

Major Causes of Child Mortality in Nepal

- **Neonatal:** Prematurity, Birth Asphyxia, Neonatal Sepsis.
- **Post-neonatal (1–59 months):** Pneumonia, Diarrheal diseases, Injuries/Accidents.

Key Public Health Interventions (Nepal)

- **CB-IMNCI:** Community-Based Integrated Management of Neonatal and Childhood Illness (focus on pneumonia, diarrhea, PSBI).
- **MSNP-III:** Multi-Sectoral Nutrition Plan (ongoing to tackle stunting and wasting).
- **IMAM:** Integrated Management of Acute Malnutrition (outpatient therapeutic centers for SAM).
- **SBA & CEONC:** Expansion of Skilled Birth Attendants and Comprehensive Emergency Obstetric and Neonatal Care.

Red Flags & Ongoing Challenges

- **NMR Stagnation:** The biggest hurdle to achieving SDG U5MR targets.
- **EBF Decline:** Rising use of commercial breast milk substitutes and rapid maternal return to work.
- **Inequity:** Severe disparities based on wealth quintile, maternal education, and geography (Madhesh and Karnali provinces lag significantly).

Exam Summary: Must-Write NDHS 2022 Statistics

- **U5MR:** 33/1,000 live births.
- **IMR:** 28/1,000 live births.
- **NMR:** 21/1,000 live births (Stagnant, >60% of U5 deaths).
- **Stunting:** 25% (Improving).
- **Wasting:** 8% (Stagnant).
- **Exclusive Breastfeeding:** 56% (Declining - key exam trap).
- **Institutional Delivery:** 79% (Improving, but quality of care needs focus).

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116. Infant and under five mortality trends

Subject: Public Health / Social Pediatrics

Definitions

- **Infant Mortality Rate (IMR):** Number of deaths of infants (<1 year of age) per 1,000 live births in a given year.
- **Under-Five Mortality Rate (U5MR):** Probability of dying between birth and exactly 5 years of age, expressed per 1,000 live births.
- **Neonatal Mortality Rate (NMR):** Deaths in the first 28 days of life per 1,000 live births (constitutes ~70% of IMR in India).

Current Trends (India - SRS 2020/Latest Data)

- **IMR Decline:** Dropped from 50 (2009) → 37 (2015) → **28 (2020)**.
- **U5MR Decline:** Dropped from 64 (2009) → 43 (2015) → **32 (2020)**.
- **NMR Decline:** Dropped to **20** per 1,000 live births.
- **Urban-Rural Divide:** Rural IMR (31) remains significantly higher than Urban IMR (19).
- **Gender Gap:** Historically Female IMR > Male IMR; currently closing (Male U5MR: 31, Female U5MR: 33).
- **State Variations:** Kerala has the lowest IMR (43).

Global Trends (UNIGME)

- Global U5MR dropped by ~60% since 1990 (from 93 to 38 per 1,000 in 2021).

- Highest burden remains in Sub-Saharan Africa and Southern Asia (>80% of global under-five deaths).

Etiology (Major Causes)

- **Neonatal (0–28 days):** Prematurity/Low Birth Weight (35%), Birth Asphyxia/Trauma (20%), Neonatal Sepsis (15%), Congenital anomalies.
- **Post-Neonatal (1–12 months):** Acute Respiratory Infections (Pneumonia), Diarrheal diseases.
- **1 to 5 Years:** Pneumonia, Diarrhea, Injuries/Accidents, Measles.
- *Note:* Undernutrition is the underlying contributing factor in **>50%** of all under-five deaths.

Key Determinants

- **Maternal:** Age at childbirth (<20 or >35 years), short birth spacing (<3 years), maternal anemia/malnutrition.
- **Socio-Demographic:** Low female literacy, poverty, lack of women's empowerment.
- **Environmental:** Poor WASH (Water, Sanitation, Hygiene) practices, indoor air pollution.
- **Health System:** Delayed care-seeking (3 Delays model: deciding to seek care, reaching facility, receiving quality care).

Targets & Goals

- **SDG 2030 (Goal 3.2):** Reduce U5MR to **≤ 25** per 1,000 live births; Reduce NMR to **≤ 12** per 1,000 live births.
- **National Health Policy (NHP) 2017:** Target to reduce U5MR to 23 by 2025 (IMR target of 28 already achieved).
- **India Newborn Action Plan (INAP):** Target single-digit NMR (<10) by 2030.

Management & Interventions (RMNCH+A Strategy)

- **Antenatal:** Janani Suraksha Yojana (JSY) for institutional delivery, Pradhan Mantri Surakshit Matritva Abhiyan (PMSMA) for high-risk pregnancy screening, Tetanus/Td immunization.
- **Intranatal:** LaQshya (quality of labor rooms), Dakshata, Navjaat Shishu Suraksha Karyakram (NSSK) for basic newborn resuscitation.
- **Neonatal:** Special Newborn Care Units (SNCUs), Kangaroo Mother Care (KMC), Home-Based Newborn Care (HBNC) via ASHAs.
- **Post-Neonatal & U5:**
    - *Immunization:* Mission Indradhanush (targeting >90% coverage), introduction of PCV and Rotavirus vaccines.
    - *Nutrition:* POSHAN Abhiyaan, MAA (Mothers' Absolute Affection) for exclusive breastfeeding.
    - *Illness Management:* IMNCI (Integrated Management of Neonatal and Childhood Illnesses), ORS + Zinc for diarrhea, Amoxicillin for pneumonia.
    - *Screening:* Rashtriya Bal Swasthya Karyakram (RBSK) for 4 Ds (Defects, Diseases, Deficiencies, Developmental delays).

Exam Summary

- **Current SRS Data:** IMR is 28/1000; U5MR is 32/1000; NMR is 20/1000.
- **SDG 2030 Targets:** U5MR ≤ 25/1000; NMR ≤ 12/1000.
- **Top Causes:** Prematurity (neonatal) and Pneumonia (post-neonatal/U5).
- **Core Concept:** NMR constitutes ~70% of IMR; hence, reducing IMR requires aggressive focus on neonatal care (SNCUs, HBNC, KMC).
- **Underlying Factor:** Malnutrition contributes to >50% of U5 mortality.

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117. Integrated management of childhood illness

Subject: Public Health / Social Pediatrics

Basics & Rationale

- **Definition:** Holistic WHO/UNICEF strategy integrating curative and preventive care for children <5 years.
- **Goal:** Reduce mortality/morbidity and promote healthy growth/development.
- **Indian Adaptation (IMNCI):** "N" added for Neonates. Integrates care of newborns (0–2 months), prioritizing the first week of life where maximum mortality occurs.
- **Core Philosophy:** Treats the *whole child* rather than a single disease (children often present with overlapping symptoms like malnutrition + pneumonia + diarrhea).

Three Core Pillars

- **Health Worker Skills:** Standardized case management guidelines for doctors/health workers.
- **Health Systems:** Ensuring availability of essential drugs, equipment, and efficient referral pathways.
- **Community Practices:** Educating families on home care, nutrition, and timely care-seeking behavior.

Target Age Groups

- **Young Infant:** 0 up to 2 months (Assess for bacterial infection, jaundice, diarrhea, feeding/weight issues).
- **Child:** 2 months up to 5 years (Assess for cough, diarrhea, fever, ear problems, malnutrition, anemia).

General Danger Signs (2 months – 5 years) *Must be checked in EVERY child before specific systemic assessment. Presence of any = Urgent Referral.*

- Inability to drink or breastfeed.
- Vomits everything.
- History of convulsions during current illness.
- Lethargic or unconscious. *(Note: For young infants <2 months, danger signs include stopped feeding well, convulsions, fast breathing ≥60/min, severe chest indrawing, fever ≥37.5°C, hypothermia <35.5°C, movement only when stimulated).*

The IMNCI Case Management Process Strict algorithmic sequence used by healthcare workers:

1. **Assess:** Check danger signs, main symptoms, nutritional/immunization status.
2. **Classify:** Use color-coded triage (Pink, Yellow, Green).
3. **Identify Treatment:** Based on classification.
4. **Treat:** Administer pre-referral drugs (if Pink) or specific outpatient drugs (if Yellow).
5. **Counsel:** Advise mother on feeding, fluids, and "when to return immediately".
6. **Follow-up:** Reassess at specified intervals (e.g., 2 days for pneumonia).

Color-Coded Triage System

- **Pink (Severe Illness):**
  - *Action:* Urgent facility referral/admission.
  - *Management:* Give first dose of appropriate pre-referral antibiotic/antimalarial, prevent hypoglycemia, keep warm.
- **Yellow (Moderate Illness):**
  - *Action:* Outpatient management.
  - *Management:* Specific oral drugs (e.g., oral amoxicillin for pneumonia, ORS/Zinc for diarrhea), advise mother, schedule follow-up.
- **Green (Mild Illness):**
  - *Action:* Home management.
  - *Management:* No specific medical intervention; counsel on home fluids, continued feeding, and danger signs to watch for.

Condition-Specific Highlights (WHO/IAP Guidelines)

- **Pneumonia:** Assessed primarily by respiratory rate (Fast breathing: ≥60/min in <2m; ≥50/min in 2-12m; ≥40/min in 1-5y) and lower chest indrawing.
- **Diarrhea:** Classified by dehydration status (Severe = Pink; Some = Yellow; No dehydration = Green). Plan A, B, or C applied accordingly. Zinc for 14 days is mandatory.
- **Fever:** Assessed for Malaria (blood smear/RDT in endemic areas), Measles, and Dengue.
- **Malnutrition:** Use MUAC (<11.5 cm = Severe Acute Malnutrition) and check for bilateral pitting edema.

Recent Updates & Variants

- **F-IMNCI (Facility-Based IMNCI):** Extension for inpatient management at First Referral Units (FRUs) to manage referred "Pink" cases (e.g., severe pneumonia, asphyxia, sepsis).
- **WHO PSBI Update (2015/Current):** If a young infant has Possible Serious Bacterial Infection (PSBI) and referral is *refused/impossible*, outpatient management is now authorized using simplified regimens (Oral Amoxicillin + IM Gentamicin for 2-7 days depending on clinical sub-classification).
- **Early Childhood Development (ECD):** New WHO modules integrate responsive caregiving and early learning counseling into standard IMNCI visits.

Exam Summary

- **IMNCI = WHO/UNICEF strategy** adapted in India to include 0-2 month neonates.
- **4 General Danger Signs:** Cannot drink, vomits everything, convulsions, lethargic/unconscious.
- **Color Codes:** Pink (Referral + pre-referral Rx), Yellow (OPD Rx), Green (Home care).
- **Process:** Assess → Classify → Identify Rx → Treat → Counsel → Follow-up.
- **Key Update:** Outpatient management of PSBI in young infants is permitted if hospital referral is not feasible.

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118. Conjugate vaccines in childhood immunization

Subject: Public Health / Social Pediatrics

Definition

- Covalent linkage of a poorly immunogenic bacterial capsular polysaccharide antigen to a highly immunogenic carrier protein.

Mechanism (Immunology)

- **Pure Polysaccharide (Unconjugated):** T-cell *independent* antigen; stimulates B-cells directly; IgM predominantly; no memory; poor immunogenicity in children <2 years due to immature marginal zone B-cells.
- **Conjugate Vaccine:** T-cell *dependent* antigen.
- Carrier protein is processed and presented via MHC-II to CD4+ T-helper cells.
- T-cells provide costimulatory signals (CD40-CD40L) and cytokines (IL-4, IL-21).
- **Result:** Germinal center formation, isotype class switching (IgM to IgG), affinity maturation, and generation of long-lived memory B-cells.

Common Carrier Proteins

- **CRM197:** Non-toxic mutant of diphtheria toxin (used in PCV13, PCV15, Menveo).
- **Tetanus Toxoid (TT):** Used in Hib (PRP-T), Typhoid Conjugate Vaccine (Vi-TT), MenAfriVac.
- **Diphtheria Toxoid (DT):** Used in Menactra.
- **OMPC:** *Neisseria meningitidis* outer membrane protein complex (used in PedvaxHIB).
- *Note:* Carrier proteins do *not* confer protective immunity against diphtheria or tetanus; primary DPT vaccination is still required.

Key Conjugate Vaccines & Schedules

- **Hib (Haemophilus influenzae type b):**
    - *Antigen:* Polyribosylribitol phosphate (PRP).
    - *IAP Schedule:* 6, 10, 14 weeks; booster at 16–18 months (usually given as pentavalent/hexavalent).
- **PCV (Pneumococcal Conjugate Vaccine):**

- *Types:* PCV10, PCV13, PCV15, PCV20.
- *National Immunization Schedule (NIS India):* 6, 14 weeks + booster at 9 months.
- *IAP 2023 Schedule:* 6, 10, 14 weeks + booster at 15–18 months.
- *AAP 2023 Update:* PCV15 or PCV20 now recommended over PCV13 for routine use.

- **TCV (Typhoid Conjugate Vaccine):**
  - *Antigen:* Vi-polysaccharide conjugated to TT (Vi-TT).
  - *IAP 2023 Schedule:* Single dose at 6–9 months (minimum age 6 months). No booster currently required.
- **MCV (Meningococcal Conjugate Vaccine):**
  - *Types:* Quadrivalent (MenACWY).
  - *Indications:* High-risk children (complement deficiency, asplenia), travelers, outbreak control.
  - *Schedule:* Depends on brand (typically starting at 9–12 months, 2 doses 3 months apart).

Advantages Over Pure Polysaccharides

- **Age:** Highly immunogenic in infants <2 years.
- **Memory:** Elicits robust anamestic (booster) response upon re-exposure.
- **Antibody Quality:** Higher avidity and predominantly IgG class.
- **Herd Immunity:** Eradicates nasopharyngeal carriage, preventing transmission to unvaccinated individuals.

Adverse Effects & Contraindications

- *Adverse Effects:* Mild local injection site reactions (pain, erythema), low-grade fever, irritability.
- *Contraindications:* Severe allergic reaction (anaphylaxis) to a previous dose or to the specific carrier protein.

Exam Summary

- Conjugation shifts immune response from T-cell independent (poor in infants) to T-cell dependent.
- Key triad of benefits: Works in <2 years, induces immunologic memory, reduces mucosal carriage (herd immunity).
- Major carrier proteins: CRM197, TT, DT, OMPC.
- Core examples: Hib, PCV, TCV, MCV.
- *Exam Trap:* Do not confuse TCV (conjugated, given at 6 months) with older Typbar (unconjugated polysaccharide, given >2 years, needs revaccination every 3 years).

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119. Pneumococcal vaccine in Nepal

Subject: Public Health / Social Pediatrics

Background & Burden in Nepal

- **Pathogen:** *Streptococcus pneumoniae* (leading cause of vaccine-preventable child mortality globally).
- **Disease Burden:** Historically responsible for a massive share of community-acquired pneumonia (CAP), meningitis, and bacteremia in Nepalese children.
- **Introduction:** Integrated into Nepal's National Immunization Programme (NIP) in January 2015 with GAVI support.
- **Goal:** Accelerate progress toward Sustainable Development Goal (SDG) 3 (reducing under-5 mortality).

Vaccine Types

- **PCV10 (Pneumococcal Conjugate Vaccine 10-valent):** Used in Nepal's NIP (Synflorix).
- **Serotypes covered (PCV10):** 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F.
- **PCV13 / PCV15:** Available in Nepal's private sector; adds broader coverage (e.g., serotypes 3, 6A, 19A).
- **PPSV23 (Pneumococcal Polysaccharide Vaccine):** Not in NIP; strictly for high-risk children >2 years old.

Nepal NIP Schedule (Crucial Exam Points)

- **Schedule Type:** "2 + 1" schedule (2 primary doses + 1 booster).
- **Timing:** 6 weeks, 10 weeks, and 9 months.
- **Dose:** 0.5 mL.
- **Route:** Intramuscular (IM).
- **Site:** Right anterolateral mid-thigh (Pentavalent is given on the left thigh to prevent mixing of local reactions).
- **Co-administration:** Given safely alongside Pentavalent, OPV, and Rotavirus (at 6/10 weeks) and Measles-Rubella (MR) vaccine (at 9 months).

Clinical Protection

- **Invasive Pneumococcal Disease (IPD):** Prevents bacteremia, meningitis, osteomyelitis, and septic arthritis.
- **Non-Invasive Disease:** Reduces severity and incidence of lobar pneumonia, acute otitis media (AOM), and sinusitis.
- **Herd Immunity:** Widespread infant vaccination in Nepal has reduced nasopharyngeal carriage, protecting unvaccinated older adults and siblings.

High-Risk Indications (Requires PCV13/15 + PPSV23)

- *Note: These children require customized schedules outside the standard NIP.*
- **Anatomic/Functional Asplenia:** Sickle cell disease, post-splenectomy.
- **Immunocompromised:** HIV/AIDS, Nephrotic syndrome, primary immunodeficiencies, oncology patients.

- **Anatomic Defects:** CSF leaks, cochlear implants.
- **Protocol:** Complete PCV series first ⇒give PPSV23 at $\geq$ 2 years of age (wait at least 8 weeks after last PCV dose).

Adverse Effects & Contraindications

- **Mild (Common):** Pain, erythema at injection site, low-grade fever, irritability.
- **Severe (Rare):** Anaphylaxis.
- **Contraindications:** Severe allergic reaction to a previous dose or to any diphtheria toxoid-containing vaccine (since PCV uses CRM197 or Protein D carrier proteins).

Impact & Surveillance in Nepal

- **Surveillance Sites:** Patan Hospital and Kanti Children's Hospital (part of invasive bacterial disease surveillance).
- **Outcomes:** Demonstrated dramatic >70% reduction in vaccine-serotype IPD and pediatric meningitis admissions since 2015.

Exam Summary: Must-Write Points

- **Nepal NIP Schedule:** 6 weeks, 10 weeks, and 9 months (2+1 schedule).
- **Vaccine Used:** PCV10 (0.5 ml, IM, Right anterolateral thigh).
- **Introduced:** 2015 via GAVI support to reduce under-5 mortality from pneumonia and meningitis.
- **High-Risk Exception:** Children >2 years with asplenia, HIV, or nephrotic syndrome need PPSV23 in addition to PCV.
- **Impact:** Significant drop in IPD and nasopharyngeal carriage (herd immunity) documented in major Nepalese pediatric centers.

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120. Typhoid conjugate vaccine campaign

Subject: Public Health / Social Pediatrics

Rationale for Campaign

- **High Burden:** Typhoid causes ~11–20 million cases and ~160,000 deaths annually (highest in South Asia and Sub-Saharan Africa).
- **AMR Threat:** Rapid emergence of Multi-Drug Resistant (MDR) and Extensively Drug-Resistant (XDR) *Salmonella typhi* (resistant to chloramphenicol, ampicillin, cotrimoxazole, fluoroquinolones, and ceftriaxone).
- **WASH limitations:** Water, Sanitation, and Hygiene (WASH) improvements are slow; vaccination provides immediate, equitable protection.

Vaccine Profile (TCV)

- **Composition:** Purified Vi capsular polysaccharide conjugated to a carrier protein (Tetanus Toxoid [Vi-TT] or CRM197 [Vi-CRM]).

- **Mechanism:** Carrier protein converts T-cell independent response (Vi-PS) to a **T-cell dependent response** (induces germinal center formation, mucosal immunity, and long-term memory).
- **Dose & Route:** 0.5 mL, Intramuscular (IM) injection.
- **Efficacy:** >80–85% protection; duration of protection expected to be long-term (ongoing studies show >4–5 years).

TCV vs. Older Vaccines (Must-Know)

- **Older Vi-Polysaccharide (Vi-PS):** Minimum age 2 years, short immunity (2–3 years), requires repeated boosters, no herd immunity.
- **Older Ty21a (Live Oral):** Minimum age 6 years, 3–4 doses required, poor compliance.
- **TCV Advantage:** Usable from **6 months of age**, single dose for primary immunity, long-lasting memory, induces herd immunity.

Current Guidelines

- **WHO Recommendations:**
  - Routine introduction for infants/children >6 months in endemic countries.
  - Catch-up campaigns targeting children up to 15 years to rapidly reduce disease burden.
- **IAP 2023/2024 Schedule:**
  - **Routine:** Single dose at **6 months** of age.
  - **Catch-up:** Recommended up to 18 years for unimmunized children.
  - **Boosters:** *Previously:* Revaccination recommended every 3 years for Vi-PS. *Now (TCV):* No routine booster currently recommended after a single TCV dose.

Campaign Strategy & Implementation

- **Target Population:** Typically 9 months to 15 years (covers highest incidence age groups).
- **Delivery Modes:** School-based vaccination (high coverage for >5 years) combined with community/outreach centers (for <5 years).
- **Co-administration:** Safe to give with Measles-Rubella (MR), OPV/IPV, Yellow Fever, and MenA vaccines without immune interference.
- **Adverse Events Following Immunization (AEFI):** Extremely safe. Most common are mild injection site pain, erythema, and transient fever. Severe allergic reactions are rare.

Real-World Impact

- **Pakistan (2019):** First country to introduce TCV into routine immunization via a massive campaign in Sindh province to combat an explosive XDR typhoid outbreak.
- **Navi Mumbai, India (2018):** Successful large-scale public sector campaign demonstrating feasibility, high coverage, and significant reduction in local incidence.
- **Prognosis:** Mass campaigns drastically reduce transmission, protect the unvaccinated via herd immunity, and slow the spread of XDR strains.

Exam Summary

- **TCV Composition:** Vi-polysaccharide conjugated to Tetanus Toxoid (Vi-TT).
- **Key Advantage:** Induces T-cell dependent memory; effective from 6 months of age (unlike Vi-PS which is >2 years).
- **IAP Schedule:** Single dose at 6 months; no boosters currently recommended.
- **Campaign Target:** 9 months to 15 years (WHO recommended) to rapidly achieve herd immunity.
- **Global Driver:** The rise of XDR Typhoid (ceftriaxone resistant) makes TCV a critical public health tool.

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121. Vaccine technology and advances

Subject: Public Health / Social Pediatrics

Basics

- **Definition:** Biological preparation providing active acquired immunity to a particular infectious disease.
- **Goal:** Induce robust, long-lasting immunological memory (B and T cell responses) without causing pathogenesis.
- **Conventional platforms:** Live-attenuated (e.g., MMR, OPV), Inactivated (e.g., wP, IPV), Toxoids (e.g., Diphtheria, Tetanus).

Advanced Vaccine Technologies

- **Conjugate Technology:**
    - *Mechanism:* Covalently links poorly immunogenic polysaccharides to a carrier protein (e.g., CRM197, Tetanus toxoid).
    - *Advantage:* Converts T-cell **independent** response to T-cell **dependent** response; highly effective in children <2 years.
    - *Examples:* PCV (PCV13, PCV15, PCV20), Hib, MenACWY.
- **Recombinant Protein Technology:**
    - *Mechanism:* Insertion of pathogen gene into a vector (yeast/bacteria) to produce pure antigenic proteins.
    - *Advantage:* Highly safe, no risk of reversion.
    - *Examples:* Hepatitis B (HBsAg produced in yeast), HPV (Virus-Like Particles - VLPs).
- **Nucleic Acid Technology (mRNA):**
    - *Mechanism:* Synthetic mRNA encoding pathogen antigen is encapsulated in Lipid Nanoparticles (LNPs) for cellular entry; host ribosomes translate it into antigen.
    - *Advantage:* Rapid development, easily scalable, induces both humoral and cellular immunity.
    - *Examples:* COVID-19 (BNT162b2, mRNA-1273).
- **Nucleic Acid Technology (DNA):**

- *Mechanism:* Plasmid DNA containing antigen gene injected into host; requires entry into the nucleus for transcription.
- *Advantage:* Highly temperature-stable (avoids ultra-cold chain).
- *Updates:* **ZyCoV-D** (India) is the world's first approved plasmid DNA vaccine for human use (COVID-19), delivered via needle-free applicator.

- **Viral Vector Technology:**
  - *Mechanism:* Uses a harmless, modified virus (e.g., Adenovirus) as a "Trojan horse" to deliver genetic code of the target pathogen.
  - *Advantage:* Strong immune response mimicking natural infection.
  - *Examples:* Ebola (rVSV-ZEBOV), COVID-19 (ChAdOx1 / Covishield).
- **Reverse Vaccinology:**
  - *Mechanism:* Uses whole-genome sequencing and bioinformatics to identify novel immunogenic antigens without needing to culture the pathogen.
  - *Classic Example:* Meningococcal B vaccine (MenB - Bexsero).
- **Structure-Based Vaccine Design:**
  - *Mechanism:* Freezing viral surface proteins in their highly immunogenic "pre-fusion" 3D conformation.
  - *Examples:* RSV maternal vaccine (RSVpreF), COVID-19 spike protein stabilization.

Novel Adjuvant Technologies

- *Purpose:* Enhance magnitude, breadth, and durability of immune response; dose-sparing.
- **AS01:** Liposome-based adjuvant containing TLR4 agonist (MPL) and saponin (QS-21). Used in Malaria (RTS,S) and Recombinant Zoster vaccines.
- **Matrix-M:** Saponin-based adjuvant. Used in the newer Malaria vaccine (R21/Matrix-M) and Novavax COVID-19 vaccine.
- **CpG 1018:** Synthetic DNA mimicking bacterial/viral genetic material (TLR9 agonist). Used in newer Hepatitis B vaccines (Heplisav-B).

Advances in Delivery Systems

- **Microarray Patches (MAPs):** Painless, thermostable microneedles dissolving in the skin (rich in antigen-presenting cells). Under trial for Measles-Rubella (MR).
- **Needle-free Jet Injectors:** Uses high-pressure fluid stream to penetrate skin (e.g., ZyCoV-D delivery).
- **Mucosal Vaccines:** Intranasal or oral delivery to induce local secretory IgA (sterilizing immunity). *Example:* iNNCOVACC (Intranasal COVID-19).

Recent Clinical Breakthroughs (WHO/IAP Updates)

- **Malaria:**
  - *RTS,S/AS01:* First WHO-recommended malaria vaccine (targets *P. falciparum* circumsporozoite protein).

  - *R21/Matrix-M (2023 Update):* Second WHO-approved malaria vaccine; highly efficacious, lower cost, easier to manufacture.

- **Respiratory Syncytial Virus (RSV):**
  - *Maternal Vaccine (Abrysvo):* Bivalent RSVpreF vaccine given at 32–36 weeks gestation for passive protection of infants up to 6 months.
- **Dengue:**
  - *TAK-003 (Qdenga):* Live-attenuated chimeric vaccine. *Advantage over older CYD-TDV (Dengvaxia):* Does not require pre-vaccination screening for serostatus.
- **Typhoid:**
  - *Typhoid Conjugate Vaccine (TCV):* Vi polysaccharide linked to tetanus toxoid. Approved from 6 months of age, long-lasting immunity (replaces older Vi-polysaccharide vaccine).

Exam Summary

- **Conjugate vaccines** (PCV, Hib) convert T-independent to T-dependent responses, crucial for infants <2 years.
- **mRNA vaccines** (LNP-encapsulated) and **DNA vaccines** (ZyCoV-D) represent the fastest scalable platforms of the modern era.
- **Reverse vaccinology** uses genomics to find antigens; classically yielded the **MenB** vaccine.
- **WHO latest approvals:** R21/Matrix-M for Malaria and maternal RSVpreF vaccine for infant protection.
- Novel adjuvants like **AS01** and **Matrix-M** are key to the success of modern recombinant vaccines (Malaria, Zoster).

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122. Polio eradication strategy

Subject: Public Health / Social Pediatrics

Current Status

- **Global:** Wild Poliovirus (WPV) Type 2 eradicated (2015), Type 3 eradicated (2019). WPV Type 1 remains endemic in 2 countries (Afghanistan, Pakistan).
- **India:** Last case on Jan 13, 2011 (Howrah, West Bengal). Officially certified polio-free by WHO on March 27, 2014.

Core Eradication Strategies (The 4 Pillars)

- **Routine Immunization:** Sustaining high coverage (>90%) with primary doses of OPV and IPV in the first year of life.
- **Supplementary Immunization Activities (SIAs):** National Immunization Days (NIDs / "Pulse Polio") and Sub-NIDs. Mass campaigns vaccinating all children <5 years, regardless of prior immunization status, to interrupt wild poliovirus transmission.
- **Surveillance:**

    - **AFP Surveillance:** Identifying Acute Flaccid Paralysis in any child <15 years, or paralytic illness in any age when polio is suspected.
    - **Stool Sampling:** 2 stool samples collected 24 hours apart, within 14 days of paralysis onset. Transported via strictly maintained *reverse cold chain* (2–8°C).
    - **Environmental Surveillance:** Routine testing of sewage/wastewater samples to detect silent transmission.
- **Mopping-Up Operations:** Targeted, intensive house-to-house OPV administration in high-risk areas/districts within 4 weeks of identifying a suspected case.

Polio Endgame Strategy (GPEI 2022–2026)

- **Objective:** Complete eradication of both WPV and Vaccine-Derived Poliovirus (VDPV).
- **The "Switch":** Global synchronized withdrawal of Sabin type 2 strain. Shift from tOPV (trivalent) to bOPV (bivalent: types 1 & 3) occurred on April 25, 2016.
- **IPV Introduction:** Introduced to maintain population immunity against Type 2 post-switch and prevent cVDPV2 outbreaks.
    - *India Schedule:* Fractional IPV (fIPV - 0.1 ml intradermal) at 6 weeks, 14 weeks, and 9 months.
- **nOPV2 (novel OPV type 2):** Genetically modified, highly stable type 2 OPV introduced under WHO Emergency Use Listing (EUL) specifically to contain cVDPV2 outbreaks without seeding new VDPV cases.

Challenges & Complications

- **VAPP (Vaccine-Associated Paralytic Polio):** Paralysis in a vaccine recipient or close contact (risk ~1 in 2.7 million doses); strictly an individual adverse event.
- **cVDPV (Circulating Vaccine-Derived Poliovirus):** Sabin strain mutates during prolonged replication in under-immunized populations, regaining neurovirulence and transmissibility. >90% of current global outbreaks are cVDPV2.
- **Socio-political factors:** Vaccine hesitancy, conflict zones, and inaccessible terrains in endemic regions.
- **iVDPV (Immunodeficiency-associated VDPV):** Prolonged viral shedding in patients with primary immunodeficiency disorders (B-cell defects).

Exam Summary

- **4 Pillars:** Routine immunization, SIAs (Pulse Polio), AFP/Environmental surveillance, Mopping-up.
- **AFP Criteria:** Any child <15 years with acute flaccid weakness; requires 2 stool samples 24h apart within 14 days.
- **The Switch:** tOPV to bOPV occurred in April 2016 to eliminate type 2 VAPP/cVDPV.
- **Current Update:** nOPV2 is the primary tool for managing cVDPV2 outbreaks; fractional IPV is used in routine immunization to maintain type 2 immunity.
- **India Status:** Certified polio-free in March 2014; current focus is on maintaining high immunity and stringent surveillance to prevent importation.

123. Role of NGOs in child health

Subject: Public Health / Social Pediatrics

Basics

- **Definition:** Non-profit, voluntary citizens' groups organized on a local, national, or international level.
- **Primary Objective:** To complement and supplement government efforts in healthcare, welfare, and child rights.
- **Operational Scope:** Grassroots community action, national policy advocacy, and international disaster relief.

Core Roles

- **Service Delivery:** Filling gaps in public health infrastructure (e.g., mobile clinics, rural health camps).
- **Advocacy & Policy:** Lobbying for child rights, drafting legislation (e.g., IMS Act, POCSO Act).
- **Capacity Building:** Training frontline workers (ASHAs, Anganwadi workers) and community volunteers.
- **Research & Innovation:** Conducting pilot projects (e.g., community-based SAM management) later scaled up by governments.
- **Awareness & IEC:** Information, Education, and Communication campaigns for hygiene, immunization, and nutrition.

Domain-Specific Contributions

- **Nutrition:**
    - Promoting exclusive breastfeeding and complementary feeding.
    - Implementation of Mid-Day Meal schemes.
    - Community-level screening and management of Severe Acute Malnutrition (SAM).
- **Immunization & Disease Control:**
    - Mobilizing communities to reduce vaccine hesitancy.
    - Organizing outreach camps in hard-to-reach areas.
- **Child Rights & Protection:**
    - Rescuing and rehabilitating child laborers and victims of trafficking.
    - Providing legal and psychological support for abused children.
- **Disability & Rehabilitation:**
    - Early intervention centers for developmental delays.
    - Special education and vocational training for children with special needs.
- **Emergencies & Disaster Relief:**

- Rapid deployment of medical teams, nutritional kits, and trauma counseling during natural disasters or conflicts.

Major NGOs & Classic Associations (Exam High-Yield)

- **BPNI (Breastfeeding Promotion Network of India):** Crucial in enacting/monitoring the IMS Act (Infant Milk Substitutes Act); promotes baby-friendly hospitals.
- **Rotary International:** Historic role in Global Polio Eradication Initiative (Pulse Polio).
- **CRY (Child Rights and You):** Advocacy for education, child protection, and eradicating child labor.
- **Save the Children:** Maternal-child health, emergency relief, and neonatal survival programs.
- **MSF (Médecins Sans Frontières):** Emergency medical care, vaccination campaigns in conflict zones.
- **Akshaya Patra Foundation:** Operates the world's largest NGO-run Mid-Day Meal program (school nutrition).
- **Bachpan Bachao Andolan:** Eradication of child labor and rescue operations.

Strengths & Advantages

- **Grassroots Reach:** Deep community trust and cultural acceptability.
- **Flexibility:** Quick decision-making without bureaucratic delays.
- **Innovation:** Ability to test novel, cost-effective health delivery models.
- **Vulnerable Focus:** Targeted reach to marginalized, tribal, and urban slum populations.

Challenges & Limitations

- **Funding Dependency:** Reliance on donor grants leads to financial instability.
- **Duplication of Efforts:** Poor coordination with state health departments can lead to overlapping services.
- **Geographical Skew:** Urban or easily accessible areas often have NGO clustering, leaving remote areas unserved.
- **Sustainability:** Projects often collapse once external funding ceases.

Exam Summary

- NGOs act as vital catalysts supplementing government efforts via service delivery, advocacy, and capacity building.
- **Must-know examples:** BPNI (Breastfeeding/IMS Act), Rotary (Polio eradication), Akshaya Patra (Mid-day meals).
- Core strengths include grassroots penetration, flexibility, and innovative pilot projects.
- Major focus areas span the entire pediatric spectrum: SAM management, immunization outreach, child protection (POCSO/labor), and disaster relief.

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124. Environmental health hazards affecting children

Subject: Public Health / Social Pediatrics

Pediatric Vulnerability

- **Higher Exposure:** Greater minute ventilation (breathe faster), higher metabolic rate, larger surface-area-to-mass ratio.
- **Behavioral Factors:** Hand-to-mouth activity, crawling (closer to ground-settled toxicants), pica.
- **Physiologic Immaturity:** Immature blood-brain barrier (BBB), developing organ systems, immature hepatic/renal detoxification pathways.
- **Longer Life Expectancy:** More time to develop diseases with long latency periods (e.g., cancers, COPD).

Major Hazards & Clinical Impact

- **Indoor Air Pollution:**
    - *Source:* Biomass fuels (wood, dung), secondhand tobacco smoke (SHS), volatile organic compounds (VOCs).
    - *Impact:* Acute lower respiratory infections (ALRI/pneumonia), asthma exacerbations, sudden infant death syndrome (SIDS), otitis media.
- **Outdoor Air Pollution:**
    - *Source:* Vehicular exhaust, industrial emissions (PM2.5, PM10, ozone, NO2, SO2).
    - *Impact:* Decreased lung growth, low birth weight (LBW), preterm birth, childhood asthma.
    - *Update:* **WHO 2021 Air Quality Guidelines** drastically lowered acceptable limits (e.g., PM2.5 annual mean reduced from 10 to 5 $\mu g/m^3$).
- **Heavy Metals:**
    - *Lead (Pb):* Paint, contaminated soil, spices, traditional medicines. Causes irreversible neurocognitive decline, ADHD, microcytic anemia, abdominal colic.
    - *Mercury (Hg):* Methylmercury via contaminated fish. Causes neurodevelopmental delay, visual/hearing impairment (Minamata disease).
    - *Arsenic:* Groundwater contamination. Causes hyperkeratosis, melanosis, peripheral neuropathy, future malignancies.
- **Chemicals & Toxins:**
    - *Pesticides (Organophosphates):* Inhibit acetylcholinesterase. Causes neurodevelopmental delays, acute cholinergic crisis (SLUDGE syndrome).
    - *Endocrine Disrupting Chemicals (EDCs):* Bisphenol A (BPA), phthalates in plastics. Linked to precocious puberty, cryptorchidism, hypospadias, childhood obesity.
- **Water, Sanitation, & Hygiene (WASH):**
    - *Source:* Fecal-contaminated drinking water, poor sanitation.
    - *Impact:* Recurrent diarrheal diseases, environmental enteric dysfunction (EED), severe acute malnutrition (SAM), stunting.

- **Climate Change (AAP 2024 Focus):**
    - *Impacts:* Increased vector-borne diseases (dengue, malaria), heat-related illness, eco-anxiety, food/water insecurity leading to malnutrition.

Diagnosis & Screening

- **History:** Detailed environmental history (CH2OPD2 mnemonic: Community, Home, Hobbies, Occupation, Personal habits, Diet, Drugs).
- **Lead Screening:**
    - *Update (CDC 2021):* Blood lead reference value (BLRV) lowered to **3.5 µg/dL** (Previously 5 µg/dL).
    - *Labs:* Venous blood lead level (BLL), peripheral smear (basophilic stippling), X-ray long bones (lead lines at metaphysis).
- **Biomarkers:** Blood/urine heavy metal panels, RBC cholinesterase levels (pesticide exposure).
- **Growth & Development:** Serial anthropometry (stunting from EED), developmental screening (Denver II/Ages & Stages) for neurotoxicants.

Management

- **Source Eradication:** Primary step (e.g., remove lead paint, switch to clean cooking fuels).
- **Medical Therapy:**
    - *Lead Toxicity:* Chelation (Succimer/DMSA orally; EDTA/BAL IV for severe/encephalopathy) indicated if BLL ≥ 45 µg/dL.
    - *Pesticide Toxicity:* Atropine, Pralidoxime (PAM) for organophosphates.
    - *Asthma/ALRI:* Standard GINA/WHO management protocols.
- **Nutritional Support:** Iron, calcium, and vitamin C supplementation (decreases intestinal absorption of lead).

Prevention (Public Health Strategies)

- **Policy & Legislation:** Banning lead in petrol/paint, enforcing industrial emission standards, regulating EDCs in baby products.
- **WASH Initiatives:** Safe drinking water provision, community-led total sanitation (CLTS) to end open defecation.
- **Clean Energy:** Promoting LPG/electric cooking (e.g., PMUY scheme in India) to replace biomass.
- **Anticipatory Guidance:** Pediatricians must counsel parents on smoking cessation, safe chemical storage, and washing fruits/vegetables.

Exam Summary

- Children are uniquely vulnerable due to higher minute ventilation, hand-to-mouth behavior, and immature BBB.
- **WHO 2021 Update:** PM2.5 limits halved; outdoor air pollution is a major driver of pediatric asthma and poor lung growth.

- **CDC Update:** Blood Lead Reference Value is now 3.5 µg/dL. No safe level of lead exists; causes irreversible cognitive deficits.
- Biomass fuel use is the leading cause of indoor air pollution, strongly linked to recurrent ALRI (pneumonia) in developing nations.
- Management always begins with environmental source removal, followed by specific medical therapy (e.g., chelation for lead >45 µg/dL) and nutritional optimization.

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125. Child abuse in Nepal

Subject: Public Health / Social Pediatrics

Definition & Types

- **Definition:** Any intentional physical, sexual, or psychological harm, neglect, or exploitation of a child (<18 years) by a caregiver or person in power.
- **Core Types:** Physical abuse, Sexual abuse, Emotional/Psychological abuse, Neglect.
- **Nepal-specific additions:** Severe exploitation via child labor, cross-border trafficking, and child marriage.

Nepal-Specific Epidemiology & Drivers

- **Child Labor:** High prevalence in brick kilns, carpet factories, agriculture, and as domestic workers (Kamalari system, though legally abolished, remnants exist).
- **Trafficking:** High rates of cross-border trafficking to India for commercial sexual exploitation and forced labor.
- **Child Marriage:** Among the highest rates in Asia; driven by poverty, dowry, and traditional norms.
- **Corporal Punishment:** Culturally normalized and widely practiced in homes and schools.
- **Key Drivers:** Extreme poverty, porous borders, patriarchal social structures, illiteracy, and post-disaster vulnerability (e.g., 2015 earthquake).

Clinical Features (Red Flags)

- **History:** Changing narrative, delayed presentation, injury mechanism incompatible with child's developmental age.
- **Physical Abuse:** Patterned bruises (belt/cord marks), glove-and-stocking burns, cigarette burns, frenulum tears in infants.
- **Abusive Head Trauma (Shaken Baby Syndrome):** Triad of subdural hematoma, retinal hemorrhages, and hypoxic-ischemic encephalopathy.
- **Sexual Abuse:** Genital/anal trauma, unexplained STIs, prepubertal pregnancy, sudden onset enuresis/encopresis, hypersexualized behavior.
- **Neglect:** Non-organic Failure to Thrive (FTT), Severe Acute Malnutrition (SAM), poor hygiene, medical neglect (missed vaccines).

Diagnosis & Evaluation

- **Examination:** Complete head-to-toe exam; document all injuries with body maps and photographs (with consent).
- **Imaging:**
    - **Skeletal Survey:** Mandatory in suspected physical abuse in children <2 years (look for classic metaphyseal lesions/corner fractures, posterior rib fractures).
    - **NCCT Head:** For infants with altered sensorium, enlarging head circumference, or suspected abusive head trauma.
- **Laboratory:**
    - Coagulation profile (PT, aPTT, vWF) to rule out bleeding disorders in bruised children.
    - STI screening (HIV, Syphilis, Gonorrhea, Chlamydia) and forensic swabs in sexual abuse.

Management Protocol

- **Medical Stabilization:** Resuscitate, treat fractures/injuries, nutritional rehabilitation.
- **Sexual Abuse Specifics:** Administer Post-Exposure Prophylaxis (PEP) for HIV, empirical STI treatment, and emergency contraception (if post-menarchal and within 72 hrs).
- **Psychosocial Support:** Trauma-informed cognitive behavioral therapy (TF-CBT), psychiatric evaluation.
- **Protection & Shelter:** Do not discharge the child to the abuser. Coordinate with medical social workers for safe placement.

Reporting & Legal Framework (Nepal)

- **Mandatory Reporting:** Healthcare workers are legally bound to report suspected abuse.
- **Agencies to Notify:**
    - Women, Children, and Senior Citizen Service Directorate (Nepal Police) - Dial **104**.
    - Child Helpline (run by CWIN) - Dial **1098**.
    - National Child Rights Council (NCRC).
- **Key Legislation:**
    - *The Constitution of Nepal (Article 39):* Guarantees fundamental child rights.
    - *Act Relating to Children, 2018 (2075 BS):* Criminalizes corporal punishment and defines child protection mechanisms.
    - *National Penal Code (Muluki Aparadh Samhita, 2017):* Strict sentencing for rape, child marriage, and human trafficking.

Prevention Strategies

- **Primary:** Poverty alleviation, female education, community awareness campaigns against child marriage/labor.
- **Secondary:** Training pediatricians, teachers, and frontline health workers (FCHVs) to identify early warning signs.

- **Tertiary:** Rehabilitation and reintegration programs by NGOs (e.g., Maiti Nepal, CWIN) to prevent re-trafficking or repeat abuse.

Exam Summary: Must-Write Points

- **Nepal Context:** Always mention child labor (brick kilns), cross-border trafficking, and child marriage as dominant forms of abuse.
- **Red Flags:** History inconsistent with developmental age, classic metaphyseal lesions, retinal hemorrhages.
- **First Step:** Medical stabilization followed immediately by ensuring child safety (do not discharge to abuser).
- **Nepal Legal/Action:** Mention Child Helpline (1098), Police (104), and the Act Relating to Children (2018).

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126. Adolescent health services

Subject: Public Health / Social Pediatrics

Basics & Rationale

- **Definition:** Adolescence spans 10–19 years (WHO); accounts for ~21% of the Indian population.
- **Rationale:** Transitional phase marked by rapid physical, cognitive, and psychosocial changes.
- **"Triple Dividend":** Investing in adolescent health yields benefits now (healthy teens), into adulthood (healthy adults), and for the next generation (healthy offspring).
- **Morbidity/Mortality Profile:** Primarily preventable (road traffic accidents, suicide, interpersonal violence, maternal mortality, and substance abuse).

National Framework: Rashtriya Kishor Swasthya Karyakram (RKSK)

- **Launch:** 2014 (Ministry of Health and Family Welfare, India).
- **Paradigm Shift:** Moved from clinic-based to community-based; disease-centric to wellness-centric.
- **Target Population:** Universal (10–14 and 15–19 years; boys/girls; married/unmarried; rural/urban/school dropouts).
- **Six Strategic Priorities (The 6 Pillars):**
    1. Nutrition (malnutrition, anemia, obesity).
    2. Sexual and Reproductive Health (SRH).
    3. Non-Communicable Diseases (NCDs).
    4. Substance Misuse.
    5. Injuries and Violence.
    6. Mental Health.

Service Delivery Mechanisms

- **Community-based:** Peer Educators (*Saathiya* program) and quarterly Adolescent Health Days (AHDs).
- **School-based:** School Health and Wellness Programme (SHWP) under Ayushman Bharat.
- **Facility-based:** Adolescent Friendly Health Clinics (AFHCs) at PHC, CHC, and District Hospital levels.

Adolescent Friendly Health Clinics (AFHCs) - WHO Criteria

- **Accessible:** Convenient working hours, free/affordable, easy to reach, no stigma.
- **Acceptable:** Guarantees privacy and confidentiality; non-judgmental staff.
- **Equitable:** Services for all (marginalized, disabled, varying sexual orientations).
- **Appropriate:** Comprehensive package (curative, preventive, promotive, counseling).
- **Effective:** Evidence-based protocols, trained healthcare providers.

Clinical Assessment Approach

- **Golden Rule:** Always interview the adolescent alone for a portion of the visit to ensure confidentiality.
- **Psychosocial Screening (HEEADSSS Tool):**
    - **H**ome environment.
    - **E**ducation and Employment.
    - **E**ating (body image, eating disorders).
    - **A**ctivities (peer groups, screen time, hobbies).
    - **D**rugs (tobacco, alcohol, illicit substances).
    - **S**exuality (orientation, safe sex, contraception).
    - **S**uicide/Depression (mood, self-harm).
    - **S**afety (driving, abuse, violence).

Key Preventive Interventions (India)

- **WIFS (Weekly Iron and Folic Acid Supplementation):** 100 mg elemental iron + 500 µg folic acid weekly to prevent anemia.
- **National Deworming Day:** Tab Albendazole 400 mg biannually.
- **Menstrual Hygiene Scheme (MHS):** Provision of subsidized sanitary napkins (Freedays) to rural adolescent girls.
- **Immunization (IAP 2024 Updates):**
    - **Tdap:** Recommended at 10–12 years (replaces TT/Td).
    - **HPV:** *IAP 2024:* 2 doses for 9–14 years (0, 6 months); 3 doses for ≥15 years (0, 1-2, 6 months). *WHO 2022 Update:* 1 or 2 doses for 9–14 years is now considered highly efficacious.
    - **MenACWY:** Recommended for high-risk teens or those traveling for higher education/hostels.

Challenges & Barriers

- **Legal/Policy:** Ambiguity regarding the age of consent for medical procedures and contraception (POCSO Act implications for sexually active minors).
- **Social:** Stigma surrounding SRH and mental health seeking.
- **Systemic:** High attrition rate of trained counselors; lack of dedicated space for AFHCs in crowded public hospitals.

Exam Summary

- **Must-write keywords:** "Triple Dividend", RKSK (2014), AFHCs, HEEADSSS assessment.
- **RKSK 6 Pillars:** Nutrition, SRH, NCDs, Substance abuse, Violence, Mental health.
- **WHO AFHC criteria:** Accessible, Acceptable, Equitable, Appropriate, Effective.
- **Core programs:** WIFS (100mg Fe + 500µg FA weekly), Menstrual Hygiene Scheme, Peer Educator (*Saathiya*).
- **Confidentiality:** The cornerstone of adolescent medicine; must be explicitly stated to the patient unless there is risk of harm to self or others.

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127. Perinatal audit

Subject: Public Health / Social Pediatrics

Definition

- Systematic, critical, and multidisciplinary analysis of perinatal deaths (stillbirths and early neonatal deaths <7 days) and morbidities.
- Aimed at evaluating the quality of perinatal care, identifying modifiable factors, and implementing changes to improve outcomes.

Core Principles

- **Non-punitive:** Strict "No blame, no shame" culture.
- **Confidentiality:** Anonymized data presentation to protect staff and patient identities.
- **Action-oriented:** Focuses on systemic improvements rather than individual faults.
- **Multidisciplinary:** Involves obstetricians, pediatricians, nurses, midwives, and administrators.

Guidelines & Frameworks

- **WHO Update:** Shifted from traditional mortality reviews to **MPDSR** (Maternal and Perinatal Death Surveillance and Response) to emphasize the *action/response* component.
- **Classifications used in audit:**
    - **ICD-PM (WHO):** Applies ICD-10 to perinatal deaths; links timing of death, fetal/neonatal cause, and maternal condition.
    - **Wigglesworth Classification:** Groups deaths by pathophysiology (e.g., lethal malformations, unexplained stillbirths, asphyxia, prematurity).

The Audit Cycle (Steps)

- **1. Case Identification:** Notification of all perinatal deaths (facility or community-based).
- **2. Data Collection:** Gathering case records, partographs, nursing notes, and conducting verbal autopsies (for community deaths).
- **3. Case Analysis:** Multidisciplinary committee reviews the timeline to identify the exact cause of death and substandard care.
- **4. Identifying Delays:** Utilizing the **"Three Delays Model"**:
    - *Delay 1:* Deciding to seek care (family/community level).
    - *Delay 2:* Reaching the healthcare facility (transport/roads).
    - *Delay 3:* Receiving adequate care at the facility (staff skills, equipment availability, triage).
- **5. Recommendations:** Drafting specific, measurable, achievable, relevant, and time-bound (SMART) action plans.
- **6. Implementation:** Executing the recommended changes (e.g., staff training, equipment procurement).
- **7. Re-audit:** Evaluating the impact of changes after a set period (**"Closing the loop"**).

Types of Perinatal Audit

- **Facility-Based Perinatal Death Review (FBPDR):** Conducted within the hospital; focuses heavily on "Delay 3".
- **Community-Based Review:** Utilizes Verbal Autopsy (VA) via ASHAs/health workers; focuses heavily on "Delay 1 and 2".
- **Near-Miss Audit:** Reviewing cases of severe perinatal morbidity where the infant survived (often yields better systemic insights as the family/staff are less defensive).

Key Prerequisites

- Administrative support and dedicated time for meetings.
- Accurate and complete medical record-keeping (partographs are crucial).
- Standardized abstraction forms (e.g., Government of India FBPDR formats).
- Trained nodal officer to facilitate the review.

Common Modifiable Factors Identified

- **Maternal:** Unrecognized severe preeclampsia, delayed referral for obstructed labor.
- **Fetal/Neonatal:** Failure to monitor fetal heart rate (FHR), delayed/inadequate neonatal resuscitation (Golden Minute non-compliance), hypothermia during transport.
- **Systemic:** Non-availability of blood products, CPAP, or trained personnel on night shifts.

Challenges & Pitfalls

- **Fear of litigation/punishment:** Leads to defensive documentation or underreporting.
- **Incomplete data:** Missing partographs or illegible notes make analysis impossible.

- **Failure to close the loop:** Conducting meetings without implementing or funding the recommended changes.

Exam Summary

- **Must-write buzzwords:** "No blame, no shame", "Closing the loop", WHO MPDSR framework, "Three Delays model".
- **Core objective:** Identify modifiable factors/substandard care, not to assign individual guilt.
- **Audit cycle:** Identify → Collect → Analyze → Recommend → Implement → Re-audit.
- **Classification:** Mention ICD-PM (WHO) as the standard for classifying perinatal deaths linking maternal and fetal factors.

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128. Natural disaster coping strategies for children

Subject: Public Health / Social Pediatrics

Basics

- **Definition:** Strategies to mitigate psychological trauma, physical displacement, and routine disruption in children following natural disasters (earthquakes, floods, hurricanes).
- **Vulnerability:** Children are disproportionately affected due to limited cognitive processing, physical vulnerability, and absolute dependence on caregivers.
- **Core Principle:** A child's coping ability directly mirrors the caregiver's coping ability (**Co-regulation**).

Age-Specific Stress Responses

- **Infants/Toddlers:** Increased crying, clinging, altered sleep/feeding, heightened startle response.
- **Preschoolers: Regression** (enuresis, thumb-sucking, loss of milestones), separation anxiety, trauma-themed play, fear of darkness.
- **School-Age (6–12 yrs):** Somatic complaints (headaches, abdominal pain), irritability, aggressive behavior, poor concentration, school refusal.
- **Adolescents:** Withdrawal, risk-taking behaviors (substance abuse), sleep/appetite changes, depression, somatic symptoms.

Immediate Coping & Management (0–4 Weeks)

- **Psychological First Aid (PFA):** WHO framework focusing on pragmatic care—*Listen* (without pressing for details), *Protect* (ensure physical safety), *Connect* (reunite with family).
- **Parental/Caregiver Strategies:**
    - **"Oxygen Mask" Principle:** Caregivers must manage their own acute stress to effectively support the child.
    - **Communication:** Provide honest, age-appropriate information; avoid false promises; validate feelings ("It is okay to be scared").
    - **Media Restriction:** Strictly limit exposure to television/social media coverage of the disaster to prevent secondary trauma (AAP recommendation).

    - **Re-establish Routine:** Rapidly restore consistent sleep, meal, and play schedules to provide a sense of predictability and safety.

- **Community Interventions:** Establish child-friendly spaces in shelters; ensure rapid reunification of separated families.

Intermediate to Long-Term Coping (>1 Month)

- **School Return:** Prioritize early return to school to restore peer networks and daily structure.
- **Trauma-Focused Cognitive Behavioral Therapy (TF-CBT):** First-line evidence-based therapy for children with persistent distress or PTSD.
- **Empowerment:** Involve children in age-appropriate recovery efforts (e.g., sorting donations) to build resilience and self-efficacy.

Role of the Pediatrician

- **Screening:** Actively screen for Acute Stress Disorder (ASD) within the first month and PTSD after 1 month.
- **Trauma-Informed Care:** Avoid re-traumatization during physical exams; ask "What happened to you?" instead of "What is wrong with you?".
- **Advocacy:** Coordinate with schools, child protective services, and mental health professionals.

Red Flags (Indications for Psychiatric Referral)

- Symptoms persisting >1 month with functional impairment (PTSD).
- Suicidal or homicidal ideation.
- Severe regression or complete mutism.
- Onset of substance abuse in adolescents.
- Caregiver inability to cope (severe depression/psychosis).

Preparedness & Prevention (AAP Guidelines)

- **Family Disaster Plan:** Pre-assign roles, establish meeting places, and conduct emergency drills.
- **Emergency Kits:** Include child-specific items (comfort objects, formula, pediatric medications, diapers).
- **Anticipatory Guidance:** Pediatricians should discuss disaster readiness during routine well-child visits in high-risk geographic areas.

Exam Summary

- **Must-write concepts:** Psychological First Aid (PFA), Co-regulation (caregiver stability dictates child stability), and Media Restriction.
- **Classic presentation:** Regression in preschoolers (bedwetting); Somatic complaints in school-age children.
- **First-line therapy:** Trauma-Focused CBT for persistent symptoms (>1 month).

- **Core intervention:** Rapid re-establishment of daily routines and early return to school.

Developmental / Behavioral Pediatrics

129. Juvenile delinquency

Subject: Developmental / Behavioral Pediatrics

Definition

- **Legal term:** Antisocial, illegal, or criminal behavior committed by a minor.
- **Age criteria:** Varies by jurisdiction (In India, under the *Juvenile Justice [Care and Protection of Children] Act, 2015*, a juvenile is <18 years).
- **Medical correlate:** Closely maps to **Conduct Disorder (CD)** or **Oppositional Defiant Disorder (ODD)** in DSM-5.

Etiology (Biopsychosocial Model)

- **Biological:** Male gender, genetic predisposition, maternal smoking/substance use during pregnancy, low IQ.
- **Psychological:** Difficult temperament, poor executive function, high impulsivity, lack of empathy.
- **Family:** Harsh/inconsistent parenting, parental criminality or substance abuse, domestic violence, neglect/abuse, broken homes.
- **Sociocultural:** Poverty, delinquent peer association (gangs), neighborhood violence, exposure to media violence, school failure.

Neurobiology

- **Prefrontal cortex:** Underdeveloped or underactive (impaired impulse control and decision-making).
- **Amygdala:** Reduced volume/reactivity (impaired fear conditioning and lack of empathy).
- **Autonomic nervous system:** Lower resting heart rate and skin conductance (associated with sensation-seeking and fearlessness).
- **Neurotransmitters:** Altered serotonin (aggression) and dopamine (reward-seeking) pathways.

Clinical Features (Red Flags)

- **Aggression:** Bullying, physical fights, weapon use, cruelty to people or animals.
- **Property destruction:** Deliberate fire-setting, vandalism.
- **Deceitfulness/Theft:** Shoplifting, breaking and entering, "conning" others.
- **Rule violations:** Early-onset truancy (before age 13), running away from home, breaking curfews.
- **Comorbidities:** Substance abuse, early sexual activity, reckless driving.

Diagnosis

- **Clinical evaluation:** Detailed history from child, parents, and teachers (using standardized questionnaires like Child Behavior Checklist - CBCL).
- **Psychiatric criteria:** Assess for DSM-5 Conduct Disorder (requires ≥3 criteria in the past 12 months, with ≥1 in the past 6 months).
- **Comorbidity screening:** Must screen for ADHD (highly co-occurrent), depression, anxiety, and Specific Learning Disabilities (SLD).
- **Psychological testing:** IQ assessment and psychoeducational evaluation.

Management

- **Psychosocial (First-Line):**
    - **Multisystemic Therapy (MST):** Gold standard; intensive family- and community-based treatment.
    - **Parent Management Training (PMT):** Teaches parents positive reinforcement and consistent, non-punitive discipline.
    - **Cognitive Behavioral Therapy (CBT):** Focuses on anger management, problem-solving, and moral reasoning.
- **Pharmacological (Adjunctive only):**
    - *No FDA-approved drug specifically for CD/delinquency.*
    - **ADHD co-morbidity:** Stimulants (Methylphenidate) or Atomoxetine (reduces impulsive aggression).
    - **Severe, refractory aggression:** Atypical antipsychotics (Risperidone, Aripiprazole) – *use cautiously, low dose*.
    - **Mood lability:** Mood stabilizers (Divalproex, Lithium) or SSRIs for comorbid depression.
- **Legal/Rehabilitative (India - JJ Act 2015):**
    - Handled by **Juvenile Justice Board (JJB)**.
    - Focus is strictly on *rehabilitation*, not retribution.
    - Placement in Observation Homes or Special Homes with vocational training and counseling.
    - *Update (JJ Act 2015):* Juveniles aged 16–18 committing "heinous crimes" can be tried as adults after a preliminary assessment by the JJB.

Complications

- Progression to Antisocial Personality Disorder (ASPD) in adulthood.
- Substance Use Disorders (SUD).
- Incarceration and criminal record.
- High rates of traumatic injury, homicide, and suicide.

Prognosis

- **Childhood-onset type (<10 years):** Worse prognosis, higher risk of violent behavior and adult ASPD.

- **Adolescent-onset type (≥10 years):** Better prognosis, often limited to adolescent years (maturity gap), higher chance of remission.
- **Callous-unemotional (CU) traits:** Presence indicates a much poorer response to treatment and higher risk of psychopathy.

Prevention

- **Primary:** Nurse-Family Partnership (prenatal/infancy home visits), preschool enrichment programs, parenting education.
- **Secondary:** Early identification and aggressive treatment of ADHD and ODD; school-based bullying prevention and social skills programs.

Exam Summary

- **Definition:** Legal term for minor committing a crime; medical correlate is Conduct Disorder (CD).
- **Key Etiology:** Biopsychosocial mix (ADHD, inconsistent parenting, delinquent peers).
- **Classic Tetrad (CD):** Aggression to people/animals, destruction of property, deceitfulness/theft, serious rule violations.
- **Gold Standard Therapy:** Multisystemic Therapy (MST) + Parent Management Training (PMT).
- **Prognostic Trap:** Childhood-onset (<10 yrs) has a significantly worse prognosis (progression to ASPD) than adolescent-onset.

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130. Neurodevelopmental disorders detection

Subject: Developmental / Behavioral Pediatrics

Definition

- Group of conditions with onset in the early developmental period (DSM-5)
- Characterized by developmental deficits producing impairments of personal, social, academic, or occupational functioning
- Includes: Intellectual Disability (ID), Global Developmental Delay (GDD), Autism Spectrum Disorder (ASD), ADHD, Specific Learning Disorders, Motor Disorders

Etiology & Risk Factors

- **Prenatal:** Genetic syndromes (Down, Fragile X), congenital anomalies, TORCH infections, teratogens (Fetal Alcohol Spectrum), maternal morbidities
- **Perinatal:** Prematurity (<32 weeks), extremely low birth weight, Hypoxic-Ischemic Encephalopathy (HIE), severe hyperbilirubinemia, hypoglycemia
- **Postnatal:** CNS infections (meningitis/encephalitis), traumatic brain injury, lead toxicity, severe psychosocial deprivation

Detection Strategy: Surveillance vs. Screening

- **Developmental Surveillance:** Continuous, longitudinal process performed at *every* preventive care visit

  - *AAP 5 Components:* Eliciting parental concerns, maintaining developmental history, making accurate observations, identifying risk/protective factors, documenting findings

- **Developmental Screening:** Administration of standardized, validated tools at specific intervals or when surveillance indicates risk
  - *AAP General Screening Ages:* 9, 18, and 30 months
  - *AAP ASD-Specific Screening Ages:* 18 and 24 months
  - *Prematurity correction:* Correct for gestational age until 24 months chronologic age

Screening Tools

- **General/Broad-Band:**
  - Ages and Stages Questionnaire (ASQ-3)
  - Parents' Evaluation of Developmental Status (PEDS)
  - *IAP Recommendation (India):* Trivandrum Developmental Screening Chart (TDSC), DDST-II (Denver)
- **Autism-Specific:**
  - Modified Checklist for Autism in Toddlers, Revised with Follow-Up (M-CHAT-R/F)
- **Motor-Specific:**
  - Alberta Infant Motor Scale (AIMS)

Absolute Red Flags (Indications for Immediate Referral)

- **Any age:** Loss of previously acquired language or social skills
- **By 6 months:** Absent smiles/joyful expressions, marked hypotonia/hypertonia, extreme asymmetry
- **By 9 months:** Absent back-and-forth sharing of sounds, smiles, or facial expressions
- **By 12 months:** No babbling, no pointing/reaching/waving
- **By 16 months:** No single meaningful words
- **By 24 months:** No two-word spontaneous (non-echolalic) meaningful phrases

Diagnostic Evaluation (Post-Detection)

- **Sensory Testing:** Formal Audiology (BAER/OAE) and Vision testing are *mandatory first steps* for any developmental delay
- **Standardized Psychometric Assessment:** Bayley Scales of Infant and Toddler Development (BSID-III/IV), Wechsler Intelligence Scale for Children (WISC-V), Autism Diagnostic Observation Schedule (ADOS-2)
- **Genetic Testing (AAP/ACMG Guidelines):**
  - *First-line for unexplained GDD/ID/ASD:* Chromosomal Microarray (CMA)
  - *Targeted:* Fragile X DNA testing (especially in males), MECP2 (Rett syndrome in females)
  - *Now:* Whole Exome Sequencing (WES) is increasingly replacing CMA as first-tier in severe/complex phenotypes

- **Neuroimaging (MRI Brain):** Indicated for microcephaly, macrocephaly, seizures, focal neurologic signs, or loss of milestones (avoid routine MRI in isolated, non-syndromic ASD)
- **Metabolic/Lab Workup:** Thyroid function tests, serum lead levels, CK (if delayed walking/hypotonia to rule out DMD), targeted metabolic screen (ammonia, lactate, tandem mass spectrometry) if episodic decompensation or regression

Management Principles

- **Early Intervention (EI):** Do not wait for a definitive diagnosis to start therapies; refer immediately upon detection of delay
- **Multidisciplinary Therapy:** Physiotherapy (PT), Occupational Therapy (OT), Speech-Language Pathology (SLP), Applied Behavior Analysis (ABA) for ASD
- **Educational Support:** Individualized Education Program (IEP) for school-aged children
- **Medical Management:** Treat comorbidities (epilepsy, spasticity, ADHD, sleep disturbances, constipation)

Prognosis & Prevention

- **Prognosis:** Depends heavily on etiology and timing of intervention; neuroplasticity is highest <3 years of age, making early detection critical
- **Prevention:** Universal newborn screening (metabolic, hearing), folic acid supplementation, optimizing maternal health, strict NICU protocols (cooling for HIE), routine immunizations

Exam Summary

- **Key Distinction:** Surveillance is done at *every* visit; Screening uses standardized tools at 9, 18, and 30 months.
- **ASD Screening:** Specifically required at 18 and 24 months (use M-CHAT-R/F).
- **Rule out Sensory Deficits:** Hearing and vision evaluation is the absolute first step in evaluating a child with suspected delays.
- **First-line Genetics:** Chromosomal Microarray (CMA) and Fragile X testing are first-line for unexplained GDD/ID/ASD.
- **Golden Rule:** Never adopt a "wait and see" approach for developmental red flags; refer immediately to Early Intervention.

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131. Autism spectrum disorder

Subject: Developmental / Behavioral Pediatrics

Definition & Epidemiology

- Neurodevelopmental disorder characterized by persistent deficits in social communication and restricted, repetitive patterns of behavior (DSM-5-TR).
- **Prevalence:** 1 in 36 children (**CDC 2023 update**).
- **Gender:** Male-to-female ratio is 4:1.

Etiology

- **Idiopathic:** Majority of cases (polygenic/epigenetic interactions).
- **Genetic Syndromes (15–20%):** Fragile X syndrome (most common inherited cause), Tuberous Sclerosis Complex (TSC), Rett syndrome, PTEN hamartoma syndrome.
- **Copy Number Variants:** Chromosomal microdeletions/duplications (e.g., 16p11.2, 15q11-13).
- **Maternal/Environmental:** Advanced maternal/paternal age, extreme prematurity (<26 weeks), maternal use of valproic acid or thalidomide during pregnancy.

Pathophysiology

- Accelerated early brain overgrowth (macrocephaly seen in ~20% of ASD children by age 1).
- Defective synaptic pruning and abnormal dendritic spine formation.
- Altered neural connectivity: Local hyperconnectivity (focus on details) and long-range hypoconnectivity (impaired complex social processing).

Clinical Features (DSM-5-TR Domains)

- **Domain A: Social Communication & Interaction Deficits**
    - Absent/poor joint attention (inability to share interest using pointing/gaze).
    - Poor eye contact and absent social smile.
    - Delayed speech, echolalia, pronoun reversal ("you" instead of "I").
    - Inability to understand non-verbal cues or maintain peer relationships.
- **Domain B: Restricted & Repetitive Behaviors**
    - Motor stereotypies (hand-flapping, spinning, rocking).
    - Inflexible adherence to routines (extreme distress at small changes).
    - Highly restricted, fixated interests (e.g., memorizing train schedules).
    - Sensory processing issues: Hyper- or hyporeactivity (e.g., indifference to pain, covering ears to specific sounds, sniffing/licking objects).
- **Absolute Red Flags (Indicating immediate evaluation):**
    - No babbling or pointing by 12 months.
    - No single words by 16 months.
    - No meaningful 2-word phrases by 24 months.
    - **Any loss** of speech, babbling, or social skills at **any age**.

Diagnosis

- **Screening (AAP 2020 Guidelines):** Universal screening using **M-CHAT-R/F** (Modified Checklist for Autism in Toddlers) at **18 and 24 months**.
- **Clinical Diagnosis:** Based strictly on DSM-5-TR criteria (symptoms must be present in early developmental period and cause significant impairment).
- **Gold Standard Tools:** ADOS-2 (Autism Diagnostic Observation Schedule) and ADI-R (Autism Diagnostic Interview-Revised).

Investigations

- **Mandatory:** Formal audiometry (to rule out hearing impairment as a cause of speech delay).
- **First-line Genetics (AAP/ACMG):** Chromosomal Microarray (CMA) and Fragile X DNA testing for all children with ASD.
- **Targeted Workup (Only if clinically indicated):**
    - **EEG:** If history of clinical seizures or severe language regression (Landau-Kleffner syndrome).
    - **MRI Brain:** If microcephaly, severe macrocephaly, focal neurologic signs, or TSC suspected.
    - **Wood's Lamp Exam:** To look for ash-leaf spots (TSC).
    - **Metabolic Panel:** If dysmorphism, cyclic vomiting, or lethargy is present.

Management

- **Non-Pharmacological (Mainstay):**
    - **Early Intensive Behavioral Intervention (EIBI):** Applied Behavior Analysis (ABA) is the standard of care (minimum 25 hours/week).
    - Speech and Language Therapy (SLT) including Picture Exchange Communication System (PECS) for non-verbal children.
    - Occupational Therapy (OT) for sensory integration and daily living skills.
- **Pharmacological (Targets comorbidities ONLY; no drug treats core ASD symptoms):**
    - **Irritability/Severe Aggression:** Risperidone or Aripiprazole (FDA-approved for ASD-associated irritability).
    - **ADHD symptoms:** Stimulants (Methylphenidate) or Alpha-2 agonists (Guanfacine, Clonidine).
    - **Sleep onset insomnia:** Melatonin (first-line).

Comorbidities & Complications

- **Intellectual Disability (ID):** Present in ~30% (trend is decreasing due to broader diagnostic criteria).
- **ADHD:** Co-occurs in 50–70%.
- **Epilepsy:** 10–30% risk (bimodal onset: infancy and adolescence).
- **Gastrointestinal:** Chronic functional constipation, feeding selectivity (picky eating).
- **Psychiatric:** Anxiety disorders, depression (especially in high-functioning teens).

Prognosis

- Lifelong condition, but severity of impairment can significantly decrease with early intervention.
- **Best prognostic indicators:** IQ > 70, development of functional communicative language by age 5, and early initiation of ABA.

Exam Summary: Must-Write Points

- **Core criteria:** Deficits in social communication + restricted/repetitive behaviors (DSM-5-TR).
- **Red flag:** ANY regression of language or social skills warrants immediate evaluation.
- **Screening:** M-CHAT-R/F universally at 18 and 24 months.
- **First-line investigations:** Formal hearing test, Chromosomal Microarray (CMA), and Fragile X testing.
- **Management:** Applied Behavior Analysis (ABA) is the gold standard; drugs (risperidone/aripiprazole) are strictly for severe irritability/aggression, not core symptoms.

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132. Language development and learning problems

Subject: Developmental / Behavioral Pediatrics

Definitions

- **Language Disorder:** Persistent difficulties in acquisition and use of language across modalities (spoken, written, sign) due to deficits in comprehension (receptive) or production (expressive).
- **Specific Learning Disorder (SLD):** Neurodevelopmental disorder with persistent difficulties learning and using academic skills (reading, writing, math) despite normal intelligence and adequate schooling (DSM-5-TR).

Normal Language Milestones

- **2 months:** Cooing (vowel sounds).
- **6 months:** Monosyllabic babbling (*ba, da*).
- **9 months:** Bisyllabic babbling (*baba, dada* non-specifically); responds to name.
- **12 months:** 1–3 clear words with meaning; points to objects.
- **15 months:** Jargon (unintelligible speech with adult-like intonation).
- **18 months:** 10–25 words; identifies 1–2 body parts.
- **24 months:** 2-word phrases (noun + verb); 50+ words; 50% intelligible to strangers.
- **36 months:** 3-word sentences; asks "why" questions; 75% intelligible.
- **48 months:** Tells stories; 100% intelligible to strangers.

Red Flags (Must Evaluate)

- **6 months:** No vocalization.
- **9 months:** No babbling.
- **12 months:** No pointing or communicative gestures.
- **18 months:** No single meaningful words.
- **24 months:** No spontaneous 2-word phrases (echolalia does not count).

- **Any age:** Loss of previously acquired speech/language skills.

Etiology of Language/Learning Problems

- **Hearing Impairment:** *Most common preventable cause* of language delay.
- **Intellectual Disability (ID):** *Most common overall cause* of global language delay.
- **Autism Spectrum Disorder (ASD):** Classically presents with impaired pragmatics (social use of language) and poor eye contact.
- **Environmental/Psychosocial:** Severe neglect, lack of stimulation, bilingualism (causes temporary expressive delay, but normalizes).
- **Specific Language Impairment (SLI):** Isolated language delay with normal non-verbal IQ and normal hearing.
- **Anatomical:** Cleft palate, ankyloglossia (tongue-tie - affects articulation, not language acquisition).
- **Genetic Syndromes:** Fragile X syndrome, Klinefelter syndrome, Landau-Kleffner syndrome (acquired epileptic aphasia).

Clinical Features: Learning Problems (SLD)

- **Dyslexia (Impaired Reading):** Poor phonological awareness, slow/inaccurate word recognition, poor spelling. *Most common SLD (80%)*.
- **Dysgraphia (Impaired Written Expression):** Poor handwriting, spelling errors, poor grammatical organization.
- **Dyscalculia (Impaired Mathematics):** Difficulty with number sense, memorizing arithmetic facts, accurate calculation.
- **Comorbidities:** High overlap with ADHD (up to 30%), anxiety, and oppositional defiant disorder (ODD).

Diagnostic Approach

- **Step 1: Hearing Assessment:** Mandatory for *every* child with language delay. Use OAE/BERA (infants) or pure-tone audiometry (>4 years).
- **Step 2: Developmental Screening:** Use standardized tools (ASQ-3, PEDS).
- **Step 3: Autism Screening:** M-CHAT-R/F at 18 and 24 months.
- **Step 4: IQ Testing:** Differentiate SLD (normal IQ) from Intellectual Disability (IQ < 70). Use WPPSI (preschool) or WISC-V (school-age).
- **Step 5: Psychoeducational Assessment:** Woodcock-Johnson or specific reading/math batteries to formally diagnose SLD (requires ≥6 months of difficulty despite targeted help).

Management

- **Speech-Language Therapy:** First-line for language disorders; involves Speech-Language Pathologist (SLP).
- **Medical Intervention:** Hearing aids/cochlear implants for sensorineural hearing loss; tympanostomy tubes for chronic otitis media with effusion.

- **Educational Accommodations (IEP):** Individualized Education Program under statutory rights (e.g., RPwD Act in India, IDEA in USA).
    - *Dyslexia:* Extra time in exams, reading aloud, audiobooks.
    - *Dysgraphia:* Scribes, oral exams, use of a computer/keyboard.
    - *Dyscalculia:* Use of calculators, visual math aids.
- **Comorbidity Management:** Treat underlying ADHD with stimulants (Methylphenidate) if attention deficit exacerbates learning failure.

Prognosis & Outcomes

- **Receptive vs. Expressive:** Pure expressive delays have an excellent prognosis. Receptive delays carry a higher risk of evolving into learning disabilities or ASD.
- **Early Intervention:** Therapy initiated before age 3 significantly improves school-readiness and long-term academic outcomes.

Exam Summary

- **Rule #1:** Always rule out hearing loss first in *any* child with language delay (OAE/BERA).
- **Normal intelligibility:** 50% at 2 years, 75% at 3 years, 100% at 4 years.
- **Red Flag:** No babbling by 9 months or no single words by 18 months warrants immediate referral.
- **SLD vs. ID:** Specific Learning Disorder requires a *normal* IQ; Intellectual Disability has an IQ < 70 with adaptive deficits.
- **Management triad for SLD:** Psychoeducational assessment + Remedial education + IEP accommodations (extra time, scribe).

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133. Sleep problems in children

Subject: Developmental / Behavioral Pediatrics

Classification

- **Behavioral Insomnia of Childhood (BIC):**
    - *Sleep-onset association type:* Relies on external cues (rocking, feeding, parent's presence) to fall asleep; cannot self-soothe upon normal nocturnal awakenings.
    - *Limit-setting type:* Bedtime stalling/refusal due to caregiver's inability to enforce rules (common in toddlers/preschoolers).
- **Parasomnias (Abnormal sleep behaviors):**
    - *NREM (Deep sleep / 1st third of night):* Sleep terrors, sleepwalking (somnambulism), confusional arousals.
    - *REM (Dream sleep / Last third of night):* Nightmares.
- **Sleep-Related Breathing Disorders (SRBD):** Obstructive Sleep Apnea (OSA).

- **Sleep-Related Movement Disorders:** Restless Legs Syndrome (RLS), Periodic Limb Movements in Sleep (PLMS).
- **Circadian Rhythm Disorders:** Delayed sleep-wake phase disorder (common in adolescents).

Clinical Features & Differentiation

- **Night Terrors vs. Nightmares (Classic Exam Trap):**
    - *Night Terrors:* NREM sleep (1st third of night), child appears awake but is unresponsive/inconsolable, autonomic arousal (tachycardia, sweating), amnesia of event the next morning.
    - *Nightmares:* REM sleep (last third of night), child wakes up fully alert, easily consoled, vividly recalls the scary dream.
- **Obstructive Sleep Apnea (OSA):** Habitual snoring, witnessed pauses in breathing, mouth breathing, secondary enuresis. Paradoxically presents as daytime hyperactivity/ADHD-like symptoms in children (rather than sleepiness).
- **Restless Legs Syndrome (RLS):** "Creepy-crawly" sensation in legs at bedtime, relieved by movement; strongly associated with iron deficiency.

Diagnosis

- **BEARS Screening Tool (Must-write):**
    - **B**edtime issues
    - **E**xcessive daytime sleepiness
    - **A**wakenings during the night
    - **R**egularity and duration of sleep
    - **S**noring
- **Sleep Diary:** 2-week log of sleep-wake times, naps, and night wakings (First-line diagnostic tool for behavioral sleep issues).
- **Polysomnography (PSG):** Gold standard for OSA, PLMS, and narcolepsy. *Not* indicated for routine behavioral insomnias or uncomplicated parasomnias.
- **Labs:** Serum ferritin (if RLS is suspected).

Management: Behavioral & Environmental (First-Line)

- **Sleep Hygiene:** Consistent sleep/wake schedule, cool/dark/quiet bedroom, avoid caffeine.
- **Screen Time (AAP 2024):** No screens 1–2 hours before bedtime (blue light suppresses endogenous melatonin).
- **For Sleep-Onset Association:** "Unmodified extinction" (cry-it-out) or "Graduated extinction" (Ferber method - progressively increasing intervals of checking on the child without picking them up).
- **For Limit-Setting Insomnia:** Bedtime routine, "bedtime pass" (allows one acceptable exit from the bedroom), positive reinforcement.

- **For NREM Parasomnias:** Reassurance (benign, self-limiting). Use "Scheduled Awakenings" (waking child 15 mins before usual event time) for severe/frequent sleep terrors. Secure the environment for sleepwalkers.

Management: Medical & Surgical

- **Pharmacotherapy:** Generally discouraged as first-line.
    - *Melatonin:* 1–3 mg given 30–60 mins before bed. Indicated for Circadian Rhythm Disorders and sleep-onset insomnia in Autism Spectrum Disorder (ASD) or ADHD.
    - *Contraindication:* AAP strongly advises against OTC antihistamines (diphenhydramine) due to paradoxical excitation and daytime grogginess.
- **OSA:** Adenotonsillectomy (first-line for adenotonsillar hypertrophy); CPAP or weight loss if surgery is contraindicated or ineffective.
- **RLS/PLMS:** Oral iron supplementation if serum ferritin is < 50 ng/mL.

Complications of Untreated Sleep Disorders

- **Neurocognitive:** Poor academic performance, impaired memory consolidation.
- **Behavioral:** Hyperactivity, impulsivity, aggression (frequently misdiagnosed as ADHD).
- **Physical:** Growth failure (GH is secreted in deep sleep), obesity, cardiovascular complications (cor pulmonale in severe, prolonged OSA).

Exam Summary

- **BEARS** mnemonic is the standard screening tool for pediatric sleep history.
- **Night terrors** = NREM, 1st third of night, amnesia, inconsolable. **Nightmares** = REM, last third of night, recalled, consolable.
- **Behavioral Insomnia** is managed with sleep hygiene and extinction (Ferber method); avoid sedatives.
- **Pediatric OSA** often presents with daytime hyperactivity, not just sleepiness; gold standard diagnosis is PSG, treatment is adenotonsillectomy.
- **RLS** requires checking a serum ferritin level (target > 50 ng/mL).

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134. Childhood disabilities

Subject: Developmental / Behavioral Pediatrics

Definition & Framework

- **WHO ICF Model** (International Classification of Functioning, Disability and Health): Evaluates disability across three interconnected domains:
    - *Impairment:* Abnormality in body structure or physiological function (e.g., brain injury).
    - *Activity Limitation:* Difficulty executing a task at the individual level (e.g., inability to walk).
    - *Participation Restriction:* Inability to engage in life situations at the societal level (e.g., cannot attend regular school).

- **Indian Legal Context:** Rights of Persons with Disabilities (RPWD) Act, 2016 recognizes 21 disabling conditions (expanded from 7).

Major Categories

- **Neurodevelopmental:** Intellectual Disability (ID) / Global Developmental Delay (GDD), Autism Spectrum Disorder (ASD), ADHD, Specific Learning Disabilities (SLD).
- **Neuromotor:** Cerebral Palsy (CP), Muscular Dystrophies, Spina Bifida.
- **Sensory:** Hearing Impairment, Visual Impairment, Deaf-blindness.
- **Multiple Disabilities:** Presence of two or more disabling conditions.

Etiology

- **Prenatal (Genetics & Environment):** Chromosomal anomalies (Down syndrome), Microdeletions, Fragile X, TORCH infections, Teratogens (Fetal Alcohol Spectrum Disorder), Placental insufficiency.
- **Perinatal (Acquired):** Hypoxic Ischemic Encephalopathy (HIE), Extreme prematurity, Low birth weight, Kernicterus, Neonatal sepsis/meningitis, Hypoglycemia.
- **Postnatal (Insults):** CNS infections (encephalitis/meningitis), Traumatic brain injury (TBI), Severe Acute Malnutrition (SAM), Status epilepticus, Lead toxicity.

Clinical Red Flags (Require Immediate Referral)

- **General:** Loss of any previously acquired milestone at any age.
- **Motor:** Early rolling (<3 months - suggests spasticity), persistent fisting (>4 months), inability to sit without support by 9 months, not walking by 18 months.
- **Speech/Language:** No babbling by 12 months, no single words by 16 months, no 2-word spontaneous phrases by 24 months.
- **Social/Cognitive:** No social smile by 3 months, lack of eye contact, lack of joint attention or pointing by 18 months.

Screening & Diagnosis

- **Surveillance:** Continuous process at every well-child visit (eliciting parental concerns).
- **Screening (AAP Guidelines):**
    - General developmental screening at 9, 18, and 30 months.
    - Specific ASD screening at 18 and 24 months (using M-CHAT-R/F).
- **Screening Tools (IAP recommended):** Trivandrum Developmental Screening Chart (TDSC), Ages and Stages Questionnaire (ASQ-3).
- **Diagnostic Evaluation:**
    - *Development/Intelligence:* Bayley Scales of Infant Development (BSID-III), WISC-V, Malin's Intelligence Scale for Indian Children (MISIC).
    - *Autism:* CARS, ISAA (Indian Scale for Assessment of Autism), ADOS-2.

- *Medical Workup:* Hearing/Vision testing (mandatory for all delays), Thyroid profile, Microarray/Karyotype, MRI Brain, Inborn Errors of Metabolism (IEM) screen, EEG (if seizures).

Management (Multidisciplinary Approach)

- **Early Intervention (EI):** Initiation of therapy <3 years of age to maximize neuroplasticity.
- **Therapies:**
  - *Physiotherapy (PT):* Motor milestones, spasticity management, orthotics.
  - *Occupational Therapy (OT):* Fine motor skills, Activities of Daily Living (ADLs), sensory integration.
  - *Speech Therapy (ST):* Language acquisition, alternative/augmentative communication (AAC), swallowing/feeding issues.
- **Educational Support:** Individualized Education Program (IEP), special schooling vs. inclusive education (preferred).
- **Medical/Surgical:** Management of comorbidities (anti-seizure meds, baclofen/botulinum toxin for spasticity, methylphenidate for ADHD, orthopedic corrective surgeries).
- **Psychosocial:** Parental counseling, support groups, respite care.

Complications

- **Physical:** Contractures, scoliosis, hip dislocation, osteopenia, aspiration pneumonia.
- **Psychological:** Poor self-esteem, depression, behavioral outbursts, self-injurious behavior.
- **Family:** Caregiver burnout, financial toxicity, sibling neglect.

Prevention & Public Health (India)

- **Primary:** Rubella immunization, periconceptional folic acid, institutional deliveries, prevention of Rh isoimmunization.
- **Secondary:** Newborn Screening (NBS) for congenital hypothyroidism and hearing loss (OAE/BERA).
- **RBSK (Rashtriya Bal Swasthya Karyakram):** National program screening children (0-18 years) for 4 Ds: Defects at birth, Diseases, Deficiencies, and Developmental delays including disabilities.
- **Social Support:** UDID (Unique Disability ID) card generation for availing government benefits, disability pension, tax rebates.

Exam Summary

- Define disability using the **WHO ICF model** (Impairment → Activity Limitation → Participation Restriction).
- Always mention **loss of milestones** as the ultimate red flag requiring urgent neurological workup.
- **Early Intervention (<3 years)** is the cornerstone of management due to maximum brain neuroplasticity.
- Routine screening is mandatory: General at **9, 18, 30 months**; Autism at **18, 24 months** (AAP).

- Management is strictly **multidisciplinary** (PT, OT, ST, Special Educator, Pediatrician) and family-centered.
- Mention **RBSK (4 Ds)** and **RPWD Act 2016 (21 disabilities)** for extra marks in the Indian context.

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135. Adolescent friendly health clinics

Subject: Developmental / Behavioral Pediatrics

Definition & Scope

- **Target Group:** Adolescents aged 10–19 years (WHO definition).
- **Programmatic Basis (India):** Integral component of **Rashtriya Kishor Swasthya Karyakram (RKSK)** (MoHFW, 2014); previously known as ARSH (Adolescent Reproductive and Sexual Health) clinics.
- **Goal:** To provide comprehensive, stigma-free, and holistic health care addressing the unique transitional needs of adolescents.

WHO Core Principles (The 5 'A's / 'E's)

- **Accessible:** Convenient location, flexible timings (e.g., after-school hours), free/affordable services.
- **Acceptable:** Non-judgmental, friendly, and respectful environment.
- **Equitable:** Services for all (unmarried/married, rural/urban, in-school/out-of-school, marginalized).
- **Appropriate:** Comprehensive package addressing specific adolescent morbidities.
- **Effective:** Evidence-based care provided by trained healthcare providers.

Key Characteristics of the Clinic

- **Privacy:** Audio-visual privacy during consultation and examination.
- **Confidentiality:** Strict assurance that information will not be shared with parents/teachers without consent (except for mandatory reporting like POCSO/suicide risk).
- **Infrastructure:** Separate waiting area with IEC (Information, Education, Communication) materials, edutainment, and drop-boxes for anonymous questions.
- **Staffing:** Specially trained Medical Officer (MO), ANM, and dedicated Adolescent Health Counselor.
- **Community Linkage:** Supported by Peer Educators (*"Saathiyas"* under RKSK) who mobilize adolescents.

Clinical Approach (HEEADSSS Screening) *Must be used by physicians in AFHCs to build rapport and screen for psychosocial issues:*

- **H**ome environment
- **E**ducation and Employment
- **E**ating

- **A**ctivities (peer group, screen time)
- **D**rugs (substance abuse)
- **S**exuality (STI risk, contraception, abuse)
- **S**uicide / Depression
- **S**afety (violence, driving)

Services Provided (RKSK 6 Thematic Areas)

- **Nutrition:** BMI monitoring, Weekly Iron Folic Acid Supplementation (WIFS), management of anemia, counseling for obesity and eating disorders.
- **Sexual & Reproductive Health (SRH):** Menstrual hygiene management (provision of sanitary napkins), syndromic management of RTIs/STIs, contraception counseling/provision, teenage pregnancy care, safe abortion referral.
- **Mental Health:** Screening for depression, anxiety, suicide risk; stress management counseling.
- **Substance Misuse:** Screening for tobacco, alcohol, and illicit drugs; brief intervention; referral to de-addiction centers.
- **Non-Communicable Diseases (NCDs):** Blood pressure monitoring, lifestyle modification (diet, physical activity).
- **Violence & Injuries:** Screening for gender-based violence, bullying, and abuse; providing medico-legal support and counseling.

Operational Tiers (India)

- **Sub-center / Health & Wellness Center (HWC):** Basic counseling, WIFS, sanitary napkins, referral.
- **Primary Health Centre (PHC):** MO and ANM run the clinic (fixed days/timings), basic clinical management.
- **Community Health Centre (CHC) / District Hospital (DH):** Dedicated AFHCs with full-time trained counselors, comprehensive clinical care, and referral linkages (e.g., ICTC, mental health professionals).

Challenges & Pitfalls

- Lack of awareness among adolescents about clinic existence.
- High attrition rate of trained counselors.
- Reluctance of unmarried adolescents to seek SRH services due to societal stigma.
- Legal barriers regarding age of consent for medical treatments and POCSO Act mandatory reporting (often deters adolescents from disclosing consensual sexual activity).

Exam Summary

- **Core Mandate:** RKSK (MoHFW India) initiative targeting 10–19 years.
- **Pillars:** Privacy, Confidentiality, Accessibility, Acceptability.
- **Clinical Tool:** HEEADSSS psychosocial interview.

- **Key Services:** WIFS (anemia), SRH (menstruation, contraception, STIs), Mental Health, Substance abuse, NCDs, Violence prevention.
- **Community Link:** Mobilization via Peer Educators (*Saathiyas*).

Metabolic Diseases

136. Approach to child with inborn errors of metabolism

Subject: Metabolic Diseases

Basics & Classification

- **Definition:** Single gene defects resulting in absent/deficient enzymes, leading to substrate accumulation or product deficiency.
- **Group 1 (Intoxication):** Normal at birth, symptom-free interval, then acute crisis (vomiting, lethargy, coma). *Examples:* Urea Cycle Defects (UCD), Organic Acidemias (OA), Aminoacidopathies (MSUD).
- **Group 2 (Energy Deficit):** Inadequate energy production. Presents with hypoglycemia, hypotonia, cardiomyopathy, myopathy, failure to thrive. *Examples:* Glycogen Storage Diseases (GSD), Fatty Acid Oxidation Defects (FAOD), Mitochondrial disorders.
- **Group 3 (Complex Molecules):** Progressive accumulation. Dysmorphism, organomegaly, neurodegeneration. *Examples:* Lysosomal storage (Gaucher, MPS), Peroxisomal (Zellweger).

Clinical Clues (When to Suspect)

- **Neonatal:** "Sepsis-like" illness unresponsive to antibiotics, unexplained encephalopathy, intractable seizures, altered tone.
- **Infancy/Childhood:** Developmental regression, recurrent coma/vomiting triggered by fasting or illness, hepatosplenomegaly, coarse facies, cataracts, unexplained myopathy/cardiomyopathy.
- **Peculiar Odors:**
    - Musty/Mousy: Phenylketonuria (PKU)
    - Maple syrup/Burnt sugar: MSUD
    - Sweaty feet: Isovaleric acidemia
    - Boiled cabbage: Tyrosinemia type 1

Diagnostic Approach (Stepwise)

- **Step 1: Emergency / Bedside Labs**
    - Blood glucose, Arterial Blood Gas (ABG - check anion gap).
    - Serum Ammonia, Serum Lactate.
    - Urine ketones and reducing substances.
- **Step 2: Algorithmic Interpretation**
    - *Hypoglycemia + Hepatomegaly:* GSD.

- *Hypoglycemia + Absent/Low Ketones:* FAOD or Hyperinsulinism.
- *High Ammonia + Normal Anion Gap + No Ketones:* UCD.
- *High Ammonia + High Anion Gap + Ketones:* Organic Acidemia.
- *High Lactate + Normal Anion Gap:* Mitochondrial / Pyruvate defect.

- **Step 3: Specific Metabolic Screening**
  - *Tandem Mass Spectrometry (TMS):* Dried blood spot for acylcarnitine profile and amino acids.
  - *Gas Chromatography-Mass Spectrometry (GC-MS):* Urine organic acids.
  - *HPLC:* Plasma amino acid quantification.
- **Step 4: Confirmatory Tests**
  - **Update (ACMG/IAP):** Next-Generation Sequencing (NGS) / Clinical Exome Sequencing is now the preferred first-line confirmatory test, largely replacing individual tissue enzyme assays.
  - *Enzyme analysis:* Leukocytes or skin fibroblasts (if genetics inconclusive).

Acute Management (Metabolic Emergency)

- **Goal:** Halt catabolism, promote anabolism, remove toxins.
- **Stop Offending Intake:** Immediately halt all enteral protein and fat.
- **Reverse Catabolism:** Provide high-dose IV Dextrose (10% or higher, Glucose Infusion Rate 8–10 mg/kg/min). Add IV lipids *only* if FAOD is definitively ruled out.
- **Treat Triggers:** Broad-spectrum antibiotics for concurrent sepsis; maintain normothermia.
- **Toxin Scavenging (Hyperammonemia):**
  - IV Sodium Benzoate / Sodium Phenylacetate (diverts nitrogen excretion).
  - IV Arginine (primes the urea cycle).
  - *Indication for Hemodialysis:* Ammonia >500 µmol/L or rapidly rising despite medical therapy, or severe encephalopathy.
- **Metabolic Cocktail (Empiric Cofactors):**
  - Thiamine (B1), Riboflavin (B2), Biotin, Vitamin B12.
  - L-Carnitine (binds toxic acyl-CoA). *Contraindication:* Acute long-chain FAOD (risk of lethal arrhythmias).

Chronic Management

- **Dietary Modification:** Medical formulas (e.g., phenylalanine-free for PKU), avoidance of fasting (frequent cornstarch in GSD).
- **Enzyme Replacement Therapy (ERT):** Standard of care for Gaucher, Pompe, Fabry, and specific MPS types.
- **Organ Transplantation:** Liver transplant (curative for severe UCD, Tyrosinemia), Hematopoietic Stem Cell Transplant (HSCT) for Krabbe, Adrenoleukodystrophy.

- **Substrate Reduction Therapy:** Miglustat (Gaucher, Niemann-Pick C).

Complications & Prognosis

- **Acute:** Cerebral edema, irreversible brain damage, multi-organ failure, death.
- **Chronic:** Intellectual disability, movement disorders, cirrhosis, cardiomyopathy.
- **Prognosis:** Highly variable. Excellent if detected early via newborn screening (e.g., PKU, MCAD); uniformly fatal in severe untreated forms (e.g., Zellweger, severe UCD).

Prevention

- **Newborn Screening (NBS):** Expanded NBS via TMS detects >40 treatable IEMs before symptoms begin.
- **Prenatal Diagnosis:** Chorionic villus sampling (CVS) or amniocentesis for targeted genetic testing if index case mutation is known.
- **Genetic Counseling:** Autosomal recessive (25% recurrence risk) is the most common inheritance pattern; OTC deficiency and Hunter syndrome are X-linked recessive.

Exam Summary: Must-Write Points

- **Classic Triad of IEM crisis:** Unexplained encephalopathy, respiratory alkalosis/acidosis, and hypoglycemia in a previously well infant.
- **Core ER Labs:** Glucose, ABG (Anion Gap), Ammonia, Lactate, Urine Ketones.
- **Diagnostic Algorithm:** High Ammonia + Normal AG = UCD; High Ammonia + High AG = Organic Acidemia; Hypoglycemia + Non-ketotic = FAOD.
- **Acute Rx Rule:** Stop protein/fat immediately → Start high GIR (8-10 mg/kg/min) dextrose to reverse catabolism → Dialyze if ammonia >500 µmol/L.
- **Confirmatory Paradigm Shift:** NGS/Whole Exome Sequencing has overtaken tissue enzyme assays as the definitive diagnostic standard.

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137. Important inborn errors of metabolism in children including clinical features and management

Subject: Metabolic Diseases

Definition

- Genetic disorders (typically Autosomal Recessive) causing defects in enzymes, receptors, or transport proteins
- Results in toxic accumulation of substrates, deficiency of essential products, or energy failure

Pathophysiological Classification

- **Group 1: Intoxication Disorders** (Symptom-free interval followed by acute crisis)
    - Aminoacidopathies (e.g., Phenylketonuria, Maple Syrup Urine Disease)
    - Organic acidemias (e.g., Methylmalonic acidemia)
    - Urea Cycle Defects (UCDs)

- **Group 2: Energy Deficiency Disorders** (Hypoglycemia, hypotonia, organomegaly, cardiac/muscle involvement)
    - Glycogen Storage Diseases (GSDs)
    - Fatty Acid Oxidation Defects (FAODs - e.g., MCAD deficiency)
    - Mitochondrial disorders
- **Group 3: Complex Molecule Disorders** (Progressive neurodegeneration, dysmorphism, organomegaly)
    - Lysosomal Storage Disorders (LSDs - e.g., Gaucher, MPS)
    - Peroxisomal disorders (e.g., Zellweger syndrome)

General Clinical Clues (When to Suspect)

- **History:** Consanguinity, unexplained neonatal death in siblings, maternal HELLP syndrome (associated with fetal LCHAD deficiency)
- **Precipitants:** Fasting, intercurrent illness, introduction of specific foods (protein/weaning)
- **Neurological:** Unexplained encephalopathy, intractable seizures, alternating hypotonia/hypertonia, loss of milestones
- **Systemic:** Sepsis-like picture with negative cultures, recurrent vomiting
- **Peculiar Odors:**
    - Mousy/Musty: Phenylketonuria (PKU)
    - Burnt sugar/Sweet: Maple Syrup Urine Disease (MSUD)
    - Sweaty feet: Isovaleric acidemia
    - Boiled cabbage: Tyrosinemia

General Diagnostic Approach

- **Tier 1 (Emergency Bedside/Lab):** Glucose, ABG (anion gap acidosis), Ammonia, Lactate, Ketones (urine/blood), LFTs, Uric acid
- **Tier 2 (Metabolic Screening):**
    - Tandem Mass Spectrometry (TMS): Blood spots for acylcarnitines and amino acids
    - Gas Chromatography-Mass Spectrometry (GC-MS): Urine organic acids
- **Tier 3 (Confirmatory):** Specific enzyme assays (fibroblasts/leukocytes), Clinical Exome Sequencing (CES) / Targeted gene panels

High-Yield Specific IEMs: Features & Management

1. Phenylketonuria (PKU) - *Aminoacidopathy*

- **Defect:** Phenylalanine hydroxylase (PAH) deficiency
- **Clinical Features:** Microcephaly, severe intellectual disability, blonde hair/blue eyes, eczema, musty odor
- **Diagnosis:** Elevated Phenylalanine, normal/low Tyrosine

- **Management:**
    - Lifelong low-phenylalanine diet
    - Tyrosine supplementation
    - Sapropterin (BH4) trial (cofactor for PAH)

2. Maple Syrup Urine Disease (MSUD) - *Organic Acidemia*

- **Defect:** Branched-chain alpha-keto acid dehydrogenase (BCKD) complex
- **Clinical Features:** Neonatal encephalopathy, bicycling movements, opisthotonos, burnt sugar urine odor
- **Diagnosis:** Elevated Leucine, Isoleucine, Valine; presence of alloisoleucine (pathognomonic)
- **Management:**
    - Restrict branched-chain amino acids (BCAAs)
    - Thiamine supplementation (cofactor)
    - Liver transplant (curative)

3. Classic Galactosemia - *Carbohydrate Metabolism*

- **Defect:** Galactose-1-phosphate uridyltransferase (GALT)
- **Clinical Features:** Jaundice, hepatomegaly, "oil-drop" cataracts, *E. coli* sepsis, premature ovarian failure (females)
- **Diagnosis:** Non-glucose reducing substances in urine (Clinitest positive, Dipstick negative), absent GALT enzyme activity
- **Management:** Strict lifelong lactose/galactose-free diet (soy-based formula)

4. Glycogen Storage Disease Type I (Von Gierke) - *Energy Defect*

- **Defect:** Glucose-6-phosphatase
- **Clinical Features:** Doll-like facies, massive hepatomegaly (kidneys also enlarged), normal heart/muscle
- **Metabolic Tetrad:** Severe fasting hypoglycemia, Lactic acidosis, Hyperuricemia, Hypertriglyceridemia
- **Management:**
    - Frequent daytime feeds, continuous nocturnal nasogastric drip
    - Uncooked cornstarch (maintains steady glucose)
    - Restrict fructose and galactose

5. Urea Cycle Defects (e.g., OTC Deficiency) - *Intoxication*

- **Defect:** Ornithine transcarbamylase (X-linked recessive; others are AR)
- **Clinical Features:** Rapid neonatal coma, recurrent vomiting, protein aversion
- **Diagnosis:** Massive hyperammonemia (>200 µmol/L), *respiratory alkalosis*, normal glucose/lactate, elevated urine orotic acid

- **Management:**
    - Stop protein intake immediately
    - Ammonia scavengers: IV Sodium benzoate, Sodium phenylacetate
    - Arginine/Citrulline supplementation
    - Hemodialysis (if ammonia > 500 µmol/L or no response to drugs)

Acute Crisis Management (General Protocol)

- **Stop offending agent:** Halt all protein, galactose, or fructose intake (usually for 24–48 hours max)
- **Reverse catabolism (Anabolism promotion):**
    - High-rate IV Dextrose (10% or higher) to maintain glucose >120 mg/dL
    - IV Intralipids (2-3 g/kg/day) *Note: Contraindicated if FAOD is suspected*
- **Toxin removal:** L-carnitine (binds toxic acyl-CoAs), ammonia scavengers, Hemodialysis/CRRT
- **Empiric Cofactor Cocktail:** Thiamine, Riboflavin, Biotin, B12, Pyridoxine (given while awaiting specific diagnosis)

Complications & Prognosis

- **Neurological:** Irreversible intellectual disability, cerebral edema (major cause of death in MSUD/UCD), spasticity
- **Hepatic:** Cirrhosis, hepatocellular carcinoma (Tyrosinemia Type 1, GSD Type 1)
- **Prognosis:** Excellent if picked up on Newborn Screening (NBS) and managed strictly; poor if prolonged encephalopathy occurs before diagnosis

Prevention

- **Newborn Screening (NBS):** Expanded NBS via TMS at 48-72 hours of life is the standard of care globally
- **Prenatal Diagnosis:** Chorionic villus sampling (CVS) at 10-12 weeks or amniocentesis at 15-18 weeks for at-risk pregnancies (enzyme assay or targeted mutation analysis)

Exam Summary

- **Hypoglycemia + Hepatomegaly + Lactic acidosis:** Think GSD Type 1.
- **Hyperammonemia + Respiratory alkalosis + Normal glucose:** Think Urea Cycle Defect.
- **Cataracts + Hepatomegaly + E. coli Sepsis:** Classic Galactosemia (Stop breast milk, start soy formula).
- **Odor Clues:** Mousy = PKU; Burnt Sugar = MSUD; Sweaty feet = Isovaleric acidemia.
- **First step in acute metabolic crisis:** Stop protein, start high-concentration IV dextrose (± lipids) to reverse catabolism. Hemodialysis is the definitive treatment for severe hyperammonemia.

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138. Lesch Nyhan syndrome biochemical abnormality and enzyme deficiency

Subject: Metabolic Diseases

Basics & Genetics

- **Inheritance:** X-linked recessive (almost exclusively affects males)
- **Gene:** *HPRT1* gene mutation (Xq26.2-q26.3)
- **Core Defect:** Inborn error of purine metabolism

Enzyme Deficiency

- **Deficient Enzyme:** Hypoxanthine-guanine phosphoribosyltransferase (HGPRT)
- **Severity:** Complete deficiency (<1% enzyme activity) causes classic Lesch-Nyhan syndrome
- *Note:* Partial deficiency (1–20% activity) causes Kelley-Seegmiller syndrome (hyperuricemia/gout/renal stones, but lacks severe neurologic/behavioral features)

Biochemical Abnormality & Pathophysiology

- **Failed Purine Salvage:** Inability to recycle hypoxanthine into inosine monophosphate (IMP) and guanine into guanosine monophosphate (GMP)
- **Loss of Feedback Inhibition:** Decreased IMP and GMP removes normal feedback inhibition on the *de novo* purine synthesis pathway
- **PRPP Accumulation:** Phosphoribosyl pyrophosphate (PRPP) accumulates and further drives *de novo* purine synthesis
- **Uric Acid Overproduction:** Massive amounts of purines are degraded into uric acid, leading to severe hyperuricemia and hyperuricosuria
- **Neurologic Mechanism:** Not caused by uric acid; hypothesized to result from severe dopamine depletion in the basal ganglia due to impaired purine salvage during brain development

Clinical Features

- **Onset:** Normal at birth; presents with delayed motor milestones at 3–6 months
- **Uric Acid Overproduction:** "Orange sand" in diapers (urate crystalluria), nephrolithiasis, urate nephropathy, late-onset gouty tophi/arthritis
- **Neurologic:** Extrapyramidal (choreoathetosis, severe dystonia) and pyramidal (spasticity, hyperreflexia) signs; usually wheelchair-bound
- **Behavioral (Hallmark):** Compulsive self-mutilation emerging at 2–3 years (biting lips, tongue, and fingers), often requiring restraints despite normal pain sensation
- **Cognitive:** Mild to moderate intellectual disability
- **Hematologic:** Macrocytic/megaloblastic anemia (rapid purine turnover depletes folic acid/B12)

Diagnosis

- **Screening:** Elevated urinary uric acid-to-creatinine ratio (typically > 2.0 in infants)
- **Serum:** Hyperuricemia (often > 8 mg/dL, though can be normal due to high renal clearance)

- **Definitive (Gold Standard):** HGPRT enzyme activity < 1% measured in erythrocytes or cultured skin fibroblasts
- **Molecular:** *HPRT1* gene sequencing for confirmation and carrier screening in female relatives
- **Neuroimaging:** Typically normal; MRI may show reduced basal ganglia volume

Management

- **Hyperuricemia:**
    - **First-line:** Allopurinol (xanthine oxidase inhibitor) to prevent urate nephropathy and gout
    - **Hydration:** Aggressive fluid intake to flush kidneys
    - **Urine Alkalinization:** Potassium citrate to increase urate solubility
- **Behavioral/Self-mutilation:**
    - Physical restraints (arm splints), mouth guards, or specialized seating
    - Dental extraction (often necessary for lower anterior teeth to prevent severe lip/tongue destruction)
- **Neurologic:** Baclofen, diazepam, or botulinum toxin for severe spasticity/dystonia; Deep Brain Stimulation (DBS) of the globus pallidus is an emerging therapy for dystonia/self-mutilation
- *Crucial Trap:* Allopurinol treats the hyperuricemia but has **no effect** on neurologic or behavioral symptoms

Complications & Prognosis

- **Complications:** End-stage renal disease (urate nephropathy), aspiration pneumonia (due to severe dysphagia/dystonia), severe tissue loss from self-injury
- **Prognosis:** Poor; most patients are severely disabled and succumb to renal failure or respiratory infections in their 2nd or 3rd decade

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Exam Summary

- **Enzyme:** Complete HGPRT deficiency.
- **Biochemistry:** Failed purine salvage → ↑ PRPP → massive ↑ *de novo* purine synthesis → severe hyperuricemia.
- **Classic Tetrad:** Hyperuricemia ("orange sand"), choreoathetosis/dystonia, intellectual disability, and self-mutilation (lip/finger biting).
- **Diagnosis:** Erythrocyte HGPRT activity <1%.
- **Treatment Trap:** Allopurinol saves the kidneys but does *not* improve brain/behavioral symptoms.

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4. Write short notes on storage disorders, including lysosomal storage disorders and glycogen storage disorders.

Subject: Important Questions

OVERVIEW: STORAGE DISORDERS

Definition

- Inborn errors of metabolism (IEM) characterized by the intra-cellular accumulation of unmetabolized complex macromolecules due to specific enzyme deficiencies.
- Progressive in nature, affecting multiple organ systems.

PART 1: LYSOSOMAL STORAGE DISORDERS (LSDs)

Basics & Genetics

- **Defect:** Deficiency of specific lysosomal acid hydrolases or transport proteins.
- **Inheritance:** Autosomal Recessive (AR) in >90%.
- **X-linked Recessive Exceptions:** Hunter syndrome (MPS II), Fabry disease, Danon disease.

Classification & Classic Buzzwords

- **Sphingolipidoses:**
    - **Gaucher (Glucocerebrosidase):** Massive splenomegaly, pancytopenia, bone crises, Erlenmeyer flask deformity of distal femur.
    - **Niemann-Pick A/B (Sphingomyelinase):** Hepatosplenomegaly, neuroregression, cherry-red spot at macula.
    - **Tay-Sachs (Hexosaminidase A):** Neuroregression, hyperacusis, cherry-red spot, *no organomegaly*.
    - **Fabry (Alpha-galactosidase A):** Angiokeratomas, acroparesthesia, corneal verticillata, progressive renal/cardiac failure.
- **Mucopolysaccharidoses (MPS):**
    - **MPS I - Hurler (Alpha-L-iduronidase):** Coarse facies, severe dysostosis multiplex, corneal clouding, umbilical hernia.
    - **MPS II - Hunter (Iduronate-2-sulfatase):** Similar to Hurler but *no corneal clouding*; X-linked; nodular skin lesions.
- **Glycoproteinoses:** e.g., I-cell disease (severe coarse facies, gingival hyperplasia present at birth).

Clinical Clues for LSDs

- Progressive neuroregression (loss of milestones).
- Coarse facial features & organomegaly.
- Skeletal abnormalities (Dysostosis multiplex: J-shaped sella, oar-shaped ribs, bullet-shaped phalanges).
- Ophthalmologic findings (Cherry-red spot, corneal clouding).

Diagnosis

- **Screening:** Dried Blood Spot (DBS) for multiplex enzyme assays (now part of newborn screening in developed nations).
- **Urine:** Glycosaminoglycans (GAGs) elevated in MPS.
- **Gold Standard:** Leukocyte or fibroblast specific enzyme activity assay.
- **Confirmation:** Molecular genetic testing (Clinical Exome/Targeted gene panel).
- **Histopathology:** "Gaucher cells" (wrinkled tissue paper macrophages), "Foam cells" (Niemann-Pick).

Management

- **Enzyme Replacement Therapy (ERT):** Available for Gaucher (Imiglucerase), Fabry, Pompe, MPS I, II, IVA, VI, and VII.
- **Hematopoietic Stem Cell Transplant (HSCT):** Treatment of choice for severe MPS I (Hurler) if done before 2 years to preserve cognition; Krabbe disease; metachromatic leukodystrophy.
- **Substrate Reduction Therapy (SRT):** Miglustat, Eliglustat (for Gaucher Type 1, Niemann-Pick C).
- **Chaperone Therapy:** Migalastat (Fabry disease with amenable mutations).

PART 2: GLYCOGEN STORAGE DISORDERS (GSDs)

Basics & Genetics

- **Defect:** Enzymes involved in glycogen synthesis or degradation.
- **Inheritance:** Autosomal Recessive (Exception: GSD IXa is X-linked).
- **Classification:** Divided into Hepatic (hypoglycemia/hepatomegaly) and Muscular (myopathy/energy deficit) types.

Hepatic GSDs (I, III, VI, IX)

- **GSD I (Von Gierke - Glucose-6-phosphatase defect):**
    - *Clinical:* Severe fasting hypoglycemia, "doll-like" facies, massive hepatomegaly, nephromegaly, epistaxis (platelet dysfunction).
    - *Labs:* High lactate, high uric acid, high triglycerides, normal AST/ALT, normal CK.
- **GSD III (Cori - Debranching enzyme defect):**
    - *Clinical:* Milder hypoglycemia, hepatomegaly (improves with age), cardiac/skeletal myopathy.
    - *Labs:* Normal lactate, normal uric acid, elevated CK, elevated transaminases.

Muscle GSDs (V, VII)

- **GSD V (McArdle - Muscle phosphorylase defect):**
    - *Clinical:* Exercise intolerance, muscle cramps, myoglobinuria (burgundy urine) after brief intense exercise.

- *Buzzword:* "Second wind" phenomenon (relief of fatigue after 10 mins of exercise due to switch to fatty acid oxidation).
- *Labs:* High CK, flat venous lactate curve on ischemic forearm exercise test.

Mixed (Systemic) GSD

- **GSD II (Pompe - Acid alpha-glucosidase / Acid maltase defect):**
  - *Note:* Functions as both a GSD and an LSD.
  - *Clinical:* Severe hypotonia ("floppy infant"), massive cardiomegaly, macroglossia, heart failure by 6 months. *No hypoglycemia*.

Diagnosis

- **First-line:** Critical sample during fasting (glucose, lactate, uric acid, lipid profile, ketones).
- **Diagnostic Standard (Current):** Molecular genetic testing (Gene panels).
- **Historical/Secondary:** Liver or muscle biopsy for enzyme assay and glycogen quantification (replaced largely by genetics).

Management

- **Hepatic GSDs:**
  - Avoid fasting; frequent small meals.
  - **Uncooked Cornstarch (UCCS):** Slowly digested glucose polymer; given at 1-2 g/kg every 4-6 hours (including overnight) to maintain normoglycemia.
  - High-protein diet for GSD III (protein provides gluconeogenic precursors).
  - GSD I specific: Restrict galactose/fructose (cannot be converted to free glucose), allopurinol for hyperuricemia.
- **Muscle GSDs:**
  - Avoid intense, anaerobic exercise.
  - Oral sucrose loading prior to planned exercise.
- **Pompe Disease:**
  - Early ERT (Alglucosidase alfa) drastically improves cardiac function and survival.

EXAM SUMMARY (MUST-WRITE POINTS)

- **Inheritance Trap:** Storage disorders are AR, *except* Hunter, Fabry, Danon, and GSD IXa (X-linked).
- **Cherry-Red Spot DDx:** Tay-Sachs (no hepatosplenomegaly) vs. Niemann-Pick (massive hepatosplenomegaly).
- **Corneal Cloulding DDx:** Hurler (MPS I - present) vs. Hunter (MPS II - absent).
- **GSD I vs GSD III:** GSD I has lactic acidosis and hyperuricemia; GSD III has normal lactate and elevated CK.

- **Pompe Disease (GSD II):** The only GSD that is also an LSD; classic triad of cardiomegaly, hypotonia, and normal blood glucose. ERT is life-saving.

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5. Write short notes on disorders of intermediary metabolism, including amino acid disorders, organic acidemias, and urea cycle disorders.

Subject: Important Questions

Overview

- **Definition:** Inborn errors of metabolism (IEMs) involving enzymatic defects in the breakdown of dietary proteins (amino acids), leading to accumulation of toxic metabolites.
- **Pathophysiology:** "Intoxication" type IEMs. Characterized by a symptom-free interval (hours to days) followed by acute clinical deterioration upon protein feeding or catabolic stress (infection, fasting).
- **Inheritance:** Autosomal Recessive (AR), except Ornithine Transcarbamylase (OTC) deficiency (X-linked recessive).

General Clinical Features

- **Neonatal presentation:** Lethargy, poor feeding, intractable vomiting, tachypnea, seizures, coma.
- **Late-onset:** Recurrent vomiting, ataxia, psychiatric symptoms, developmental delay, protein avoidance.
- **Classic odors:**
    - Musty/mousy: Phenylketonuria (PKU)
    - Burnt sugar/maple syrup: Maple Syrup Urine Disease (MSUD)
    - Sweaty feet: Isovaleric acidemia (IVA)
    - Boiled cabbage: Tyrosinemia type 1

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1. Amino Acid Disorders (Aminoacidopathies)

- **Mechanism:** Defect in initial steps of amino acid breakdown. Toxins remain in the form of amino acids.
- **Key Disorders:**
    - **PKU:** Phenylalanine hydroxylase defect. Causes irreversible intellectual disability, microcephaly, hypopigmentation.
    - **MSUD:** Branched-chain alpha-keto acid dehydrogenase (BCKAD) defect. Accumulation of Leucine (neurotoxic), Isoleucine, Valine.
    - **Tyrosinemia Type 1:** Fumarylacetoacetate hydrolase defect. Causes severe liver failure, renal tubular acidosis (Fanconi), rickets, hepatocellular carcinoma.
- **Lab Profile:** Normal ammonia, normal acid-base (except MSUD which has ketosis/acidosis), normal glucose.
- **Diagnosis:** Plasma amino acids (elevated specific AAs).

2. Organic Acidemias (OAs)

- **Mechanism:** Defect in downstream pathways of amino acid (VOMIT: Valine, Odd-chain fatty acids, Methionine, Isoleucine, Threonine) breakdown.
- **Key Disorders:** Methylmalonic acidemia (MMA), Propionic acidemia (PA), Isovaleric acidemia (IVA).
- **Lab Profile (Classic Exam Triad):**
    - High Anion Gap Metabolic Acidosis (severe)
    - Hyperammonemia (secondary, inhibits urea cycle)
    - Hypoglycemia & Ketonuria
- **Other findings:** Bone marrow suppression (neutropenia, thrombocytopenia).
- **Diagnosis:** Urine organic acids via GC-MS (Gas Chromatography-Mass Spectrometry).

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3. Urea Cycle Disorders (UCDs)

- **Mechanism:** Defect in nitrogen detoxification pathway, preventing conversion of ammonia to urea.
- **Key Disorders:** OTC deficiency (most common), Citrullinemia, Argininosuccinic aciduria (ASA).
- **Lab Profile:**
    - Severe Hyperammonemia (often >1000 µmol/L)
    - Respiratory Alkalosis (ammonia directly stimulates respiratory center)
    - Normal blood glucose, absent/trace ketones
- **Diagnosis:** Plasma amino acids (high glutamine/alanine, low arginine), Urine orotic acid (High in OTC deficiency, low in CPS1/NAGS deficiency).

Diagnostic Approach (The "Metabolic Crash" Algorithm)

- **Step 1:** Check Blood Gas, Ammonia, Glucose, and Urine Ketones.
- **Step 2 (Interpretation):**
    - *Acidosis + Ketosis + Normal NH3:* MSUD or Carbohydrate defect.
    - *Acidosis + Ketosis + High NH3:* Organic Acidemia (MMA, PA, IVA).
    - *Alkalosis + No Ketosis + Very High NH3:* Urea Cycle Disorder.
- **Step 3 (Confirmatory):**
    - Tandem Mass Spectrometry (TMS) for acylcarnitine profile & amino acids.
    - GC-MS for urine organic acids.
    - Genetic testing (gold standard).

Management

- **Acute Crisis (Stop Catabolism & Toxin Removal):**
  - **NPO:** Immediately stop all enteral protein intake (max 24-48 hours).
  - **Anabolism:** IV D10W or D12.5W with high GIR (Glucose Infusion Rate: 8–10 mg/kg/min) + Intralipids to stop endogenous protein breakdown.
  - **Ammonia Scavengers:** IV Sodium benzoate, Sodium phenylacetate, L-arginine (except in arginase deficiency).
  - **Dialysis:** Continuous Renal Replacement Therapy (CRRT) or Hemodialysis if Ammonia > 500 µmol/L or rapidly rising.
  - **Cofactor Cocktails:** Thiamine (MSUD), Biotin (PA), Vitamin B12 (MMA), Pyridoxine.
- **Chronic Maintenance:**
  - Dietary protein restriction + special medical formulas (amino acid mixtures lacking the offending precursor).
  - Liver transplantation (curative for severe UCDs, Tyrosinemia, severe OAs).
  - *Tyrosinemia specific:* Nitisinone (NTBC) prevents toxic succinylacetone formation.

Complications & Prognosis

- **Acute:** Cerebral edema (ammonia toxicity), herniation, death.
- **Chronic:** Intellectual disability, movement disorders (chorea/dystonia in OAs), chronic kidney disease (MMA), liver failure/HCC (Tyrosinemia).
- **Prognosis:** Depends heavily on rapid identification via Newborn Screening (NBS) and time to intervention during acute crises.

Exam Summary: Must-Write Points

- **UCDs:** Severe hyperammonemia + respiratory alkalosis + normal glucose. OTC is X-linked; urine orotic acid differentiates OTC from CPS1.
- **Organic Acidemias:** Hyperammonemia + high anion gap metabolic acidosis + ketonuria + hypoglycemia.
- **Aminoacidopathies:** Present with specific odors (PKU=musty, MSUD=burnt sugar); diagnosed via plasma amino acids.
- **First-line acute management:** Stop protein, start high-glucose IV fluids (push anabolism), give ammonia scavengers (benzoate/phenylacetate).
- **Absolute indication for dialysis:** Ammonia > 500 µmol/L or neurologic deterioration despite medical therapy.

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6. Write short notes on energy metabolism disorders, including fatty acid oxidation defects, mitochondrial disorders, and carbohydrate metabolism disorders (e.g., galactosemia, fructose disorders).

Energy Metabolism Disorders: Overview

- **Definition:** Inborn errors of metabolism (IEMs) characterized by defective ATP production.
- **Target Organs:** Primarily affect tissues with high energy demand (brain, skeletal muscle, heart, liver).
- **Shared Triggers:** Fasting, intercurrent illness, fever, or specific dietary intake.

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1. Fatty Acid Oxidation Defects (FAODs)

- **Etiology:** Autosomal Recessive (AR). Most common is Medium-Chain Acyl-CoA Dehydrogenase Deficiency (MCADD).
- **Pathophysiology:** Inability to undergo β-oxidation during fasting → failure to produce ketones (alternative brain fuel) and impaired gluconeogenesis.
- **Clinical Features:**
    - **Classic triad:** Hypoglycemia, hepatomegaly, encephalopathy.
    - Precipitated by fasting or acute illness (e.g., gastroenteritis).
    - Mimics Reye syndrome or Sudden Infant Death Syndrome (SIDS).
    - Cardiomyopathy and myopathy (more common in VLCADD/LCHADD).
- **Diagnosis:**
    - **Metabolic hallmark: Non-ketotic hypoglycemia** (low glucose, absent/trace urine ketones).
    - **Screening:** Tandem Mass Spectrometry (TMS) on newborn dried blood spot.
    - **Acylcarnitine profile:** Elevated C8, C8:1, C10:1 (diagnostic for MCADD).
    - **Urine organic acids:** Dicarboxylic aciduria (without ketones).
- **Management:**
    - **Acute:** Immediate IV 10% Dextrose (bolus + maintenance) to stop catabolism.
    - **Prevention: Strict avoidance of fasting**. Frequent feeds.
    - **Diet:** High-carbohydrate, low-fat diet. MCT (medium-chain triglyceride) oil supplementation is *contraindicated* in MCADD, but used in VLCADD.
    - **Supplements:** L-carnitine (controversial, but often used to clear toxic acyl-CoAs).

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2. Mitochondrial Disorders

- **Etiology:** Mutations in mitochondrial DNA (maternal inheritance) or nuclear DNA (AR/AD). Defective Oxidative Phosphorylation (OXPHOS).
- **Classic Syndromes:**
    - **MELAS:** Mitochondrial Encephalomyopathy, Lactic Acidosis, Stroke-like episodes.
    - **MERRF:** Myoclonic Epilepsy with Ragged Red Fibers.

- **Leigh Syndrome:** Subacute necrotizing encephalomyelopathy.

- **Clinical Features:**
  - Multisystemic, progressive course.
  - **Neuro:** Encephalopathy, intractable seizures, developmental regression, hypotonia.
  - **Muscular:** Myopathy, exercise intolerance, ptosis, progressive external ophthalmoplegia (PEO).
  - **Other:** Sensorineural hearing loss, hypertrophic cardiomyopathy, diabetes mellitus.
- **Diagnosis:**
  - **Biomarkers:** Lactic acidosis, elevated Lactate:Pyruvate ratio (>20:1).
  - **Muscle Biopsy: Ragged red fibers** (Gomori trichrome stain).
  - **Neuroimaging (MRI):** Bilateral symmetric basal ganglia/brainstem lesions (Leigh syndrome); stroke-like lesions non-conforming to vascular territories (MELAS).
  - **Genetics:** Next-Generation Sequencing (NGS) panel for mtDNA and nDNA (Current Gold Standard).
- **Management:**
  - **Supportive:** No definitive cure.
  - **"Mito Cocktail":** Coenzyme Q10 (Ubiquinone), Riboflavin, L-carnitine, Thiamine, Vitamins C & E.
  - **Red Flag: Avoid Valproate** (causes fatal acute liver failure, especially in *POLG* mutations).

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3. Carbohydrate Metabolism Disorders

A. Classic Galactosemia

- **Etiology:** AR; severe deficiency of Galactose-1-Phosphate Uridyltransferase (GALT).
- **Pathophysiology:** Accumulation of toxic Galactose-1-Phosphate and galactitol (causes cataracts).
- **Clinical Features:**
  - Onset in first week of life after starting milk feeds (breast milk or cow's milk formula).
  - Vomiting, lethargy, jaundice, hepatomegaly, bleeding diathesis.
  - **Cataracts:** "Oil-drop" cataracts (can appear within days).
  - **Complication:** Extremely high risk of ***E. coli* sepsis**.
  - **Long-term:** Premature ovarian insufficiency (POI) in females, learning disabilities, speech apraxia (even with strict diet).
- **Diagnosis:**
  - Urine: Positive for non-glucose reducing substances (Clinitest positive, Dipstick negative).

- **Confirmatory:** Beutler test (absent GALT enzyme activity in RBCs).

- **Management:**
  - Lifelong, strict galactose-free diet.
  - Immediate switch to **Soy-based formula**.

B. Hereditary Fructose Intolerance (HFI)

- **Etiology:** AR; deficiency of **Aldolase B**.
- **Clinical Features:**
  - Asymptomatic while exclusively breastfeeding.
  - Onset occurs at **weaning** (around 4-6 months) when fruits, juices, or sweetened foods are introduced.
  - Severe post-prandial hypoglycemia, vomiting, jaundice, hepatomegaly.
- **Diagnosis:**
  - Molecular genetic testing for Aldolase B gene mutations.
  - *Previously:* Fructose tolerance test (now obsolete/dangerous due to risk of fatal hypoglycemia).
- **Management:** Complete dietary elimination of fructose, sucrose, and sorbitol.

Exam Summary (Must-Write Points)

- **FAODs (MCADD):** Presents with *non-ketotic hypoglycemia* during fasting/illness. Diagnose via TMS acylcarnitine profile. Treatment is strict avoidance of fasting + IV dextrose in crisis.
- **Mitochondrial:** Multisystemic (brain/muscle/heart). Look for *lactic acidosis* and *ragged red fibers*. Avoid valproate.
- **Galactosemia:** Onset with *milk feeds*. Triad: Liver failure, cataracts, *E. coli* sepsis. Diagnose via absent RBC GALT activity. Treat with soy formula.
- **Fructose Intolerance:** Onset delayed until *weaning* (fruit/juice introduction). Causes hypoglycemia and hepatomegaly. Treat via fructose/sucrose elimination.

Cardiology

139. Heart failure management general and recent concepts

Subject: Cardiology

Definition

- Clinical syndrome where the heart cannot pump sufficient blood to meet the metabolic demands of the body, or does so only at elevated filling pressures.

Etiology

- **Neonates:** Obstructive lesions (Coarctation, HLHS, AS), severe AV valve regurgitation, ALCAPA, arrhythmias (SVT, congenital heart block).
- **Infants:** Large L-to-R shunts (VSD, PDA, AVSD).
- **Children/Adolescents:** Acquired (Rheumatic heart disease, myocarditis, Kawasaki disease), Cardiomyopathies (Dilated, Hypertrophic, Restrictive), anthracycline toxicity.

Clinical Features & Grading

- **Infants:** Feeding difficulty (prolonged feeds >30 mins), diaphoresis during feeds, failure to thrive (FTT), unexplained tachycardia/tachypnea.
- **Older Children:** Exercise intolerance, fatigue, orthopnea, dependent edema.
- **Signs:** Tachycardia, gallop rhythm (S3), hepatomegaly (most reliable sign of systemic venous congestion in infants), cardiomegaly, crackles (late sign in peds).
- **Modified Ross Classification:**
    - **Class I:** Asymptomatic.
    - **Class II:** Mild tachypnea/diaphoresis with feeds (infants) or exertion (older); no growth failure.
    - **Class III:** Marked tachypnea/diaphoresis with feeds; prolonged feeding time; growth failure.
    - **Class IV:** Symptoms at rest (tachypnea, retractions, grunting, diaphoresis).

Diagnosis

- **CXR:** Cardiomegaly (Cardiothoracic ratio >0.6 in neonates, >0.5 in children), pulmonary venous congestion, pleural effusion.
- **ECG:** Chamber enlargement, arrhythmias, ischemia (q waves in ALCAPA), low voltage (myocarditis).
- **Echocardiography (Gold Standard):** Assesses anatomy, LV ejection fraction (LVEF), fractional shortening (FS), diastolic function, and valve competency.
- **Biomarkers:** BNP and NT-proBNP (excellent for diagnosis, prognosis, and monitoring response to therapy).

Acute Management (Decompensated HF)

- **Position & O2:** Propped up position; judicious O2 (Avoid hyperoxia in duct-dependent systemic circulation or large L-to-R shunts as it drops PVR and worsens pulmonary flooding).
- **Diuretics:** IV Furosemide (1–2 mg/kg/dose). Add Thiazide (Chlorothiazide) for sequential nephron blockade if refractory.
- **Inotropes/Inodilators:**
    - **Milrinone:** PDE-3 inhibitor (inodilator). First-line for low cardiac output with high systemic vascular resistance (SVR).
    - **Dobutamine:** Beta-1 agonist. Used if hypotensive.
    - **Epinephrine:** For severe cardiogenic shock (increases both contractility and SVR).

- **Respiratory Support:** CPAP/BiPAP decreases work of breathing and reduces LV afterload.
- **Red Flag:** Do NOT initiate or up-titrate Beta-blockers during acute decompensation.

Chronic Management (Standard Therapy)

- **ACE Inhibitors:** Enalapril, Captopril. Reduces afterload and prevents maladaptive remodeling. Monitor BP, K+, and creatinine.
- **Beta-Blockers:** Carvedilol (non-selective β + $\alpha_1$blockade), Metoprolol. Reverses sympathetic overdrive. Start "low and go slow" only in stable patients.
- **Mineralocorticoid Receptor Antagonists (MRA):** Spironolactone. Prevents myocardial fibrosis; potassium-sparing.
- **Oral Diuretics:** Furosemide (lowest effective dose to maintain euvolemia).

Recent Concepts & Advances (Highly Tested)

- **ARNI (Sacubitril/Valsartan):**
  - *Update (FDA 2019 / PANORAMA-HF Trial):* Approved for symptomatic HF with systemic LV systolic dysfunction in children ≥1 year.
  - *Mechanism:* Neprilysin inhibitor (increases beneficial natriuretic peptides) + ARB.
  - *Trap:* Requires a 36-hour washout period when switching from an ACE inhibitor to prevent severe angioedema.
- **Ivabradine:**
  - *Update (FDA 2019):* Approved for children ≥6 months with stable, symptomatic HF (LVEF $\le$ 45%) and elevated resting heart rate.
  - *Mechanism:* Selective I_f channel inhibitor in the SA node. Prolongs diastole (improves coronary perfusion) without negative inotropy.
- **SGLT2 Inhibitors (Dapagliflozin / Empagliflozin):**
  - Currently standard of care in adult HFrEF/HFpEF. Off-label use increasing in older pediatric/adolescent patients with refractory HF or syndromic cardiomyopathies (e.g., Duchenne).
- **Biomarker-Guided Therapy:** Serial NT-proBNP profiling to titrate ARNI and Beta-blocker doses, rather than relying solely on clinical symptoms.

Device Therapy & Surgery

- **Cardiac Resynchronization Therapy (CRT):** Biventricular pacing indicated for severe HF with LVEF $\le$ 35% and prolonged QRS (LBBB morphology).
- **Mechanical Circulatory Support (MCS):**
  - *ECMO:* Short-term bridge to recovery or decision.
  - *VADs:* Berlin Heart EXCOR (pulsatile, for infants/small children), HeartMate 3 (continuous flow, older children). Bridge to transplant.
- **Heart Transplantation:** Definitive therapy for end-stage, refractory heart failure.

Exam Summary

- **Modified Ross Criteria:** Essential for grading pediatric HF severity and guiding therapy.
- **Hepatomegaly & Feeding Diaphoresis:** Classic, earliest signs of right and left heart failure in infants.
- **Milrinone:** Drug of choice for acute pediatric cardiogenic shock/low-output states (inodilator).
- **ARNI (Sacubitril/Valsartan):** Now preferred over ACEi for chronic HFrEF in kids ≥1 year; requires 36h ACEi washout.
- **Ivabradine:** Lowers HR without dropping contractility; approved for peds ≥6 months.

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140. Superior vena cava syndrome

Subject: Cardiology

Definition

- Clinical constellation resulting from obstruction of blood flow through the superior vena cava (SVC).
- **Superior Mediastinal Syndrome (SMS):** Frequently co-exists in pediatrics; involves concurrent compression of the highly compressible pediatric trachea/airway.

Etiology

- **Malignancy (Most Common):**
    - Non-Hodgkin Lymphoma (especially T-cell lymphoblastic lymphoma).
    - Acute Lymphoblastic Leukemia (T-ALL).
    - Hodgkin Lymphoma.
    - Solid tumors: Neuroblastoma, Germ cell tumors, Sarcomas.
- **Benign/Iatrogenic (Increasing Incidence):**
    - Central Venous Catheter (CVC) related thrombosis (common in NICU/PICU/Oncology).
    - Post-cardiac surgery (e.g., Glenn shunt, Mustard/Senning procedures, pacemaker leads).
    - Mediastinal infections (fibrosing mediastinitis - rare).

Pathophysiology

- SVC compression/thrombosis ⇒severely impaired venous return from head, neck, and upper extremities.
- Increased venous hydrostatic pressure ⇒extravasation of fluid.
- Leads to cerebral edema, laryngeal/tracheal edema, and decreased cardiac preload (low cardiac output).
- Gradual occlusion allows collateral vessel formation (azygos system); rapid occlusion causes severe, acute symptoms.

Clinical Features

- **Classic Triad:** Edema of face/neck, cyanosis/plethora, distended neck/chest veins.

- **Respiratory (SMS overlap):** Cough, hoarseness, stridor, orthopnea, dyspnea (worse when supine).
- **Neurological:** Headache, visual changes, altered sensorium, syncope (due to cerebral edema/elevated ICP).
- **Signs:**
    - Conjunctival suffusion/edema.
    - Pemberton sign: Facial flushing/cyanosis and respiratory distress upon raising both arms above the head.

Diagnosis

- *Red Flag:* **Avoid sedation and supine positioning** during imaging; loss of airway muscle tone can cause fatal airway collapse.
- **Imaging:**
    - **CXR:** Widened mediastinum, pleural effusion, tracheal deviation/compression.
    - **Echocardiography:** Detects SVC thrombus, evaluates right heart function and cardiac tamponade (often co-exists).
    - **CT Chest with IV Contrast:** *Gold standard*. Defines site of obstruction, tumor size, airway caliber, and collaterals.
    - **Doppler USG:** Excellent for detecting CVC-related jugular/subclavian/SVC thrombosis.
- **Tissue Diagnosis (for malignancies):**
    - *Rule:* Choose the least invasive method to avoid general anesthesia.
    - Peripheral lymph node biopsy, pleural fluid cytology, or bone marrow aspiration (under local anesthesia/mild sedation).

Management

- **Immediate Supportive Care:**
    - **Positioning:** Elevate head of bed (HOB) to 30–45 degrees.
    - **Airway:** Keep child calm (crying worsens venous pressure); provide supplemental O2.
    - **IV Access:** Place IV lines in *lower extremities only* (upper extremity fluids will not reach the heart and will worsen edema).
    - **Fluid Management:** Restrict fluids; cautious use of diuretics (avoid hypovolemia as preload is already compromised).
- **Definitive Medical Therapy:**
    - **Malignancy-induced:** Empiric corticosteroids (e.g., Dexamethasone/Methylprednisolone) and/or emergency local radiation if life-threatening airway compromise occurs (Note: *May obscure future tissue diagnosis, but life-saving*).
    - **Thrombosis-induced:** Systemic anticoagulation (LMWH or Unfractionated Heparin). Thrombolysis (tPA) for acute, severe, life-threatening clots.

- **Surgical/Interventional:**
    - Endovascular stenting/balloon angioplasty (useful for post-cardiac surgery strictures or refractory thrombosis).
    - ECMO standby: Required for high-risk patients needing intubation/general anesthesia.

Complications

- Fatal airway obstruction (most immediate threat).
- Cardiovascular collapse (due to severely reduced venous return or during induction of anesthesia).
- Cerebral herniation secondary to severe cerebral venous congestion.
- Post-thrombotic syndrome.

Prognosis

- Depends heavily on the etiology. Malignancy-related SVC syndrome responds rapidly (within 24-48 hours) to chemotherapy/steroids.
- Thrombotic SVC syndrome has a good survival rate but carries a risk of chronic venous insufficiency.

Exam Summary

- **Must-Write:** Elevate HOB, place IVs in lower limbs, avoid supine position/sedation.
- **Top Causes:** T-cell Lymphoma/Leukemia (malignant) and CVC thrombosis (benign).
- **Diagnostic Trap:** Tissue diagnosis is essential for oncology protocols, but never risk general anesthesia if the airway is compromised; use steroids/radiation empirically if the patient is crashing.
- **Key finding:** Facial plethora + distended chest veins + orthopnea.

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141. Congenital obstructive heart disease

Subject: Cardiology

Definition & Classification

- Acyanotic congenital heart defects characterized by mechanical obstruction to ventricular outflow.
- **Left-sided outflow tract obstruction (LVOTO):** Aortic Stenosis (AS), Coarctation of Aorta (CoA), Interrupted Aortic Arch (IAA), Hypoplastic Left Heart Syndrome (HLHS).
- **Right-sided outflow tract obstruction (RVOTO):** Pulmonary Stenosis (PS).
- **Anatomic levels:** Valvular (most common), Subvalvular, Supravalvular.

Etiology & Syndromic Associations

- **Turner syndrome (45,XO):** Bicuspid aortic valve (most common), CoA.
- **Noonan syndrome:** Dysplastic pulmonary valve (PS).
- **Williams syndrome:** Supravalvular AS (associated with elastin gene microdeletion).

- **Congenital Rubella Syndrome:** Peripheral pulmonary artery stenosis.
- **DiGeorge syndrome (22q11.2):** Interrupted aortic arch.
- **Maternal Diabetes:** Hypertrophic cardiomyopathy with dynamic subaortic obstruction.

Pathophysiology

- **Mechanism:** Fixed outflow obstruction → Ventricular pressure overload → Concentric ventricular hypertrophy.
- **Myocardial mismatch:** Increased muscle mass + high cavity pressure → Increased oxygen demand + decreased subendocardial perfusion → Ischemia.
- **Progression:** Diastolic dysfunction (stiff ventricle) precedes systolic failure.
- **Critical Obstruction (Neonates):** Severe lesions are "duct-dependent". Closure of the ductus arteriosus causes abrupt cardiogenic shock (LVOTO) or profound cyanosis (RVOTO).

Clinical Features

- **Mild-to-Moderate:** Often asymptomatic; incidental murmur detection.
- **Severe AS:** Exertional triad (angina, syncope, dyspnea). High risk of sudden cardiac death.
- **Severe PS:** Exertional dyspnea, signs of right heart failure (hepatomegaly, edema).
- **Coarctation of Aorta:** Weak/absent femoral pulses, radio-femoral delay, upper limb hypertension, lower limb claudication.
- **Auscultation (AS):** Ejection systolic murmur (ESM) at right upper sternal border radiating to carotids. Constant ejection click. Paradoxical split S2.
- **Auscultation (PS):** ESM at left upper sternal border radiating to the back. Ejection click that *decreases* with inspiration. Wide split S2.
- **Pulses:** *Pulsus parvus et tardus* (weak and delayed) in severe AS.

Diagnosis

- **ECG:**
    - AS/CoA: LVH with "strain" pattern (ST depression/T wave inversion in left leads).
    - PS: RVH, right axis deviation.
- **Chest X-Ray (CXR):**
    - Heart size often normal until late failure.
    - AS: Post-stenotic dilatation of ascending aorta.
    - PS: Prominent main pulmonary artery segment.
    - CoA: "Figure of 3" sign (aortic indentation) and inferior rib notching (collaterals, seen >5 years of age).
- **Echocardiography (Gold Standard):** Defines anatomy, measures peak and mean transvalvular pressure gradients via continuous-wave Doppler, evaluates ventricular function.
- **Cardiac MRI:** Modality of choice for complex aortic arch anomalies (CoA, IAA) in older children.

Management

- **Neonatal Resuscitation (Critical Lesions):**
  - **Prostaglandin E1 (Alprostadil):** Continuous IV infusion (0.01–0.1 mcg/kg/min) to maintain ductal patency.
  - Inotropic support and cautious diuresis for heart failure.
- **Interventional Cardiology (First-line for many):**
  - **Balloon Valvuloplasty:** Treatment of choice for classic valvular PS and typical congenital valvular AS.
  - **Balloon Angioplasty ± Stenting:** Preferred for recurrent CoA or primary CoA in older children.
- **Surgical Interventions:**
  - **AS:** Surgical valvotomy, Ross procedure (pulmonary autograft to aortic position), or valve replacement.
  - **Sub/Supravalvular AS:** Requires surgical resection/patch augmentation (balloon is ineffective).
  - **CoA:** Resection with end-to-end anastomosis (preferred in infants).
- **Infective Endocarditis (IE) Prophylaxis:**
  - *AHA/IAP Update:* Routine prophylaxis is **no longer** recommended for isolated native AS/PS or bicuspid aortic valve.
  - Indicated only if: prosthetic valve, prior history of IE, or unrepaired cyanotic defect.

Complications

- Sudden cardiac death (especially severe AS during exertion).
- Congestive heart failure.
- Infective endocarditis.
- Post-intervention valvular regurgitation (common after balloon valvuloplasty).

Prognosis

- Excellent with timely relief of obstruction.
- Lifelong cardiology follow-up is mandatory due to high rates of restenosis or iatrogenic valvular regurgitation requiring future valve replacement.

Exam Summary

- **Williams syndrome** = Supravalvular AS; **Turner syndrome** = Bicuspid aortic valve/CoA; **Noonan syndrome** = Dysplastic PS.
- **Critical neonatal obstructions** present as shock upon ductal closure; immediately start **IV Prostaglandin E1**.
- **Severe AS** triad: Exertional angina, syncope, dyspnea. Risk of sudden death.
- **Balloon valvuloplasty** is the first-line treatment for typical valvular AS and PS.

- **Subvalvular and Supravalvular** obstructions do NOT respond to ballooning; require surgery.

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142. Important cyanotic congenital heart diseases in infants, diagnosis and management

Subject: Cardiology

Classification of Cyanotic Congenital Heart Diseases (CCHD)

- **Decreased Pulmonary Blood Flow (Oligemic lungs):**
  - Tetralogy of Fallot (TOF) – Most common overall CCHD.
  - Tricuspid Atresia (TA).
  - Pulmonary Atresia (PA).
  - Ebstein Anomaly.
- **Increased Pulmonary Blood Flow (Plethoric lungs):**
  - Transposition of the Great Arteries (TGA) – Most common neonatal CCHD.
  - Total Anomalous Pulmonary Venous Return (TAPVR).
  - Truncus Arteriosus.
  - Hypoplastic Left Heart Syndrome (HLHS).

Core Pathophysiology

- **Right-to-Left Shunt:** Deoxygenated systemic venous blood bypasses the lungs and enters the systemic circulation.
- **Ductal Dependency:** Many neonatal CCHDs rely on a Patent Ductus Arteriosus (PDA) for either pulmonary blood flow (e.g., severe TOF, PA) or systemic blood flow (e.g., HLHS) to survive.

Clinical Features

- **Central Cyanosis:** Bluish discoloration of tongue/mucous membranes; does not improve significantly with crying or 100% oxygen.
- **Hypercyanotic (Tet) Spells:** Sudden worsening of cyanosis, hyperpnea, irritability; common in TOF (peak age 2–4 months) due to infundibular spasm.
- **Chronic Signs:** Clubbing (appears >6 months of age), exertional dyspnea, squatting equivalent (infants drawing legs up).
- **Systemic Effects:** Secondary polycythemia, poor weight gain, failure to thrive.

Diagnosis

- **Pulse Oximetry Screening (AAP Guideline):** Done at 24–48 hours of life.
  - *Positive (Fail) Screen:* SpO2 <90% in either extremity, OR SpO2 <95% in both right hand/foot on 3 separate measures, OR >3% absolute difference between pre-ductal (right hand) and post-ductal (foot).
- **Hyperoxia Test:** Differentiates cardiac vs. pulmonary cyanosis.
  - Administer 100% FiO2 for 10 minutes.

- *Cardiac (CCHD):* PaO2 remains <150 mmHg (fixed right-to-left shunt).
- *Pulmonary/CNS:* PaO2 rises >150 mmHg.

- **Chest X-Ray (Classic Buzzwords):**
  - *TOF:* Boot-shaped heart (Coeur en sabot) + oligemic lungs.
  - *TGA:* Egg-on-a-string appearance + plethoric lungs.
  - *TAPVR:* Snowman sign / Figure-of-8 (usually seen >4 months).
- **ECG Findings:**
  - *RVH/RAD:* Normal in neonates, but extreme in TOF, TGA.
  - *LVH/LAD in a cyanotic infant:* Highly specific trap for **Tricuspid Atresia**.
- **Echocardiography:** Gold standard. Defines anatomy, shunt direction, and pressure gradients.

Acute Medical Management

- **Maintain Ductal Patency:** IV Prostaglandin E1 (Alprostadil).
  - *Dose:* 0.01 to 0.05 mcg/kg/min continuous infusion.
  - *Red Flag:* Apnea is a common side effect; secure airway/intubate if necessary.
- **Tet Spell Management (Stepwise):**

1. Knee-chest position (increases systemic vascular resistance [SVR]).
2. 100% Oxygen (pulmonary vasodilator).
3. IV/SC Morphine (0.1 mg/kg) to reduce respiratory drive/infundibular spasm.
4. IV Fluid bolus (10-20 ml/kg) to increase RV preload.
5. IV Beta-blockers (Propranolol or Esmolol) to relax RV outflow tract.
6. IV Phenylephrine (increases SVR to reverse right-to-left shunt).
   - *Contraindication:* Avoid Digoxin and inotropes (worsen infundibular spasm).

Surgical Management

- **Palliative Procedures (Bridge to definitive):**
  - *Balloon Atrial Septostomy (Rashkind):* Emergency for TGA with poor mixing.
  - *Modified Blalock-Taussig-Thomas (BTT) Shunt:* Subclavian artery to pulmonary artery (increases pulmonary blood flow in TOF/PA).
- **Definitive Repair Timelines:**
  - *TGA:* Arterial Switch Operation (ASO) – ideally within the first 2-3 weeks of life.
  - *TOF:* Complete intracardiac repair (VSD closure + RVOT relief) – usually at 3–6 months.

Complications & Prevention

- **Neurological:** Brain abscess (common >2 years due to bypassing pulmonary phagocytes), stroke (due to hyperviscosity/polycythemia).

- **Cardiac:** Heart failure, arrhythmias, infective endocarditis (IE).
- **IE Prophylaxis (IAP/AHA Guidelines):** Required for all *unrepaired* cyanotic CHDs, and for 6 months post-complete repair with prosthetic material. Use Amoxicillin 50 mg/kg 1 hour before dental procedures.

Exam Summary: High-Yield Must-Write Points

- **TGA** is the most common CCHD in *neonates*; **TOF** is the most common CCHD *overall*.
- Cyanosis + LVH on ECG = **Tricuspid Atresia**.
- **Hyperoxia test** (PaO2 < 150 on 100% O2) confirms fixed right-to-left shunt.
- Start **IV Prostaglandin E1** immediately for any suspected duct-dependent lesion, but watch for apnea.
- **Tet spell triad:** Knee-chest position, Morphine, IV fluids (avoid inotropes).

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143. Important acyanotic congenital heart diseases in children, diagnosis and management

Subject: Cardiology

Classification of Acyanotic CHD

- **Left-to-Right (L→R) Shunts (Volume Overload):** Ventricular Septal Defect (VSD), Atrial Septal Defect (ASD), Patent Ductus Arteriosus (PDA), Atrioventricular Septal Defect (AVSD).
- **Obstructive Lesions (Pressure Overload):** Coarctation of Aorta (CoA), Aortic Stenosis (AS), Pulmonary Stenosis (PS).

Ventricular Septal Defect (VSD)

Most common congenital heart defect.

- **Types:** Perimembranous (80%, most common), Muscular (10-15%, highest spontaneous closure rate), Inlet, Outlet (supracristal).
- **Pathophysiology:** L→R shunt during systole → Left Atrial (LA) and Left Ventricular (LV) volume overload → Pulmonary overcirculation.
- **Clinical Features:**
    - *Small (Restrictive):* Asymptomatic. Harsh pansystolic murmur (PSM) at lower left sternal border (LLSB).
    - *Large (Unrestrictive):* Congestive heart failure (CHF) at 6–8 weeks (when pulmonary vascular resistance drops), failure to thrive (FTT), recurrent lower respiratory tract infections (LRTI).
    - *Signs:* Hyperdynamic precordium, PSM at LLSB, apical mid-diastolic murmur (MDM) indicates large shunt (relative mitral stenosis).
- **Diagnosis:**
    - *ECG:* LVH (moderate shunt) or Biventricular hypertrophy (large shunt).
    - *CXR:* Cardiomegaly (LA/LV enlargement), plethoric lung fields.

- *Echocardiography (Gold Standard):* Defines location, size, gradient, and estimates pulmonary artery pressure.

- **Management:**
  - *Medical:* Anti-failure medications (Furosemide, Enalapril/Captopril, Spironolactone), fortified high-calorie feeds (120–140 kcal/kg/day).
  - *Surgical (Patch Closure):*
    - Indications: Uncontrolled CHF, FTT, severe pulmonary arterial hypertension (PAH).
    - Timing: Usually 3–6 months if symptomatic; earlier if uncontrolled.

Atrial Septal Defect (ASD)

- **Types:** Ostium Secundum (70%, most common), Ostium Primum (associated with Down syndrome/AVSD), Sinus Venosus (associated with anomalous pulmonary venous return).
- **Pathophysiology:** L→R shunt → Right Atrial (RA) and Right Ventricular (RV) volume overload.
- **Clinical Features:**
  - Mostly asymptomatic in childhood; discovered incidentally.
  - Wide, fixed split S2 (hallmark).
  - Ejection systolic murmur (ESM) at left upper sternal border (relative pulmonary stenosis).
  - MDM at lower left sternal border in large shunts (relative tricuspid stenosis).
- **Diagnosis:**
  - *ECG:* Right axis deviation (RAD), incomplete RBBB (rsR' pattern). *Note:* Primum ASD shows Left axis deviation (LAD).
  - *CXR:* RV enlargement, prominent main pulmonary artery, increased pulmonary vascular markings.
  - *Echo:* Confirms defect and rules out anomalous veins.
- **Management:**
  - Elective closure (Device closure via cath or Surgical patch) at 3–5 years of age to prevent right heart failure/arrhythmias in adulthood.

Patent Ductus Arteriosus (PDA)

- **Pathophysiology:** Failure of ductus to close → Aorta to Pulmonary Artery shunt → LA/LV volume overload.
- **Clinical Features:**
  - Wide pulse pressure, bounding peripheral pulses.
  - Continuous "machinery" murmur at left infraclavicular area, peaking at S2.

- **Diagnosis:**
    - *ECG:* LVH.
    - *CXR:* Cardiomegaly, prominent aortic knob and pulmonary artery.
    - *Echo:* Visualizes ductus and measures shunt velocity.
- **Management:**
    - *Preterms:* Medical closure with Cyclooxygenase (COX) inhibitors (Indomethacin, Ibuprofen, or Paracetamol).
    - *Term infants/Older children:* Medical closure is ineffective. Device closure (coils/amplatzer) or surgical ligation at 6–12 months.

Coarctation of Aorta (CoA)

- **Pathophysiology:** Narrowing of descending aorta (usually juxtaductal) → LV pressure overload and decreased lower body perfusion. Associated with Turner syndrome and Bicuspid Aortic Valve.
- **Clinical Features:**
    - *Neonates:* Severe heart failure/shock when ductus closes (duct-dependent systemic circulation).
    - *Older children:* Upper extremity hypertension, claudication, headache.
    - Radio-femoral delay; weak or absent femoral pulses.
- **Diagnosis:**
    - *BP:* >10–20 mmHg systolic difference between upper and lower limbs.
    - *CXR:* "Figure of 3" sign (aortic indentation), rib notching (due to collateral intercostal arteries in older children).
    - *Echo:* Confirms gradient.
- **Management:**
    - *Neonates:* Prostaglandin E1 (PGE1 / Alprostadil) infusion to keep ductus open.
    - *Definitive:* Balloon angioplasty/stenting or Surgical resection with end-to-end anastomosis.

Complications of Acyanotic CHDs

- **Congestive Heart Failure (CHF):** Common in large VSD/PDA at 2 months of age.
- **Failure to Thrive (FTT):** Due to high metabolic demand and poor feeding.
- **Recurrent LRTI:** Due to boggy, wet lungs from pulmonary overcirculation.
- **Eisenmenger Syndrome:** Irreversible severe PAH causing shunt reversal (R→L), resulting in late-onset cyanosis. Contraindicates surgical closure.
- **Infective Endocarditis (IE):** High risk in VSD and PDA (jet lesions); rare in ASD.

Key Updates & Guidelines

- **AHA/AAP IE Prophylaxis Update:** Routine antibiotic prophylaxis is *no longer* recommended for isolated, unoperated VSD, ASD, or PDA. It is strictly reserved for:
    - Prosthetic cardiac valves/material.
    - Previous history of IE.
    - Repaired CHD with residual defects at or adjacent to the site of a prosthetic patch/device.
- **Neonatal Screening:** Routine pulse oximetry screening at 24-48 hours of life helps detect duct-dependent obstructive left heart lesions (like severe CoA) before catastrophic collapse.

Exam Summary

- **VSD:** Most common CHD. Pansystolic murmur. Apical MDM = Large shunt. Treat CHF medically; patch closure at 3-6 months if uncontrolled.
- **ASD:** Wide fixed split S2. Asymptomatic child. Elective closure at 3-5 years. Primum = LAD; Secundum = RAD.
- **PDA:** Bounding pulses, continuous machinery murmur. Preterms = NSAIDs. Terms = Device/Surgery.
- **CoA:** Weak femoral pulses, radio-femoral delay, upper extremity HTN. Rib notching on CXR. Give PGE1 in neonates.
- **Red Flag:** Do not surgically close a shunt if Eisenmenger syndrome (irreversible PAH) has developed.

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144. Evaluation of neonate with congenital heart disease and shock

Subject: Cardiology

Basics & Definition

- Neonatal shock due to Congenital Heart Disease (CHD) is almost exclusively **cardiogenic shock**.
- Typically presents in the first week of life (days 2–7) coinciding with the anatomical closure of the Patent Ductus Arteriosus (PDA).
- *Core Concept:* Results from **ductal-dependent systemic circulation** lesions.

Etiology

- **Left-sided obstructive lesions:**
    - Hypoplastic Left Heart Syndrome (HLHS)
    - Critical Aortic Stenosis (AS)
    - Severe Coarctation of the Aorta (CoA)
    - Interrupted Aortic Arch (IAA)

- *Myocardial dysfunction (Non-structural):* Myocarditis, ALCAPA (Anomalous Left Coronary Artery from Pulmonary Artery), severe arrhythmias (SVT, congenital heart block).

Pathophysiology

- In utero, right ventricle (RV) supplies systemic circulation via the PDA.
- Postnatally, systemic blood flow remains entirely dependent on Right-to-Left shunting across the PDA.
- As ductus constricts ⇒abrupt cessation of systemic cardiac output ⇒severe hypoperfusion ⇒anaerobic metabolism ⇒profound lactic acidosis ⇒cardiovascular collapse.

Clinical Features

- **Timing:** Sudden collapse in a previously "well" neonate discharged from the nursery (typically 48–96 hours of life).
- **Perfusion:** Profoundly delayed capillary refill time (>3 secs), ashen/grey/mottled skin.
- **Pulses:** Weak or absent. *Classic clue:* Absent femorals with bounding brachials = CoA/IAA; globally absent/weak pulses = HLHS/Critical AS.
- **Cardiac:** Tachycardia, gallop rhythm (S3), hepatomegaly (right heart failure).
- **Respiratory:** Tachypnea, grunting (due to pulmonary venous congestion and compensatory hyperventilation for acidosis).
- *Red Flag / Trap:* Frequently misdiagnosed as neonatal sepsis. Always suspect CHD in a neonate with shock unresponsive to initial fluid boluses.

Diagnosis

- **Pulse Oximetry (Pre/Post-ductal):** Right hand (pre-ductal) vs. either foot (post-ductal). Difference of >3% indicates right-to-left ductal shunting.
- **ABG/VBG:** Severe metabolic acidosis (pH < 7.1), elevated lactate, normal or slightly low PaO2.
- **Hyperoxia Test:** Administer 100% FiO2 for 10 mins. Failure of PaO2 to rise >150 mmHg confirms right-to-left shunt (structural CHD).
- **Chest X-Ray:** Cardiomegaly with pulmonary venous congestion (pulmonary edema).
- **ECG:** RV hypertrophy (normal for age, but lack of normal LV forces suggests HLHS). Evaluate for arrhythmias.
- **Echocardiography (Gold Standard):** Defines structural anatomy, assesses ventricular function, confirms ductal size and direction of shunt.

Management (Acute Stabilization)

- **Prostaglandin E1 (Alprostadil):** *Immediate life-saving intervention*.
    - *Dose:* Start at 0.05–0.1 mcg/kg/min IV/IO continuous infusion.
    - *Side effects:* **Apnea** (prepare for intubation), fever, hypotension, jitteriness.
- **Airway/Breathing:**
    - Elective intubation often required due to PGE1-induced apnea or severe shock.

- *Crucial Trap:* **Avoid Hyperoxia**. Oxygen is a potent pulmonary vasodilator. ↑ O2 ⇒↓Pulmonary Vascular Resistance (PVR) ⇒blood shunts to lungs ("pulmonary steal") ⇒worsens systemic shock.
- *Target SpO2:* Keep between **75–85%**.

- **Circulation:**
  - *Fluids:* Cautious 10 mL/kg bolus (over-resuscitation worsens pulmonary edema).
  - *Inotropes:* Milrinone (reduces afterload, improves diastolic function) and/or low-dose Epinephrine.
- **Metabolic:** Correct severe acidosis with sodium bicarbonate (if ventilation is adequate) to improve myocardial responsiveness to inotropes. Correct hypoglycemia and hypocalcemia.

Definitive Management

- Transfer to a pediatric cardiac ICU.
- **Surgical/Catheter Interventions:**
  - *HLHS:* Norwood procedure (Stage 1 palliation).
  - *Critical AS:* Balloon aortic valvuloplasty.
  - *CoA/IAA:* Surgical arch reconstruction.

Complications & Prognosis

- **Complications:** Multi-organ dysfunction syndrome (MODS), Acute Kidney Injury (AKI), Necrotizing Enterocolitis (NEC), hypoxic-ischemic brain injury.
- **Prognosis:** Without PGE1, mortality is 100%. With early recognition and surgery, 1-year survival for complex lesions (e.g., HLHS) is now 70–85%.
- **Prevention:** Fetal echocardiography (prenatal diagnosis allows planned delivery at a cardiac center); Universal newborn pulse oximetry screening at 24 hours of life.

Exam Summary: Must-Write Points

- Neonatal shock at day 2-7 = suspect ductal-dependent systemic lesion (HLHS, CoA, Critical AS).
- Always differentiate from sepsis; absent/differential pulses are the key clinical clue.
- **PGE1 infusion** (0.05–0.1 mcg/kg/min) is the immediate, life-saving step.
- **Avoid 100% Oxygen:** Keep SpO2 75-85% to balance systemic/pulmonary circulation (prevent pulmonary steal).
- **Echo** is the gold standard for definitive diagnosis. Be prepared to intubate for PGE1-induced apnea.

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145. Ebstein anomaly and Wolff Parkinson White syndrome

Subject: Cardiology

EBSTEIN ANOMALY

Definition

- Congenital heart defect characterized by apical (downward) displacement of the septal and posterior leaflets of the tricuspid valve (TV) into the right ventricle (RV).

Etiology & Associations

- Sporadic (most common).
- **Classic association:** Maternal Lithium exposure during the 1st trimester.
- **Genetic:** Rarely associated with *MYH7* mutations.

Pathophysiology

- Displacement divides the RV into two parts:
    1. "Atrialized" RV (structurally RV, functionally RA).
    2. Functional RV (small, hypoplastic).
- Leads to severe Tricuspid Regurgitation (TR).
- Elevated RA pressure causes Right-to-Left shunting across a Patent Foramen Ovale (PFO) or Atrial Septal Defect (ASD) → Cyanosis.

Clinical Features

- **Neonates (Severe):** Profound cyanosis, heart failure, duct-dependent pulmonary circulation.
- **Older Children (Mild):** Exertional dyspnea, fatigue, palpitations (arrhythmias).
- **Auscultation:**
    - "Triple/Quadruple rhythm" (widely split S1 and S2 + S3/S4 gallops).
    - Scratchy holosystolic murmur of TR at the lower left sternal border.

Diagnosis

- **CXR:** Massive cardiomegaly (classic **"wall-to-wall"** or balloon-shaped heart), decreased pulmonary vascular markings.
- **ECG:**
    - Massive Right Atrial Enlargement (**"Himalayan" P waves**).
    - Right Bundle Branch Block (RBBB) with low voltage.
    - Pre-excitation (WPW pattern).
- **Echocardiography (Diagnostic):** Apical displacement of the TV septal leaflet >8 mm/m^2 relative to the anterior mitral valve leaflet.

Management

- **Medical (Neonates):** Prostaglandin E1 (PGE1) to maintain ductal patency; inhaled Nitric Oxide (iNO) for pulmonary hypertension; anti-failure medications.
- **Surgical:**
    - **Current Standard: Cone Procedure** (Cone reconstruction of the TV using native leaflets).

- Severe RV hypoplasia: Single-ventricle palliation pathway (Glenn → Fontan).

WOLFF-PARKINSON-WHITE (WPW) SYNDROME

Definition

- A ventricular pre-excitation syndrome caused by an abnormal accessory electrical pathway (**Bundle of Kent**) bypassing the AV node.

Pathophysiology

- Electrical impulses travel down the accessory pathway faster than through the AV node → early ventricular depolarization (pre-excitation).
- Sets up a macro-reentrant circuit leading to Atrioventricular Reentrant Tachycardia (AVRT).

Clinical Features

- Often asymptomatic (ECG finding only).
- **Symptomatic:** Episodes of Supraventricular Tachycardia (SVT) causing palpitations, lightheadedness, syncope, or chest pain.
- **Rare/Fatal:** WPW with Atrial Fibrillation (AF) degenerating into Ventricular Fibrillation (VF) → Sudden Cardiac Death (SCD).

Diagnosis (Classic ECG Triad)

- **Short PR interval** (<0.12 seconds).
- **Delta wave** (slurred upstroke of the QRS complex).
- **Wide QRS complex** (>0.12 seconds).
- Secondary ST-T wave changes (discordant to QRS vector).

Management

- **Acute SVT (Orthodromic AVRT - narrow complex):**
  - 1st line: Vagal maneuvers (ice to face, Valsalva).
  - 2nd line: IV Adenosine (rapid push).
  - 3rd line: Synchronized DC cardioversion (if hemodynamically unstable).
- **WPW with Atrial Fibrillation (Wide complex, irregular):**
  - **Contraindicated:** AV nodal blockers (Adenosine, Digoxin, Verapamil, Diltiazem, beta-blockers) → *Trap: These block the AV node, forcing all conduction down the accessory pathway, causing VF.*
  - **Treatment:** IV Procainamide or immediate DC cardioversion.
- **Definitive Therapy:** Radiofrequency Ablation (RFA) of the accessory pathway (treatment of choice for symptomatic patients >5 years/15 kg).

THE ASSOCIATION: EBSTEIN ANOMALY + WPW SYNDROME

Key Exam Points

- Up to **20–30%** of patients with Ebstein anomaly have WPW syndrome.
- The accessory pathways are almost exclusively **right-sided** (right free wall or posteroseptal).
- **Multiple accessory pathways** are common in Ebstein patients (up to 50% of those with WPW).
- Tachyarrhythmias (SVT/AVRT) are a major cause of morbidity and sudden death in Ebstein anomaly.
- **Management overlap:** Electrophysiology (EP) study and RFA are routinely recommended prior to or during surgical repair (Cone procedure) of Ebstein anomaly.

EXAM SUMMARY

- **Ebstein classic triad:** Apically displaced TV, atrialized RV, severe TR.
- **Ebstein buzzwords:** Maternal Lithium, "wall-to-wall" heart, Himalayan P waves, Cone procedure.
- **WPW classic triad:** Short PR, Delta wave, Wide QRS via Bundle of Kent.
- **WPW Trap:** Never give AV nodal blockers (Verapamil/Digoxin) in WPW with Atrial Fibrillation.
- **The Link:** Ebstein anomaly has the highest congenital association with right-sided, often multiple, WPW accessory pathways.

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146. Evaluation of a child with hypertension and management

Subject: Cardiology

Definition & Staging (AAP 2017 Guidelines)

Children < 13 years:

- **Normal:** < 90th percentile
- **Elevated BP:** ≥ 90th to < 95th percentile (or 120/80 to < 95th percentile, whichever is lower)
- **Stage 1 HTN:** ≥ 95th percentile to < 95th percentile + 12 mmHg (or 130/80 to 139/89, whichever is lower)
- **Stage 2 HTN:** ≥ 95th percentile + 12 mmHg (or ≥ 140/90, whichever is lower)

Children ≥ 13 years:

- **Normal:** < 120/< 80 mmHg
- **Elevated BP:** 120–129 / < 80 mmHg
- **Stage 1 HTN:** 130–139 / 80–89 mmHg
- **Stage 2 HTN:** ≥ 140 / ≥ 90 mmHg

Etiology (Age-Dependent)

- **Neonates/Infants:** Renal artery thrombosis (umbilical artery catheterization), Coarctation of Aorta (CoA), Congenital renal anomalies.
- **1–6 years:** Renal parenchymal disease (most common secondary cause overall), Renovascular disease.
- **7–12 years:** Renal parenchymal disease, Primary (essential) hypertension.
- **Adolescents:** Primary hypertension (strongly linked to obesity), Drug-induced (NSAIDs, stimulants, OCPs, steroids).
- **Endocrine causes (any age):** Pheochromocytoma, Cushing syndrome, Congenital Adrenal Hyperplasia (11β-hydroxylase, 17α-hydroxylase deficiency), Hyperthyroidism.

Clinical Features

- **Symptoms:** Mostly asymptomatic. May present with headache, epistaxis, visual changes, dizziness, or declining school performance.
- **Severe/Emergency:** Seizures, encephalopathy, Bell's palsy, heart failure (especially in infants).
- **Clues to Secondary Causes:**
    - Weak/absent femoral pulses, radio-femoral delay (CoA)
    - Abdominal bruit (Renovascular HTN)
    - Ambiguous genitalia (CAH)
    - Café-au-lait spots, neurofibromas (NF-1 → renal artery stenosis, pheochromocytoma)
    - Elfin facies, hypercalcemia (Williams syndrome → aortic/renal stenosis)
    - Tachycardia, flushing, diaphoresis (Pheochromocytoma)

Evaluation & Diagnosis

1. BP Measurement Rules

- **Cuff size:** Bladder width must cover 40% of mid-arm circumference; length must cover 80–100%.
- Confirm elevated oscillometric readings with **auscultation** (mercury/aneroid).
- Measure in all 4 limbs if first-time HTN detected (to rule out CoA).

2. Ambulatory BP Monitoring (ABPM)

- **Gold standard** to confirm HTN, rule out "White Coat HTN", and detect "Masked HTN".
- Indicated for all children ≥ 5 years with elevated BP for > 1 year or Stage 1 HTN over 3 clinic visits.

3. Tier 1 Investigations (For all confirmed HTN)

- Urinalysis (protein, blood)
- Renal function tests (BUN, Creatinine) & Serum electrolytes
- Lipid profile & Fasting blood glucose (screen for metabolic syndrome)
- Renal ultrasonography (mandatory if < 6 years or abnormal UA/renal function)

4. Tier 2 Investigations (Targeted)

- **Echocardiography:** Mandatory to assess Target Organ Damage (Left Ventricular Hypertrophy - LVH) before starting medications.
- **Renal Doppler / CT/MR Angiography:** Suspected renovascular disease.
- **Plasma free metanephrines:** Suspected pheochromocytoma.
- **Polysomnography:** If Obstructive Sleep Apnea (OSA) is suspected (snoring, obesity).

Management

1. Non-Pharmacological (Lifestyle Modifications)

- Indicated for Elevated BP and initial management of Stage 1 HTN.
- **DASH Diet:** High fruits/vegetables, low fat, sodium restriction (< 1.5–2 g/day).
- Weight reduction (if BMI ≥ 85th percentile).
- Vigorous aerobic exercise (30–60 mins, 3–5 days/week) — *Contraindicated in Stage 2 HTN until BP is controlled*.

2. Indications for Pharmacotherapy

- Symptomatic hypertension
- Secondary hypertension
- Target Organ Damage (e.g., LVH, retinopathy, proteinuria)
- Stage 1 HTN failing 6 months of lifestyle modifications
- Stage 2 HTN (initiate immediately alongside lifestyle changes)
- Diabetes mellitus or Chronic Kidney Disease (CKD)

3. Pharmacological Agents (First-Line)

- **ACE Inhibitors (Enalapril, Lisinopril) / ARBs (Losartan):** Drug of choice for CKD, Diabetes, and proteinuria. *Contraindicated in bilateral renal artery stenosis and pregnancy.*
- **Calcium Channel Blockers (Amlodipine):** Excellent first-line choice, safe in most ages, no lab monitoring required.
- **Thiazide Diuretics (Hydrochlorothiazide):** Good adjunct, useful in volume-dependent HTN.
- *Note: Beta-blockers are no longer recommended as initial first-line therapy.*

4. Hypertensive Emergency Management

- **Definition:** Severe HTN (Stage 2) + impending/active target organ damage (encephalopathy, acute heart failure, AKI).
- **Goal:** Reduce BP by no more than **25% of the planned reduction in the first 8 hours** to prevent cerebral/optic ischemia. Normalize over 24–48 hours.
- **IV Drugs:**
    - Labetalol (0.2–1 mg/kg/dose) — Avoid in asthma/heart failure.
    - Nicardipine infusion (0.5–3 mcg/kg/min).

- Sodium Nitroprusside (0.53–8 mcg/kg/min) — Monitor for cyanide/thiocyanate toxicity.

Complications

- Left Ventricular Hypertrophy (LVH) – most common target organ damage
- Hypertensive encephalopathy (PRES - Posterior Reversible Encephalopathy Syndrome)
- Progression of CKD
- Hypertensive retinopathy

Exam Summary

- **AAP 2017 Update:** BP tables simplified; normal is <120/<80 for ≥13 years; routine screening starts at 3 years.
- **Cuff Size Rule:** Width = 40% mid-arm circumference; Length = 80-100%.
- **Most common secondary cause:** Renal parenchymal disease.
- **Mandatory screening before meds:** Echocardiogram to check for LVH.
- **ABPM:** Gold standard to diagnose white-coat and masked HTN.
- **Hypertensive Emergency Pitfall:** Never drop BP to normal immediately; max 25% drop in first 8 hours to prevent cerebral hypoperfusion.

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147. Approach to a child with murmur

Subject: Cardiology

Basics

- **Definition:** Audible vibrations caused by turbulent blood flow through the heart or great vessels.
- **Primary Goal:** Differentiate innocent (functional/physiologic) murmurs from pathologic (structural) murmurs.

Clinical Evaluation: History

- **Neonates/Infants:** Diaphoresis during feeds, suck-rest-suck cycle, prolonged feeding time (>30 mins), failure to thrive (FTT), recurrent lower respiratory tract infections (LRTIs), cyanosis.
- **Children/Adolescents:** Exercise intolerance, exertional chest pain, syncope/presyncope, palpitations.
- **Maternal/Family History:** Maternal diabetes/lupus, teratogen exposure (lithium, alcohol), family history of Congenital Heart Disease (CHD), sudden cardiac death (SCD) <50 years, genetic syndromes (Marfan, Down, DiGeorge).

Clinical Evaluation: Physical Examination

- **Vitals:**
  - Pre- and post-ductal SpO2 (screen for critical CHD).
  - 4-limb blood pressure (rule out Coarctation of Aorta - >20 mmHg systolic gradient between arms and legs is significant).

    - Femoral pulses (radio-femoral delay).

- **Inspection:** Dysmorphic features, central cyanosis, clubbing, chest wall deformities (pectus excavatum/carinatum), visible apical impulse.
- **Palpation:** Thrills (palpable murmurs, always pathologic = Grade ≥4), parasternal heave (RV enlargement), apical thrust (LV enlargement), hepatomegaly (heart failure).
- **Auscultation (The 6 'P's):**
    - **Position:** Timing in cardiac cycle (systolic vs. diastolic).
    - **Point of maximum intensity:** Aortic, pulmonary, tricuspid, or mitral areas.
    - **Pitch:** High (pressure gradient, e.g., VSD/MR) vs. Low (flow gradient, e.g., MS).
    - **Pattern (Shape):** Crescendo, decrescendo, crescendo-decrescendo (diamond), plateau (holosystolic).
    - **Propagation:** Radiation to axilla (MR), back (PPS, Coarctation), neck/carotids (AS).
    - **Provocation (Dynamic maneuvers):** Standing/Valsalva decreases venous return (decreases most murmurs; *increases* HOCM and MVP).

Innocent Murmurs (The "7 S's")

- **Characteristics: S**ystolic (except venous hum), **S**oft (Grade $\le$ 2/6), **S**hort, **S**ingle (no clicks/gallops), **S**weet (vibratory/musical, not harsh), **S**ensitive (changes with posture), **S**mall localized area.
- **Classic Types:**
    - **Still’s Murmur (Most common):** 2–7 years; LLSB; low-pitched, vibratory/musical; louder supine; decreases with standing.
    - **Pulmonary Flow Murmur:** Older children/adolescents; LUSB; blowing crescendo-decrescendo; louder supine/expiration.
    - **Venous Hum:** 3–6 years; infraclavicular (right > left); continuous; *disappears* with jugular compression, turning head, or lying down.
    - **Peripheral Pulmonary Stenosis (PPS):** Neonates; LUSB radiating to axillae and back; resolves by 6 months.

Red Flags (Pathologic Murmurs)

- **Timing:** Any diastolic or continuous murmur (except venous hum).
- **Duration:** Pan-systolic (holosystolic) or late-systolic.
- **Intensity:** Grade ≥3/6.
- **Quality:** Harsh, blowing, or rumbling.
- **Associated sounds:** Presence of thrills, clicks, gallops, or friction rubs.
- **S2 Abnormalities:** Fixed split (ASD), single (Pulmonary atresia, Truncus, TGA), loud P2 (Pulmonary hypertension).
- **Dynamic changes:** Murmur intensity *increases* with standing/Valsalva (suggests HOCM).

Diagnosis & Investigations

- **Pulse Oximetry:** AAP recommends universal screening for critical CHD at 24-48 hours of life.
- **ECG:** Assess for chamber hypertrophy (RVH/LVH), axis deviation, conduction delays, or arrhythmias.
- **Chest X-Ray (CXR):** Evaluate cardiomegaly (Cardiothoracic ratio >0.6 in neonates, >0.5 in children), pulmonary vascularity (plethora vs. oligemia), and aortic arch sidedness.
- **Echocardiography (Gold Standard):**
    - *Indications:* Any red flag features, symptomatic child, abnormal ECG/CXR, syndromic child, or inability to confidently diagnose an innocent murmur.
- **Hyperoxia Test:** To differentiate cardiac vs. pulmonary cyanosis in neonates (PaO2 >150 mmHg on 100% FiO2 suggests pulmonary; <150 mmHg suggests cardiac).

Management & Disposition

- **Innocent Murmur:** Reassurance to parents. No activity restriction. No infective endocarditis (IE) prophylaxis required.
- **Pathologic Murmur:** Prompt referral to Pediatric Cardiology.
- **IE Prophylaxis (AHA/ACC Updates):** Only indicated for high-risk groups (prosthetic valves, prior IE, unrepaired cyanotic CHD, completely repaired CHD with prosthetic material within 6 months, repaired CHD with residual defects).

Exam Summary (High-Yield Buzzwords)

- **Still's Murmur:** Vibratory/musical, LLSB, louder supine.
- **Venous Hum:** Continuous, right infraclavicular, disappears with jugular compression.
- **HOCM Trap:** Systolic murmur that *increases* with standing or Valsalva.
- **Absolute Echo Indications:** Diastolic, continuous (non-hum), Grade ≥3, thrills, clicks, fixed split S2, symptoms of failure/cyanosis.
- **Rule of thumb:** If in doubt between innocent and pathologic, order an Echo or refer to Cardiology.

Dermatology

1. Erythema multiforme

Subject: Dermatology

Erythema Multiforme (EM)

Definition

- Acute, self-limiting, Type IV hypersensitivity reaction.
- Characterized by distinctive "target" or "iris" lesions.
- **Current Concept:** EM is now considered a distinct disease entity, separate from Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN).

Etiology

- **Infections (>90% of cases):**
    - **Herpes Simplex Virus (HSV-1 & 2):** Most common trigger (up to 70%).
    - *Mycoplasma pneumoniae*: Common in children (often presents as EM Major).
    - Others: CMV, EBV, Histoplasmosis.
- **Drugs (<10%):** NSAIDs, Sulfonamides, Antiepileptics, Penicillins.
- **Immunizations:** Rare (e.g., HBV, MMR).

Pathophysiology

- Cell-mediated immune response (Type IV hypersensitivity).
- HSV-DNA fragments are transported to keratinocytes by CD34+ cells.
- T-cell mediated cytotoxicity against keratinocytes expressing viral or drug antigens.
- Leads to epidermal basal cell liquefaction and subepidermal vesiculation.

Classification

1. **EM Minor:** Symmetrical skin lesions; no or minimal mucosal involvement; no systemic symptoms.
2. **EM Major:** Skin lesions + involvement of $\ge$1 mucosal site (usually oral); systemic symptoms (fever, malaise).

Clinical Features

- **Prodrome:** Fever, malaise, sore throat (more common in EM Major).
- **Primary Lesion:** Starts as erythematous macules/papules $\to$ evolves into "Target Lesions."
- **The Classic Target (3 Zones):**
    1. **Center:** Dusky/livid, may have a vesicle or crust.
    2. **Middle:** Pale, edematous ring.
    3. **Periphery:** Erythematous, well-defined border.
- **Distribution:**
    - Symmetrical and **Acral** (hands, feet, elbows, knees).
    - Centripetal spread (limbs to trunk).
    - Extensor surfaces > Flexor surfaces.
- **Mucosal (EM Major):** Painful erosions, crusting of lips (hemorrhagic crusts), bullae.
- **Koebner Phenomenon:** Lesions appearing at sites of physical trauma.

Diagnosis

- **Clinical:** Based on morphology and distribution.
- **Skin Biopsy (if diagnosis in doubt):**
    - Vacuolar degeneration of basal keratinocytes.

    - Subepidermal blisters.
    - Dense perivascular lymphocytic infiltrate.
- **Work-up:** PCR for HSV, *Mycoplasma* serology/PCR, CXR if respiratory symptoms present.

Differential Diagnosis

- **SJS/TEN:** Lesions are "atypical targets" (2 zones), predominantly on trunk, Nikolsky sign positive, significant skin sloughing.
- **Urticaria:** Lesions are transient (<24 hours), itchy, and lack the 3-zone architecture.
- **Fixed Drug Eruption:** Usually single or few dusky plaques; recurs at the same site.

Management

- **General:** Discontinue any suspected offending drug; supportive skin care.
- **Symptomatic:**
    - Oral antihistamines for pruritus.
    - Topical corticosteroids (mid-potency) for skin lesions.
    - Analgesics and topical anesthetics (viscous lidocaine) for oral ulcers.
- **Specific Therapy:**
    - **HSV-associated:** Oral Acyclovir (does not abort current episode but prevents future recurrences).
    - ***Mycoplasma*-associated:** Oral Azithromycin or Clarithromycin.
- **Systemic Steroids:** Controversial; may be considered in severe EM Major early in the course (e.g., Prednisolone 1 mg/kg/day for 5–7 days).
- **Ophthalmology Consult:** Mandatory if ocular mucosa is involved.

Prognosis & Prevention

- **Prognosis:** Excellent; resolves spontaneously in 2–4 weeks without scarring.
- **Recurrence:** Common in HSV-associated EM (Recurrent EM).
- **Prevention:** Long-term suppressive Acyclovir therapy for patients with >6 episodes/year.

Exam Summary (Must-Write)

- **Trigger:** HSV is the #1 cause; *Mycoplasma* is common in kids.
- **Lesion:** Classic **3-zoned target lesion** on **acral** surfaces.
- **Classification:** Minor (no mucosa) vs. Major (mucosa + systemic symptoms).
- **Distinction:** EM is NOT SJS; it is a separate immunopathologic process.
- **Treatment:** Primarily supportive; treat the underlying infection (Acyclovir/Macrolides).

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2. Angiokeratoma

Subject: Dermatology

Definition

- Benign vascular lesion characterized by ectasia of superficial dermal capillaries.
- Associated with secondary overlying epidermal changes (hyperkeratosis, acanthosis).

Pathophysiology

- **Primary event:** Dilation of papillary dermal capillaries.
- **Secondary event:** Increased pressure on the epidermis leads to reactive hyperkeratosis and downward growth of rete ridges (encasing the vessels).
- **Etiology:** Localized (trauma, increased venous pressure) or Systemic (lysosomal storage disorders).

Clinical Variants

1. **Angiokeratoma of Mibelli:**
    - Location: Dorsum of fingers and toes.
    - Trigger: Often preceded by cold injury or chilblains.
    - Age: Childhood/Adolescence.
2. **Angiokeratoma of Fordyce:**
    - Location: Scrotum or vulva.
    - Appearance: Multiple 2–4 mm purple papules.
    - Association: Increased venous pressure (e.g., varicocele).
3. **Angiokeratoma Circumscriptum:**
    - Location: Usually lower legs.
    - Timing: Present at birth or early infancy.
    - Appearance: Large, verrucous, dark-red/black plaques.
4. **Solitary/Papular Angiokeratoma:**
    - Common on lower extremities; often follows trauma.
5. **Angiokeratoma Corporis Diffusum (ACD):**
    - **Crucial Pediatric Association:** Most commonly seen in **Fabry Disease** (α-galactosidase A deficiency).
    - Also seen in: Sialidosis, Fucosidosis, GM1 Gangliosidosis.

Angiokeratoma Corporis Diffusum (Fabry Disease Focus)

- **Inheritance:** X-linked recessive.
- **Cutaneous Markers:** Symmetric, "bathing trunk" distribution (umbilicus to mid-thighs).
- **Systemic Red Flags:**
    - **Acroparesthesia:** Burning pain in hands/feet triggered by heat/fever.

- **Hypohidrosis:** Reduced sweating.
- **Corneal Opacities:** Cornea verticillata (whorl-like).
- **Organ Failure:** Progressive renal failure, hypertrophic cardiomyopathy, early stroke.

Diagnosis

- **Clinical:** Non-blanching, firm, dark-purple/black "wart-like" papules.
- **Dermoscopy:** Red-blue lacunae, whitish-yellow keratotic areas.
- **Histopathology:**
  - Dilated thin-walled capillaries in the papillary dermis.
  - Epidermal hyperkeratosis and acanthosis.
  - "Clutching" of vessels by elongated rete ridges.
- **Systemic Workup (if ACD suspected):**
  - Enzyme assay (α-galactosidase A levels).
  - Genetic testing (*GLA* gene).
  - Urinalysis (proteinuria/Maltese cross bodies).

Management

- **Localized Lesions:**
  - Treatment is usually for cosmetic reasons or bleeding.
  - **Laser:** Pulse Dye Laser (PDL), KTP, or Long-pulsed Nd:YAG (Gold standard for vascularity).
  - **Surgical:** Cryotherapy, electrocautery, or excision.
- **Systemic (Fabry Disease):**
  - **Enzyme Replacement Therapy (ERT):** Agalsidase alfa/beta.
  - **Chaperone Therapy:** Migalastat (for amenable mutations).
  - **Pain:** Gabapentin or Carbamazepine for acroparesthesia.

Complications

- Recurrent bleeding (especially Fordyce type).
- Secondary infection from scratching.
- Psychological distress (cosmetic appearance).
- **Fabry-specific:** ESRD, cardiac arrhythmias, premature death.

Exam Summary

- **Must-write:** Definition (vessel ectasia + hyperkeratosis), 5 clinical variants, and the link between ACD and Fabry Disease.
- **Buzzword:** "Bathing trunk distribution" for Fabry.

- **Histology:** Dilated capillaries in papillary dermis encased by rete ridges.
- **Treatment:** Laser is the preferred local modality; ERT is the systemic standard for Fabry.

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3. Toxic Shock Syndrome and TEN

Subject: Dermatology

This response covers **Toxic Shock Syndrome (TSS)** and **Toxic Epidermal Necrolysis (TEN)** as distinct entities, emphasizing their pediatric relevance and critical management.

TOXIC SHOCK SYNDROME (TSS)

Definition & Etiology

- **Definition:** Acute, toxin-mediated, life-threatening febrile illness with shock and multi-organ involvement.
- **Staphylococcal TSS:** *S. aureus* producing TSST-1 or Enterotoxins (Menstrual and Non-menstrual).
- **Streptococcal TSS:** *S. pyogenes* (GAS) producing Streptococcal Pyrogenic Exotoxins (SpeA/B/C); often associated with necrotizing fasciitis.

Pathophysiology

- **Superantigen Mechanism:** Toxins bypass normal MHC-II processing.
- **T-cell Activation:** Massive activation (up to 20%) of T-cells via Vβ regions.
- **Cytokine Storm:** Uncontrolled release of TNF-α, IL-1, IL-6, and IFN-γ.
- **Capillary Leak:** Results in profound hypotension and tissue edema.

Clinical Features

- **Prodrome:** Fever, chills, myalgia, vomiting, and diarrhea.
- **Rash:** Diffuse, blanching erythroderma ("sunburn-like" rash).
- **Hypotension:** Systolic BP < 5th percentile for age.
- **Desquamation:** Fine, flaky peeling (1–2 weeks after onset), especially on palms and soles.
- **Strep-specific:** Severe localized pain (often out of proportion to findings).

CDC Diagnostic Criteria (Staph TSS)

- **Fever:** >38.9°C.
- **Rash:** Diffuse macular erythroderma.
- **Desquamation:** 1–2 weeks after onset.
- **Hypotension:** Orthostatic or shock.
- **Multi-system (≥3):** GI, Muscular (CPK elevation), Renal (Cr >2x normal), Hepatic, Hematologic (Plts <100k), CNS (altered sensorium).

Management

- **Aggressive Fluid Resuscitation:** Large volumes of crystalloids (up to 60–100 ml/kg).
- **Source Control:** Remove tampons, surgical debridement of wounds, drainage of abscesses.
- **Antibiotics:**
    - **Beta-lactam:** Nafcillin/Oxacillin or Vancomycin (if MRSA suspected).
    - **Clindamycin: Mandatory** (inhibits protein synthesis/toxin production; overcomes the "Eagle effect").
- **IVIG:** High-dose (2g/kg) to neutralize circulating toxins.
- **Inotropes:** If shock is fluid-refractory.

TOXIC EPIDERMAL NECROLYSIS (TEN)

Definition & Spectrum

- **SJS/TEN Spectrum:** Delayed-type hypersensitivity reaction causing keratinocyte apoptosis.
- **SJS:** <10% Body Surface Area (BSA) detachment.
- **SJS/TEN Overlap:** 10–30% BSA.
- **TEN:** >30% BSA detachment.

Etiology (The "SATAN" Drugs)

- **S:** Sulfa drugs (Sulfamethoxazole).
- **A:** Allopurinol.
- **T:** Tetracyclines/Anticonvulsants (Phenytoin, Carbamazepine, Lamotrigine).
- **A:** NSAIDs.
- **N:** Nevirapine.
- **Infections:** *Mycoplasma pneumoniae* (more common in SJS).

Pathophysiology

- **Cytotoxic T-cells:** CD8+ cells release **Granulysin** (primary mediator of cell death).
- **Fas-Fas Ligand:** Interaction triggers widespread keratinocyte apoptosis.
- **Result:** Full-thickness epidermal necrosis and subepidermal bullae.

Clinical Features

- **Prodrome:** 1–3 days of fever, sore throat, and stinging eyes.
- **Skin Lesions:** Dusky, erythematous macules progressing to confluent bullae.
- **Nikolsky Sign:** Positive (epidermal detachment with slight lateral pressure).
- **Mucosal Involvement:** ≥2 sites (Oral, Ocular, Genital, Respiratory).
- **Pain:** Intense skin tenderness even in non-denuded areas.

Management

- **Immediate Drug Cessation:** Identify and stop the trigger.
- **Supportive (Burn Unit Model):**
    - Fluid/Electrolyte balance (less aggressive than burns).
    - Temperature regulation (neutral thermal environment).
    - Barrier nursing to prevent sepsis.
- **Skin Care:** Non-adherent dressings (e.g., Mepitel, Biobrane); avoid silver sulfadiazine (sulfa-based).
- **Specific Immunotherapy:**
    - **Cyclosporine:** (First-line in many centers) Inhibits T-cell activation.
    - **IVIG:** To block Fas-mediated apoptosis.
    - **Etanercept (TNF inhibitor):** Emerging evidence for rapid healing.
- **Ophthalmology Consult:** Urgent; prevents symblepharon and blindness.

Prognosis (SCORTEN Score)

- **Mortality:** Higher in TEN (>30%).
- **Predictors:** Age, Heart rate, Malignancy, BSA detached, BUN, Serum Bicarbonate, Glucose.

Comparison: TSS vs. TEN

Feature	Toxic Shock Syndrome (TSS)	Toxic Epidermal Necrolysis (TEN)
Primary Cause	Bacterial Toxins (Staph/Strep)	Drugs/Hypersensitivity
Pathology	Cytokine storm (Superantigen)	Keratinocyte Apoptosis (Granulysin)
Skin Finding	Erythroderma (Sunburn)	Bullae and Sloughing
Nikolsky Sign	Negative	**Positive**
Mucosal Involvement	Minimal (Hyperemia)	**Severe (Erosions/Crusting)**
Key Treatment	Fluids + Clindamycin + IVIG	Stop drug + Cyclosporine + Wound care

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Exam Summary

- **TSS Must-Write:** Superantigen mechanism, Clindamycin for toxin suppression, CDC criteria (Fever/Rash/Hypotension/3-organs).
- **TEN Must-Write:** >30% BSA, Nikolsky positive, Granulysin mediator, Mucosal involvement, SCORTEN for prognosis.
- **Red Flag:** In TSS, the rash may be subtle in early shock; in TEN, eye involvement is a medical emergency.

Rheumatology / Immunology

4. Vaccine Schedule in Nepal with dosage, indications, contraindications, special considerations with catch up schedule

Subject: Rheumatology / Immunology

This answer follows the **National Immunization Programme (NIP) of Nepal (2023-2024 updates)** and WHO/IAP standards.

National Immunization Schedule (Nepal)

Age	Vaccine	Dose	Route	Site
Birth	BCG	0.05 ml	Intradermal (ID)	Left upper arm
6 Weeks	Penta (DPT-HepB-Hib) 1, OPV 1, PCV 1, Rota 1, fIPV 1	0.5ml / 2 drops / 0.5ml / 1.5ml / 0.1ml	IM / Oral / IM / Oral / ID	Thigh / Mouth / Thigh / Mouth / Arm
10 Weeks	Penta 2, OPV 2, Rota 2	0.5ml / 2 drops / 1.5ml	IM / Oral / Oral	Thigh / Mouth / Mouth
14 Weeks	Penta 3, OPV 3, PCV 2, fIPV 2	0.5ml / 2 drops / 0.5ml / 0.1ml	IM / Oral / IM / ID	Thigh / Mouth / Thigh / Arm
9 Months	MR 1, PCV 3, fIPV 3, JE	0.5ml / 0.5ml / 0.1ml / 0.5ml	SC / IM / ID / SC	Arm / Thigh / Arm / Thigh
15 Months	MR 2, Typhoid (TCV)	0.5ml / 0.5ml	SC / IM	Arm / Thigh
45 Months	DPT Booster (Newly added)	0.5 ml	IM	Lateral Thigh

Indications

- **BCG:** Prevention of severe childhood TB (Miliary/Meningeal).
- **Pentavalent:** Protection against Diphtheria, Pertussis, Tetanus, Hepatitis B, and *H. influenzae* type b.
- **PCV (Pneumococcal):** Prevention of invasive pneumococcal disease and pneumonia.
- **fIPV/OPV:** Eradication of Poliomyelitis (fIPV covers Type 2).
- **Rotavirus:** Prevention of severe dehydrating diarrhea.
- **MR:** Elimination of Measles and Congenital Rubella Syndrome (CRS).
- **JE:** Prevention of Japanese Encephalitis in endemic districts.
- **TCV:** Prevention of Typhoid fever (introduced in 2022).

Contraindications

- **General:** Anaphylaxis or severe hypersensitivity to a previous dose of the same vaccine.
- **Live Vaccines (BCG, OPV, MR, JE):**
    - Known primary immunodeficiency (e.g., SCID).

  - Symptomatic HIV infection (exception: MR can be given if not severely immunosuppressed).
  - Pregnancy (relevant for older catch-up).
- **Pertussis (in Penta/DPT):** Progressive neurological disorders, uncontrolled epilepsy, or encephalopathy within 7 days of a previous dose.
- **Rotavirus:** History of intussusception or uncorrected GI malformation (e.g., Meckel's diverticulum).

Special Considerations

- **Preterm/LBW:**
  - Vaccinate at chronological age (not corrected age).
  - BCG: Delay until stable or >2kg (preferred but not absolute).
- **HIV Exposure:**
  - Give all routine vaccines.
  - Avoid BCG if the infant shows symptoms of HIV/AIDS.
- **Vitamin A Supplementation:**
  - 1 lakh IU at 6 months (with 9-month vaccines in some districts).
  - 2 lakh IU every 6 months from 12–59 months.
- **Deworming (Albendazole):** 200mg (12–23 months), 400mg (>24 months) every 6 months.

Catch-up Schedule (Nepal Guidelines)

- **BCG:** Up to 1 year of age.
- **Pentavalent/OPV:** Up to 5 years of age.
  - Minimum interval between doses: 4 weeks.
- **PCV:** Up to 1 year of age (NIP limit).
- **fIPV:** If missed at 6/14 weeks, provide at the earliest opportunity up to 1 year.
- **MR:** Up to 5 years of age.
- **JE:** Up to 15 years of age in endemic areas.
- **TCV:** One-time catch-up was conducted for ages 15 months to 15 years.

Updates (2022–2024)

- **TCV (Typhoid Conjugate Vaccine):** Now a routine single dose at 15 months.
- **fIPV 3rd Dose:** Nepal now includes a 3rd fractional IPV dose at 9 months to bolster mucosal immunity.
- **DPT Booster:** Re-introduced at 45 months to prevent waning immunity (Pertussis/Diphtheria).

- **HPV:** Pilot projects ongoing; planned for national rollout for girls aged 10–14 years.

Exam Summary

- **Must-Write:** The 9-month fIPV and 15-month TCV are the most recent NIP changes.
- **Dosage Trap:** BCG is 0.05ml (not 0.5ml); fIPV is 0.1ml (Intradermal).
- **Route Trap:** PCV and Penta are always IM; MR and JE are SC.
- **Catch-up:** Most NIP vaccines are focused on completion by age 1; MR and Penta can be extended to age 5.

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5. Polyarteritis nodosa and associated aneurysms

Subject: Rheumatology / Immunology

Definition

- Systemic necrotizing vasculitis involving medium and small-sized muscular arteries.
- Characterized by absence of glomerulonephritis and absence of ANCA (usually).

Classification (EULAR/PRINTO/PRES Criteria)

- **Systemic PAN:** Multisystem involvement; potentially life-threatening.
- **Cutaneous PAN:** Limited to skin and musculoskeletal system; benign course but prone to relapses.
- **DADA2 (Update):** Deficiency of Adenosine Deaminase 2; autosomal recessive mimics PAN; presents with early-onset strokes and livedo racemosa.

Pathophysiology

- Segmental transmural fibrinoid necrosis of arterial walls.
- Infiltration by neutrophils and mononuclear cells.
- Weakening of the vessel wall leads to **aneurysmal dilations**.
- Healing occurs via fibrosis, leading to luminal narrowing and organ ischemia.

Clinical Features

- **Constitutional:** High-grade fever, weight loss, severe myalgia.
- **Skin:** Livedo reticularis (starburst pattern), painful subcutaneous nodules, digital gangrene.
- **Renal:** Severe hypertension (renovascular), flank pain (infarcts); **Note:** No hematuria/proteinuria (no GN).
- **GI:** Post-prandial abdominal pain (intestinal angina), acute abdomen (perforation/hemorrhage).
- **Neurological:** Mononeuritis multiplex (foot drop/wrist drop), CNS strokes (common in DADA2).
- **Cardiac:** Coronary arteritis, heart failure.

Characteristics of PAN Aneurysms

- **Pathognomonic sign:** "String of pearls" or "Rosary sign" on angiography.
- **Mechanism:** Focal wall necrosis → weakening → saccular or fusiform outpouchings.
- **Common Sites:** Renal (most common), Mesenteric, Hepatic, and Celiac arteries.
- **Complications:** Spontaneous rupture leading to retroperitoneal or intra-abdominal hemorrhage.
- **Evolution:** May regress with intensive immunosuppression.

Diagnosis

- **EULAR/PRINTO Criteria (Mandatory + 1 of 5):**
    - **Mandatory:** Histopathology (necrotizing vasculitis) OR Angiography (aneurysms/occlusions).
    - **Criteria:** 1. Skin involvement; 2. Myalgia; 3. Hypertension; 4. Peripheral neuropathy; 5. Renal involvement.
- **Imaging:**
    - Conventional Angiography: Gold standard for micro-aneurysms.
    - MRA/CTA: Non-invasive but may miss very small aneurysms (<2mm).
- **Biopsy:** Deep skin biopsy (nodule) or sural nerve biopsy.
- **Labs:** High ESR/CRP, Leukocytosis, ANCA negative.
- **Screening:** Test for Hepatitis B (HBV) and ADA2 gene mutations.

Management

- **Induction:**
    - High-dose Corticosteroids (Pulse Methylprednisolone followed by oral Prednisone 2mg/kg/d).
    - IV Cyclophosphamide (for organ-threatening/severe disease).
- **Maintenance:** Azathioprine or Mycophenolate Mofetil (MMF).
- **DADA2 Specific:** Anti-TNF agents (Etanercept/Adalimumab) are **first-line** (highly effective for stroke prevention).
- **Hypertension:** ACE inhibitors or CCBs (aggressive control required).
- **HBV-associated:** Antivirals + Plasmapheresis + short-term steroids.

Complications & Prognosis

- **Complications:** Intestinal perforation, hypertensive encephalopathy, renal failure, aneurysm rupture.
- **Prognosis:** 5-year survival >80% with treatment; relapses common in cutaneous form.
- **Relapse triggers:** Tapering of steroids too rapidly.

Exam Summary (Must-Write)

- **Aneurysms:** Small/medium caliber, "string of pearls" on angiography, renal/mesenteric focus.

- **Distinction:** PAN has **no** glomerulonephritis (distinguishes from MPA/GPA).
- **Modern Update:** Always screen for **DADA2** in pediatric PAN; use **Anti-TNF** for DADA2.
- **Biopsy:** Necrotizing vasculitis of medium-sized vessels is the hallmark.

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6. Kawasaki disease differential diagnosis and treatment

Subject: Rheumatology / Immunology

Definition

- Acute, self-limited, medium-vessel necrotizing vasculitis.
- Leading cause of acquired heart disease in children in developed nations.

Diagnostic Criteria (AHA/AAP)

- **Fever:** ≥5 days (Mandatory).
- **Plus 4 of 5 classic features:**
    1. **Conjunctivitis:** Bilateral, bulbar, non-exudative, limbic sparing.
    2. **Mucositis:** Strawberry tongue, cracked red lips, pharyngeal erythema.
    3. **Extremity changes:** Erythema/edema (acute); periungual desquamation (subacute).
    4. **Rash:** Polymorphous, non-vesicular; often accentuates in perineal area.
    5. **Lymphadenopathy:** Cervical, usually unilateral, >1.5 cm.
- **Incomplete KD:** Fever ≥5 days + <4 criteria + elevated inflammatory markers (CRP/ESR) + supportive labs (anemia, sterile pyuria, thrombocytosis, hypoalbuminemia).

Differential Diagnosis

Viral Infections

- **Measles:** Presence of Koplik spots, cough, coryza, and cranio-caudal progression of rash.
- **Adenovirus:** Exudative pharyngitis and exudative conjunctivitis (unlike KD).
- **EBV (Infectious Mononucleosis):** Significant splenomegaly and atypical lymphocytosis.

Bacterial/Toxin-Mediated

- **Scarlet Fever:** "Sandpaper" rash, circumoral pallor, positive Strep test.
- **Toxic Shock Syndrome (TSS):** Hypotension, multi-organ involvement, diffuse erythroderma.
- **Staphylococcal Scalded Skin Syndrome (SSSS):** Positive Nikolsky sign, superficial blistering.

Immune/Inflammatory

- **MIS-C (Multisystem Inflammatory Syndrome):** History of COVID-19, more prominent GI symptoms, myocardial dysfunction, and shock.
- **Systemic JIA (Still's Disease):** Evanescent "salmon-pink" rash, daily spiking fevers, arthritis.

- **Stevens-Johnson Syndrome (SJS):** Mucosal involvement of ≥2 sites with skin sloughing/target lesions.

Acute Phase Management

- **Goal:** Prevent coronary artery aneurysms (CAA).
- **IVIG (First-line):** 2 g/kg as a single infusion over 10–12 hours.
    - *Timing:* Ideally within first 10 days of illness.
- **Aspirin (High-dose):** 30–50 mg/kg/day (IAP/UK) or 80–100 mg/kg/day (AHA) divided q6h.
    - *Purpose:* Anti-inflammatory.
    - *Duration:* Until afebrile for 48–72 hours.

Subacute & Maintenance Management

- **Aspirin (Low-dose):** 3–5 mg/kg/day single dose.
    - *Purpose:* Anti-platelet.
    - *Duration:* 6–8 weeks if Echo is normal; indefinitely if aneurysms persist.
- **Corticosteroids (Primary therapy):**
    - *Indication:* High-risk patients (Kobayashi score ≥7) or MIS-C like presentation.
    - *Regimen:* Prednisolone 2 mg/kg/day until CRP normalizes, then taper.

Refractory KD Management

- **Definition:** Persistent/recurrent fever 36 hours after initial IVIG.
- **Second dose IVIG:** 2 g/kg.
- **Pulse Steroids:** Methylprednisolone 30 mg/kg/day for 1–3 days.
- **Biologics:**
    - Infliximab (TNF-α inhibitor): 5 mg/kg single dose.
    - Anakinra (IL-1 inhibitor): For extreme resistance.
    - Cyclosporine: Inhibits calcineurin pathway (useful in IVIG resistance).

Long-term Management & Monitoring

- **Echocardiography:** At diagnosis, 2 weeks, and 6–8 weeks.
- **Z-scores:** Use body surface area-adjusted Z-scores for coronary artery diameter (Z >2.5 = Aneurysm).
- **Anticoagulation:** If Giant Aneurysm (Z ≥10 or diameter >8mm), add Warfarin or LMWH to Aspirin.

- **Vaccination:** Delay live vaccines (MMR, Varicella) for 11 months after IVIG.
- **Influenza Vaccine:** Recommended to reduce Reye Syndrome risk in children on long-term Aspirin.

Complications

- **Cardiac:** Coronary artery aneurysms (25% if untreated), myocarditis, valvular regurgitation.
- **Systemic:** Macrophage Activation Syndrome (MAS), gallbladder hydrops, aseptic meningitis, sensorineural hearing loss.

Exam Summary

- **Must-write:** IVIG 2g/kg + Aspirin is the gold standard.
- **Buzzword:** "Strawberry tongue," "Limbic sparing," "Perineal desquamation."
- **Red Flag:** Fever >5 days in an infant <6 months = Suspect Incomplete KD.
- **Update:** Primary steroid use is now recommended for high-risk patients (Kobayashi criteria).
- **Pitfall:** Do not wait for 5 days of fever if all other criteria are met; treat early to save the coronaries.

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7. JIA, types, management and prognosis

Subject: Rheumatology / Immunology

Juvenile Idiopathic Arthritis (JIA)

Definition

- Arthritis of unknown etiology.
- Onset: Age <16 years.
- Duration: ≥ 6 weeks.
- Diagnosis of exclusion (must rule out infection, malignancy, and other CTDs).

Pathophysiology

- **Autoimmune (Oligo/Poly):** T-cell mediated, HLA-associated, autoantibody production.
- **Autoinflammatory (Systemic):** Innate immune activation, IL-1 and IL-6 driven.

ILAR Classification (Subtypes)

1. **Systemic JIA (sJIA):**
    - Arthritis + daily "quotidian" fever ≥ 2 weeks).
    - Evanescent salmon-pink rash, lymphadenopathy, hepatosplenomegaly, serositis.
2. **Oligoarticular JIA (40–50%):**
    - ≤ 4 joints in first 6 months.

- *Persistent:* Remains ≤ 4joints.
- *Extended:* > 4 joints after 6 months.
- Highest risk of chronic asymptomatic uveitis (especially if ANA positive).

3. **Polyarticular JIA (RF Negative):**
   - ≥ 5joints in first 6 months; RF negative.
   - Asymmetric or symmetric involvement.
4. **Polyarticular JIA (RF Positive):**
   - ≥ 5 joints; RF positive (2 tests, 3 months apart).
   - Symmetric, small joints; resembles adult RA; aggressive.
5. **Enthesitis-Related Arthritis (ERA):**
   - Arthritis + Enthesitis (tendon insertion inflammation, e.g., Achilles).
   - HLA-B27 association; sacroiliac joint involvement; affects older boys.
6. **Psoriatic JIA:**
   - Arthritis + Psoriasis OR Arthritis + 2 of: Dactylitis ("sausage digit"), nail pitting, or family history of psoriasis.
7. **Undifferentiated:**
   - Fits no category or fits > 1 category.

Clinical Features

- **Joints:** Morning stiffness (gel phenomenon), swelling, limp, restricted range of motion.
- **Extra-articular:** Uveitis (often silent), growth retardation, micrognathia (TMJ involvement).
- **Red Flags:** Night pain, weight loss, extreme pallor (suggests malignancy/leukemia).

Diagnosis & Investigations

- **Inflammatory markers:** ESR/CRP (High in sJIA/Poly; often normal in Oligo).
- **Serology:**
  - **ANA:** Predicts uveitis risk (not diagnostic of JIA).
  - **RF & Anti-CCP:** Markers for aggressive polyarticular disease.
  - **HLA-B27:** Useful for ERA.
- **Imaging:**
  - X-ray: Soft tissue swelling, periarticular osteopenia (early); joint space narrowing, erosions (late).
  - **USG/MRI:** More sensitive for early synovitis and marrow edema.
- **Slit-lamp Exam:** Mandatory to rule out asymptomatic uveitis.

Management (ACR 2021/2022 Updates)

- **Goal:** Clinical Remission Off Medication (CROM).
- **First-line (Symptomatic):** NSAIDs (Naproxen, Ibuprofen, Indomethacin).
- **DMARDs (Anchor Therapy):**
    - **Methotrexate (MTX):** Gold standard; weekly (oral/SC) + Folic acid.
    - Sulfasalazine or Leflunomide (if MTX not tolerated).
- **Intra-articular Corticosteroids (IACS):** Triamcinolone hexacetonide; preferred for Oligoarticular JIA.
- **Biologics (If DMARDs fail):**
    - **TNF-alpha inhibitors:** Etanercept, Adalimumab, Infliximab (Best for Poly/ERA).
    - **IL-1 & IL-6 inhibitors:** Anakinra, Canakinumab, Tocilizumab (First-line for **Systemic JIA**).
    - **Abatacept:** T-cell costimulation modulator.
- **Uveitis Management:** Topical steroids ⇒MTX ⇒Adalimumab.
- **Supportive:** PT/OT, nutrition, psychological support.

Complications

- **Macrophage Activation Syndrome (MAS):** Life-threatening complication of sJIA (high ferritin, low ESR, cytopenias).
- **Joint Destruction:** Contractures, ankylosis, leg-length discrepancy.
- **Blindness:** From untreated chronic uveitis.
- **Amyloidosis:** Rare, due to chronic uncontrolled inflammation.

Prognosis

- **Best:** Persistent Oligoarticular JIA.
- **Guarded:** RF-positive Polyarticular JIA and Systemic JIA (risk of MAS).
- **Poor Prognostic Factors:** Early hip/wrist involvement, positive RF/Anti-CCP, persistent high ESR.

Exam Summary

- **Must-write:** ILAR classification criteria, ANA-uveitis link, Methotrexate as primary DMARD.
- **Buzzwords:** "Quotidian fever," "Salmon-pink rash," "Gel phenomenon," "Sausage digit."
- **Update:** Systemic JIA is now treated early with IL-1/IL-6 inhibitors rather than step-up therapy.
- **Trap:** Do not use RF to diagnose JIA; it is only for subtyping Polyarticular disease.

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8. Advances in medical treatment of polyarteritis nodosa and Takayasu arteritis

Subject: Rheumatology / Immunology

Overview

- **Scope:** Systemic vasculitides affecting medium-sized (PAN) and large-sized (TA) arteries.

- **Pediatric Shift:** Transition from non-specific immunosuppression to targeted biologic therapy and genetic screening (DADA2).

Polyarteritis Nodosa (PAN)

Standard Management

- **Corticosteroids:** Prednisolone 1–2 mg/kg/day; pulse Methylprednisolone (30 mg/kg) for organ-threatening disease.
- **Cyclophosphamide (CYC):** Indicated for "Five-Factor Score" >0 or severe organ involvement (renal, GI, CNS).
- **HBV-related PAN:** Antivirals + Plasma exchange (rare in children due to immunization).

Recent Advances & Targeted Therapy

- **DADA2 Screening:** Mandatory in all pediatric PAN (Deficiency of Adenosine Deaminase 2).
- **TNF-alpha Inhibitors (Etanercept, Infliximab, Adalimumab):**
    - **Now First-line for DADA2:** Superior to steroids/CYC.
    - Prevents catastrophic strokes and controls hematological manifestations.
- **Rituximab:** Used in refractory systemic PAN or as a steroid-sparing agent (EULAR/PRES 2023).
- **Mycophenolate Mofetil (MMF):** Emerging as a maintenance agent to reduce CYC toxicity.
- **Plasma Exchange:** Reserved for rapidly progressive glomerulonephritis or pulmonary hemorrhage.

Management of Cutaneous PAN (cPAN)

- **Stepwise approach:** NSAIDs → Colchicine/Dapsone → Methotrexate (MTX).
- **Biologics:** TNF inhibitors used if resistant to conventional DMARDs.

Takayasu Arteritis (TA)

Standard Management

- **Induction:** High-dose steroids (1–2 mg/kg/day).
- **Conventional DMARDs:** Methotrexate (MTX), Azathioprine, or Mycophenolate Mofetil (MMF).

Recent Advances in Medical Therapy

- **Tocilizumab (IL-6 Inhibitor):**
    - **Major Advance:** Most evidence-backed biologic for TA.
    - Effective in steroid-resistant cases and for achieving clinical remission.
    - *Note:* May mask ESR/CRP elevation despite active vascular inflammation.
- **TNF-alpha Inhibitors (Infliximab/Adalimumab):**
    - Highly effective for induction and maintenance in refractory pediatric TA.

    - Preferred if IL-6 inhibitors fail.
- **JAK Inhibitors (Tofacitinib, Upadacitinib):**
    - **Emerging (2023-2024):** Targets multiple cytokine pathways (IL-6, IFN-gamma).
    - Showing promise in adult trials; used off-label in refractory pediatric TA.
- **Ustekinumab (IL-12/23 Inhibitor):** Case reports suggest efficacy in difficult-to-treat TA.
- **Rituximab:** Less effective than in ANCA-vasculitis, but used in B-cell driven refractory cases.

Monitoring Advances

- **PET-CT:** Gold standard for detecting early vascular wall inflammation before structural changes occur.
- **MRA (Magnetic Resonance Angiography):** Preferred for routine pediatric follow-up to avoid radiation.

Supportive & Adjuvant Therapy

- **Antithrombotic:** Low-dose Aspirin (3-5 mg/kg) to prevent ischemic events.
- **Antihypertensives:** Aggressive BP control (ACE inhibitors/ARBs preferred, but avoid in bilateral renal artery stenosis).
- **Bone Health:** Calcium and Vitamin D supplementation for all patients on long-term steroids.

Complications & Red Flags

- **Aneurysmal Rupture:** Risk in PAN; requires urgent surgical/endovascular intervention.
- **Hypertensive Crisis:** Common in TA due to renal artery stenosis.
- **Infection:** Increased risk with combined biologic and steroid therapy.

Exam Summary: Must-Write Points

- **DADA2:** Always screen pediatric PAN for ADA2 mutations; **TNF inhibitors** are the treatment of choice, not CYC.
- **Tocilizumab:** The "game-changer" for refractory Takayasu Arteritis.
- **Steroid Sparing:** The primary goal of modern therapy is to minimize cumulative steroid dose using MTX, MMF, or Biologics.
- **Imaging:** PET-CT is the modern tool for assessing metabolic activity/remission in TA.
- **Step-down:** Transition from IV Cyclophosphamide to oral MMF/Azathioprine once remission is achieved.

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9. Approach to child with suspected immunodeficiency

Subject: Rheumatology / Immunology

Inborn Errors of Immunity (IEI): Clinical Approach

The term **Inborn Errors of Immunity (IEI)** has replaced "Primary Immunodeficiency" to reflect the inclusion of autoinflammation, autoimmunity, and malignancy alongside infection.

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1. Clinical Red Flags (The 10 Warning Signs)

Based on Jeffrey Modell Foundation criteria:

- **Family history:** Most important clue (consanguinity, unexplained early childhood deaths).
- **Failure to thrive:** Persistent weight loss or growth failure.
- **Antibiotic failure:** Lack of response to 2+ months of oral antibiotics.
- **Recurrent Pneumonia:** ≥2 episodes within 1 year.
- **Recurrent Otitis Media:** ≥4 episodes within 1 year.
- **Recurrent Sinusitis:** ≥2 episodes within 1 year.
- **Deep Abscesses:** Recurrent skin or organ abscesses (e.g., liver, lung).
- **Persistent Thrush:** After age 1 year (oral or cutaneous).
- **Opportunistic Infections:** *Pneumocystis jirovecii*, atypical mycobacteria, or severe viral infections.
- **IV Antibiotics:** Need for intravenous antibiotics to clear infections.

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2. Clinical Clues by Type of Defect

- **Antibody Defect (B-cell):** (Most common, ~50%) Recurrent sinopulmonary infections with encapsulated bacteria (*S. pneumoniae, H. influenzae*) after 6 months of age (loss of maternal IgG).
- **Cellular Defect (T-cell):** (Most severe) Early onset (infancy), FTT, chronic diarrhea, opportunistic infections (fungi, viruses), GVHD from maternal cells.
- **Phagocytic Defect:** Skin abscesses, gingivitis, delayed cord separation (>30 days), infections with catalase-positive organisms (*S. aureus, Serratia, Aspergillus*).
- **Complement Defect:** Recurrent Neisserial infections (Late components C5-C9) or SLE-like autoimmune disease (Early components C1, C2, C4).

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3. Physical Examination "Must-Finds"

- **Growth:** Weight/Height centiles (FTT is common).
- **Lymphoid Tissue:** Absence of tonsils/lymph nodes (suggests X-linked Agammaglobulinemia or SCID).
- **Skin:** Eczema (Wiskott-Aldrich), Telangiectasia (Ataxia-Telangiectasia), partial albinism (Chediak-Higashi), Erythroderma (Omenn Syndrome).
- **Dysmorphism:** Low-set ears, cleft palate, fish-mouth (DiGeorge Syndrome).

- **Chest:** Absence of thymic shadow on X-ray (SCID, DiGeorge).

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4. Stepwise Diagnostic Approach

Tier 1: Basic Screening (Available in most centers)

- **CBC & Peripheral Smear:** Absolute Neutrophil Count (ANC), Absolute Lymphocyte Count (ALC <1500/mm^3 suggests SCID), Howell-Jolly bodies (Asplenia).
- **Serum Immunoglobulins:** IgG, IgA, IgM, IgE (Age-matched controls are essential).
- **Chest X-ray:** Presence/absence of thymic shadow.

Tier 2: Advanced Screening

- **Antibody Response:** Post-vaccination titers (Isohemagglutinins, Tetanus/Diphtheria/Pneumococcal titers).
- **Flow Cytometry (Lymphocyte Subsets):** CD3 (T-cells), CD4 (Helper), CD8 (Cytotoxic), CD19/20 (B-cells), CD16/56 (NK cells).
- **Nitroblue Tetrazolium (NBT) or DHR 123 test:** For Chronic Granulomatous Disease (CGD).

Tier 3: Functional & Specialized Tests

- **T-cell Function:** Mitogen stimulation assays (PHA/ConA).
- **Complement Assays:** CH50 (Classical pathway), AH50 (Alternative pathway).
- **TREC (T-cell Receptor Excision Circles):** Newborn screening for SCID (IAP 2023: Recommended where feasible).

Tier 4: Definitive Diagnosis

- **Genetic Testing:** Targeted gene panels or Whole Exome Sequencing (WES) — now the gold standard for definitive classification.

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5. Management Principles

General Measures

- **Nutrition:** High calorie, optimized micronutrients.
- **Hygiene:** Safe water, avoidance of crowds, dental hygiene.
- **Vaccination Contraindication: Strictly avoid live vaccines** (BCG, OPV, MMR, Rotavirus, Varicella) if T-cell/B-cell defect is suspected.

Infection Prevention

- **Antibiotic Prophylaxis:** Cotrimoxazole (for PJP), Itraconazole (for fungi in CGD), Azithromycin.
- **Immunoglobulin Replacement (IVIG/SCIG):** Standard for B-cell defects; dose 400–600 mg/kg every 3–4 weeks.

Definitive Therapy

- **Hematopoietic Stem Cell Transplant (HSCT):** Curative for SCID, Wiskott-Aldrich, CGD, and many others.

- **Enzyme Replacement:** PEG-ADA for ADA-deficient SCID.
- **Gene Therapy:** Emerging for X-linked SCID and ADA-SCID.

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6. Complications & Prognosis

- **Autoimmunity:** Cytopenias, IBD-like colitis.
- **Malignancy:** High risk of Lymphoma (NHL) and Gastric carcinoma.
- **Prognosis:** Excellent if diagnosed early (especially SCID before 3.5 months of age).

Exam Summary: Must-Write Points

- **Terminology:** Use "Inborn Errors of Immunity" (IEI).
- **Age of Onset:** Infancy (T-cell) vs. >6 months (B-cell).
- **ALC:** A lymphocyte count <1500 in an infant is SCID until proven otherwise.
- **Live Vaccines:** Contraindicated in cellular/humoral defects.
- **Family History:** Consanguinity and sibling deaths are the biggest red flags.
- **Curative:** HSCT is the definitive treatment for most severe IEIs.

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10. Treatment of rheumatic disease

Subject: Rheumatology / Immunology

This answer provides a comprehensive overview of the management of pediatric rheumatic diseases, focusing on **General Principles**, **Acute Rheumatic Fever (ARF)**, and **Juvenile Idiopathic Arthritis (JIA)**, as these are the most frequently tested.

I. General Principles of Management

- **Multidisciplinary Team:** Pediatric rheumatologist, physiotherapist, occupational therapist, ophthalmologist (for uveitis screening), and nutritionist.
- **Goal:** Induce remission, prevent joint/organ damage, and ensure normal growth/development.
- **Pharmacological Pillars:**
    - **NSAIDs:** Symptomatic relief (e.g., Naproxen, Ibuprofen).
    - **Glucocorticoids:** "Bridge therapy" or life/organ-threatening flares; Pulse Methylprednisolone (30mg/kg) for rapid control.
    - **csDMARDs (Conventional Synthetic):** Methotrexate (gold standard), Sulfasalazine, Hydroxychloroquine.
    - **bDMARDs (Biologics):** TNF-inhibitors (Etanercept), IL-1 blockers (Anakinra), IL-6 blockers (Tocilizumab).

II. Acute Rheumatic Fever (ARF)

Based on IAP and Revised Jones Criteria (2015)

1. Eradication of Streptococci (Primary Prevention)

- **Inj. Benzathine Penicillin G:** 0.6 million units (<27 kg) or 1.2 million units (>27 kg) IM single dose.
- **Alternative:** Oral Penicillin V (10 days) or Azithromycin (if penicillin-allergic).

2. Anti-inflammatory Therapy

- **Arthritis only:** Aspirin 75–100 mg/kg/day in 4 divided doses for 2–4 weeks, then tapered.
- **Carditis (Mild/Moderate):** Aspirin is usually sufficient.
- **Severe Carditis/Cardiomegaly/CHF:**
    - Prednisolone: 2 mg/kg/day for 2–4 weeks.
    - Taper by 25% weekly while restarting Aspirin to prevent "rebound" phenomenon.

3. Management of Sydenham Chorea

- **Environment:** Quiet room, reduce stimuli.
- **Drugs:** Haloperidol (first line), Valproate, or Carbamazepine.
- **Refractory:** IVIG or Pulse Steroids.

4. Secondary Prophylaxis (Crucial for Marks)

- **Drug:** Inj. Benzathine Penicillin G every 3 weeks (preferred over 4 weeks in high-risk areas).
- **Duration:**
    - *ARF without Carditis:* 5 years or until age 21 (whichever is longer).
    - *ARF with Carditis (No residual heart disease):* 10 years or until age 21 (whichever is longer).
    - *ARF with persistent Valvular Disease:* 10 years or until age 40 (sometimes lifelong).

III. Juvenile Idiopathic Arthritis (JIA)

Based on ACR 2021 Guidelines

1. Non-Systemic JIA (Oligo/Polyarticular)

- **Step 1:** NSAIDs (Naproxen 10-20 mg/kg/day) for <4 weeks.
- **Step 2:** Intra-articular Corticosteroids (Triamcinolone hexacetonide) for limited joint involvement.
- **Step 3:** Methotrexate (15 mg/m^2 or 0.5 mg/kg once weekly) + Folic acid.
- **Step 4:** Biologics (TNF-alpha inhibitors like Etanercept or Adalimumab).

2. Systemic JIA (sJIA)

- **Previously:** Step-up from NSAIDs to Steroids.

- **Now (ACR 2021):** Early use of Biologics (**Anakinra** or **Tocilizumab**) is preferred to avoid steroid toxicity and prevent Macrophage Activation Syndrome (MAS).

3. Uveitis Management

- Screening: Slit-lamp exam (frequency depends on ANA status).
- Treatment: Topical steroids → Methotrexate → Adalimumab (most effective biologic for uveitis).

IV. Juvenile Systemic Lupus Erythematosus (jSLE)

- **Hydroxychloroquine (HCQ):** Mandatory for all patients (prevents flares and organ damage).
- **Corticosteroids:** Lowest effective dose for maintenance.
- **Lupus Nephritis:**
    - Induction: Mycophenolate Mofetil (MMF) or IV Cyclophosphamide.
    - Maintenance: MMF or Azathioprine.
- **Belimumab:** FDA-approved biologic for jSLE >5 years.

V. Kawasaki Disease (KD)

- **IVIG:** 2 g/kg as a single infusion (ideally within 10 days of fever onset).
- **Aspirin:**
    - *Acute phase:* 80–100 mg/kg/day (Anti-inflammatory).
    - *Convalescent phase:* 3–5 mg/kg/day (Anti-platelet) for 6–8 weeks.
- **Refractory KD:** Infliximab, Cyclosporine, or pulse Steroids.

VI. Complications & Monitoring

- **Macrophage Activation Syndrome (MAS):** Emergency in sJIA/SLE; treat with high-dose steroids, Cyclosporine, or Anakinra.
- **Growth Failure:** Minimize steroids; encourage weight-bearing exercises.
- **Toxicity Monitoring:**
    - Methotrexate: CBC, LFTs (every 8–12 weeks).
    - HCQ: Annual ophthalmology check (retinopathy).
    - Steroids: BP, Blood sugar, Growth velocity, Bone density.

Exam Summary: Must-Write Points

- **ARF:** Penicillin for eradication + Aspirin for joints + Steroids for severe carditis + 3-weekly prophylaxis.
- **JIA:** Methotrexate is the csDMARD of choice; Biologics (IL-1/IL-6) are first-line for Systemic JIA.

- **SLE:** Every patient needs Hydroxychloroquine.
- **KD:** IVIG 2g/kg + High-dose Aspirin.
- **Safety:** Always screen for Latent TB before starting Biologics (TNF-inhibitors).

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11. Advances in vaccine technology

Subject: Rheumatology / Immunology

Overview

Vaccine technology has transitioned from traditional "Isolate-Inactivate-Inject" methods to precision molecular engineering, significantly reducing development timelines (from decades to months).

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1. Nucleic Acid Vaccines (The Genetic Revolution)

- **mRNA Vaccines (e.g., COVID-19 Pfizer/Moderna):**
    - **Mechanism:** Synthetic mRNA encoding the "Spike protein" is encapsulated in **Lipid Nanoparticles (LNPs)**.
    - **Action:** Host ribosomes translate mRNA into protein; triggers both humoral (B-cell) and cellular (T-cell) immunity.
    - **Advantages:** Rapid scalability; no risk of genomic integration; no live virus used.
- **DNA Vaccines (e.g., ZyCoV-D - India):**
    - **Mechanism:** Plasmid DNA delivered into the nucleus; transcribed to mRNA, then translated to protein.
    - **Innovation:** World's first human DNA vaccine (ZyCoV-D) uses a **needle-free applicator** (Tropis) to deliver via high-pressure stream.

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2. Viral Vector Vaccines

- **Mechanism:** Uses a modified, non-pathogenic virus (e.g., Adenovirus) to carry the genetic code of the target antigen.
- **Non-replicating Vectors:** Oxford-AstraZeneca (ChAdOx1), Janssen (Ad26).
- **Replicating Vectors:** Ervebo (Ebola vaccine) uses Vesicular Stomatitis Virus (VSV).
- **Benefit:** Strong induction of CD8+ T-cell responses; mimics natural infection.

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3. Reverse Vaccinology & AI

- **Method:** Genome sequencing of the pathogen → Bioinformatic screening for antigenic epitopes → Synthetic production.
- **Classic Example: Meningococcal B vaccine (4CMenB/Bexsero)** – created because traditional methods failed due to the capsule's similarity to human neural tissue.

- **AI Integration:** Structural biology and AI (AlphaFold) predict protein folding to design "super-antigens."

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4. Protein Subunit & Nanoparticle Vaccines

- **Virus-Like Particles (VLPs):** Structural proteins that mimic the virus shape but lack genetic material (e.g., HPV, HepB).
- **Nanoparticle Vaccines (e.g., Novavax):** Recombinant proteins folded into nanoparticles; mimics the repetitive structure of viruses to enhance immune recognition.
- **Mosaic Vaccines:** Displaying antigens from multiple strains (e.g., Universal Flu or Sarbecovirus vaccines) on a single nanoparticle.

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5. Advanced Adjuvant Systems

- **Previously:** Primarily Alum (Th2 bias).
- **Now (Precision Adjuvants):**
    - **AS01 (Liposome-based):** Used in **RTS,S (Malaria)** and Shingrix; triggers potent T-cell and antibody responses.
    - **Matrix-M:** Saponin-based adjuvant used in **R21/Matrix-M (WHO 2023 Malaria vaccine)**.
    - **CpG ODN:** Toll-like receptor 9 (TLR9) agonist used in HepB (Heplisav-B).

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6. Novel Delivery Systems

- **Mucosal/Intranasal Vaccines:**
    - **Mechanism:** Induces Secretory IgA (SIgA) at the portal of entry.
    - **Example: iNCOVACC (Bharat Biotech)** – world's first intranasal COVID vaccine.
- **Microneedle Patches:** Painless, thermostable, and potentially self-administrable; currently in trials for MR (Measles-Rubella).
- **Fractional Dosing:** Use of Intradermal (ID) route to stretch vaccine supply (e.g., fIPV - Fractional Inactivated Polio Vaccine).

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7. Pediatric Specific Updates (IAP/WHO 2023-24)

- **Malaria (R21/Matrix-M):** High efficacy (>75%); easier to manufacture than RTS,S.
- **Hexavalent Vaccines:** Inclusion of IPV into the DTaP-HepB-Hib combination (reduced pricks, better compliance).
- **nOPV2 (Novel Oral Polio Vaccine type 2):** Genetically modified to prevent reversion to neurovirulence (vaccine-derived polio).

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8. Advantages of Modern Platforms

- **Thermostability:** Development of heat-stable vaccines (lyophilization) to bypass the "Cold Chain" challenge in developing nations.
- **Speed:** "Plug-and-play" platforms allow rapid adaptation to new variants (e.g., Omicron-specific boosters).
- **Safety:** Elimination of live-pathogen handling during large-scale manufacturing.

Exam Summary: Must-Write Points

- **mRNA/DNA:** Genetic templates delivered via LNPs or needle-free devices (ZyCoV-D).
- **Reverse Vaccinology:** Genome-based antigen discovery (Meningococcal B).
- **Viral Vectors:** Using Adenovirus carriers (Ebola, COVID-19).
- **Adjuvants:** Transition from Alum to AS01/Matrix-M for stronger T-cell immunity (Malaria R21).
- **Mucosal Vaccines:** Intranasal delivery for local IgA immunity (iNCOVACC).
- **nOPV2:** Specifically engineered to prevent circulating vaccine-derived poliovirus (cVDPV).

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12. Pneumococcal conjugate vaccine and newer vaccines

Subject: Rheumatology / Immunology

Pneumococcal Conjugate Vaccine (PCV) & Newer Vaccines

Basics & Mechanism

- **Type:** Inactivated subunit vaccine; capsular polysaccharide conjugated to a carrier protein (usually CRM197, a non-toxic diphtheria toxin mutant).
- **Immunology:** Conjugation converts T-cell independent response (polysaccharide alone) to **T-cell dependent** response.
- **Key Advantages:**
    - Effective in children <2 years (unlike PPSV23).
    - Induces **immunological memory** (B-cell and T-cell).
    - Reduces **nasopharyngeal carriage** (induces mucosal IgA), leading to **herd immunity**.
    - Booster response seen upon re-exposure.

Evolution of PCVs

- **PCV7:** Original vaccine; covered 7 serotypes; now largely replaced.
- **PCV10 (Synflorix):** Covers 10 serotypes; includes 1, 5, and 7F (common in developing nations).
- **PCV13 (Prevenar 13):** Covers 13 serotypes; adds 3, 6A, and **19A** (19A is a major cause of antibiotic-resistant invasive pneumococcal disease).
- **PCV10 (Pneumosil - Serum Institute of India):** WHO pre-qualified; covers 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, 23F; cost-effective for UIP.

Newer Vaccines (Recent Approvals)

- **PCV15 (Vaxneuvance):**
    - Contains all PCV13 serotypes plus **22F and 33F**.
    - Approved for use in infants and children (FDA 2022/IAP 2023-24).
- **PCV20 (Prevenar 20):**
    - Adds 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, 33F) to the PCV13 base.
    - **AAP 2023/2024 Update:** Now recommended for routine use in children as an alternative to PCV13/15.
    - Significantly simplifies the schedule for high-risk children by potentially eliminating the need for PPSV23.

IAP/National Immunization Schedule

- **Primary series:** 6, 10, and 14 weeks.
- **Booster:** 12–15 months.
- **Catch-up:**
    - 6–12 months: 2 doses (4 weeks apart) + 1 booster.
    - 12–24 months: 2 doses (8 weeks apart).
    - 2–5 years: 1 dose (PCV13/15/20).

High-Risk Groups

- **Anatomic/Functional Asplenia:** Sickle cell disease, post-splenectomy.
- **Immunocompromised:** HIV, Nephrotic syndrome, Chronic renal failure, Malignancy.
- **Leaking barriers:** CSF rhinorrhea/otorrhea, Cochlear implants.
- **Chronic Diseases:** Congenital heart disease, Chronic lung disease (asthma on high-dose steroids).

Comparison: PCV vs. PPSV23 (Pneumovax)

Feature	PCV (Conjugate)	PPSV23 (Polysaccharide)
Age	Safe < 2 years	Only > 2 years
Immune Response	T-cell Dependent	T-cell Independent
Memory	Yes (Long-term)	No (Short-term)
Carriage	Reduces carriage (Herd effect)	No effect on carriage
Efficacy	Excellent against Mucosal & IPD	Primarily against IPD (Invasive Disease)

Newer Sequential Recommendations (High-Risk Children)

- **Previously:** PCV13 followed by PPSV23 (8 weeks later).
- **Current (AAP 2024/Recent IAP updates):**
    - If **PCV20** is used: A single dose (or full series) may suffice without PPSV23.

- If **PCV15** is used: Must be followed by **PPSV23** to cover additional serotypes.

Adverse Effects & Contraindications

- **Common:** Fever, injection site redness/swelling, irritability.
- **Rare:** Febrile seizures (risk slightly higher if co-administered with Inactivated Influenza Vaccine).
- **Contraindication:** Severe allergic reaction (anaphylaxis) to any component or diphtheria toxoid.

Exam Summary

- **Must-write:** Conjugation converts T-independent to T-dependent response; 19A serotype significance in PCV13/10 (Pneumosil).
- **New updates:** Mention PCV15 and PCV20 as the "newer" generation reducing the need for multiple PPSV23 doses.
- **High-yield:** PCV reduces nasopharyngeal carriage (Herd immunity), whereas PPSV23 does not.
- **Schedule:** 3+1 (6, 10, 14 weeks + booster at 15 months).

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14. Langerhans cell histiocytosis

Subject: Important Questions

Definition & Classification

- **Definition:** Clonal proliferation of abnormal epidermal dendritic cells (Langerhans cells) accompanied by a rich inflammatory infiltrate (eosinophils, macrophages, lymphocytes).
- **Current Paradigm:** Reclassified by WHO as an **inflammatory myeloid neoplasm** (previously considered a reactive histiocytic disorder).
- **Histiocyte Society Classification:**
  - **Single System LCH (SS-LCH):** Unifocal or multifocal involvement of a single organ (usually bone, skin, or lymph node).
  - **Multisystem LCH (MS-LCH):** Involvement of ≥2 organ systems.
  - **Risk Organ (RO) Status:** Defines prognosis in MS-LCH. Risk organs include **Liver, Spleen, and Hematopoietic system (Bone Marrow)**. *(Note: Lung is no longer considered a risk organ in pediatrics).*

Pathogenesis & Genetics

- **Driver Mutations:** MAPK pathway hyperactivation is universal.
- ***BRAF V600E* mutation:** Found in 50–60% of cases (associated with higher risk of recurrence and neurodegeneration).
- ***MAP2K1* mutations:** Found in ~20% of cases (especially *BRAF*-wildtype).

Pathology (Diagnostic Hallmarks)

- **Morphology:** Large cells with grooved, "coffee-bean" shaped nuclei.
- **Immunohistochemistry (Must-write):** Positivity for **CD1a**, **CD207 (Langerin)**, and S-100.
- **Electron Microscopy: Birbeck granules** (classic "tennis-racket" shaped cytoplasmic organelles).

Clinical Features

- **Historical Eponyms (For exam context):**
    - *Eosinophilic Granuloma:* Localized bone lesions (older children).
    - *Hand-Schüller-Christian Disease:* Classic triad of skull defects, exophthalmos, and diabetes insipidus (DI).
    - *Letterer-Siwe Disease:* Acute disseminated multisystem disease in infants (rash, hepatosplenomegaly, cytopenias).
- **Bone (Most common, ~80%):** Painful swelling. Skull, femur, ribs, and vertebrae (causing "vertebra plana" / coin lesion).
- **Skin:** Refractory "seborrheic dermatitis-like" eruption in the scalp/intertriginous areas; petechial rash in infants.
- **Ear:** Chronic, refractory otitis media, aural discharge, mastoid involvement.
- **Endocrine:** Central Diabetes Insipidus (DI) is the most common endocrine defect (due to posterior pituitary/stalk infiltration).
- **CNS:** Neurodegenerative LCH (ataxia, dysarthria, behavior changes) appearing years later; or mass lesions (meninges/choroid plexus).
- **Lungs:** Cystic and nodular changes, recurrent spontaneous pneumothorax.
- **RO Involvement:** Hepatosplenomegaly, jaundice, hypoalbuminemia, pancytopenia.

Diagnosis

- **Tissue Biopsy:** Gold standard (demonstrates CD1a/Langerin positivity).
- **Skeletal Survey:** Reveals classic "punched-out" lytic bone lesions without reactive sclerosis or periosteal reaction.
- **Imaging:**
    - **MRI Brain/Pituitary:** Thickened pituitary stalk (>3 mm), absence of posterior pituitary bright spot.
    - **HRCT Chest:** Cysts and nodules with upper/middle lobe predominance.
    - **PET-CT:** Modality of choice for staging and assessing treatment response.
- **Labs:** CBC, LFTs, Coagulation profile (to assess RO involvement); Urine osmolality/water deprivation test (if DI suspected).
- **Molecular Testing:** *BRAF V600E* and *MAP2K1* sequencing on biopsy tissue (guides targeted therapy).

Management (Histiocyte Society Guidelines)

- **Single System (Bone/Skin):**
    - Observation (some regress spontaneously).
    - Curettage or intralesional methylprednisolone for symptomatic bone lesions.
    - Topical steroids or topical nitrogen mustard for isolated skin LCH.
- **Multisystem or High-Risk Single System (e.g., CNS risk lesions in face/skull):**
    - **Standard First-Line: Vinblastine + Prednisone** for 12 months (LCH-III/IV protocol).
    - 6-week response is the strongest predictor of outcome.

- **Refractory/Relapsed or Severe RO+ Disease:**
    - Cladribine (2-CdA) + Cytarabine (Ara-C).
- **Targeted Therapy (Latest Update):**
    - **BRAF Inhibitors (Vemurafenib, Dabrafenib):** Highly effective for *BRAF V600E* mutated severe/refractory LCH.
    - **MEK Inhibitors (Trametinib, Cobimetinib):** Used for *MAP2K1* mutations or *BRAF*-wildtype MAPK pathway activation.

Complications & Prognosis

- **Overall Survival:** >99% for SS-LCH and RO-negative MS-LCH. ~80-90% for RO-positive MS-LCH.
- **Late Effects:** Occur in up to 50% of MS-LCH survivors.
    - Permanent Diabetes Insipidus.
    - Anterior pituitary deficits (Growth hormone deficiency).
    - Progressive neurodegeneration (cerebellar ataxia).
    - Secondary malignancies (solid tumors or leukemias).

Exam Summary

- **Core identity:** Inflammatory myeloid neoplasm driven by MAPK pathway mutations (*BRAF V600E* in ~50%).
- **Histology buzzwords:** Grooved nuclei, CD1a+, CD207 (Langerin)+, Birbeck granules (tennis racket).
- **Classic triad:** Skull defects, Exophthalmos, Diabetes Insipidus (Hand-Schüller-Christian).
- **Risk Organs (Determine mortality):** Liver, Spleen, Bone Marrow (NOT lung).
- **Treatment cornerstone:** Vinblastine + Prednisone; Vemurafenib for *BRAF*+ refractory cases.

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13. Write short notes on dermatomyositis

Subject: Important Questions

Definition

- Rare systemic autoimmune vasculopathy of childhood (peak 4–10 years).
- Targets microvasculature of skin, striated muscle, and GI tract.

Pathophysiology

- Humoral immune response → Complement (C5b-9/MAC) deposition on endothelial cells.
- Leads to capillary destruction → microvascular ischemia → muscle necrosis and classic **perifascicular atrophy**.

Clinical Features

- **Skin (Pathognomonic):**
    - **Heliotrope rash:** Violaceous discoloration with edema over upper eyelids.
    - **Gottron papules:** Erythematous, scaly plaques over extensor surfaces of MCP, PIP, DIP joints (unlike lupus, which spares knuckles).

- **Skin (Other):** Malar rash (crosses nasolabial folds), dilated/tortuous nailfold capillaries, shawl sign (erythema over upper back/shoulders).
- **Muscle:** Insidious, symmetrical, proximal muscle weakness (pelvic/shoulder girdle). Positive Gowers sign, difficulty climbing stairs.
- **Systemic & Red Flags:**
    - Bulbar weakness: Dysphonia, dysphagia, aspiration risk (requires urgent escalation).
    - GI vasculitis: Abdominal pain, melena, high risk of bowel perforation.
    - Pulmonary: Interstitial lung disease (ILD).

Diagnosis

- **Muscle Enzymes:** ↑ Creatine Kinase (CK), Aldolase, LDH, AST, ALT.
- **Autoantibodies:**
    - ANA positive in ~70%.
    - **Myositis-Specific Antibodies (MSAs) (Update - highly prognostic):**
        - *Anti-TIF1-γ:* Severe skin disease, lipodystrophy.
        - *Anti-NXP2:* Severe weakness, high risk of calcinosis.
        - *Anti-MDA5:* Amyopathic (skin only), severe rapidly progressive ILD, skin ulcerations.
- **Imaging:** MRI with STIR/T2-weighted imaging (Modality of choice; shows diffuse muscle edema/active inflammation; guides biopsy site).
- **Muscle Biopsy:** Classic finding is **perifascicular atrophy** and perivascular CD4+ T-cell/B-cell infiltrates (frequently bypassed now if MRI and clinical picture are definitive).

Management

- **First-line (Current Standard):** Systemic Corticosteroids (oral Prednisolone or IV Methylprednisolone pulses for severe disease) + **Methotrexate** (started early as a steroid-sparing agent).
- **Severe/Refractory Disease:**
    - **IVIG:** Highly effective for prominent skin involvement and bulbar weakness.
    - **Cyclophosphamide:** Drug of choice for ILD and GI vasculitis.
    - **Biologics:** Rituximab (refractory cases); JAK inhibitors (emerging for severe calcinosis/MDA5 disease).
- **Supportive:** Strict photoprotection (UV light triggers flares), early physiotherapy (prevent contractures), Calcium/Vitamin D.

Complications

- **Calcinosis cutis:** Dystrophic calcification in skin/fascia/muscle; causes severe pain and ulceration; highly specific to juvenile (vs. adult) dermatomyositis.
- **Lipodystrophy:** Loss of subcutaneous fat, associated with insulin resistance.
- Macrophage Activation Syndrome (MAS).

Exam Summary

- **Must-write buzzwords:** Heliotrope rash, Gottron papules, symmetrical proximal weakness, perifascicular atrophy.

- **Diagnostic test of choice:** MRI (STIR sequence) showing muscle edema.
- **Prognostic markers:** MSAs (Anti-NXP2 = calcinosis; Anti-MDA5 = ILD).
- **Core therapy:** Early Methotrexate + Corticosteroids; strict sun protection.