5th Edition

Solved Papers PEDIATRICS for PG Students

A Must for MD and DNB Pediatrics, DCH, CPS and Other Examinations Across India

Recommended by the Gold Medalists of various Universities (Gorakhpur, Gujarat, Karnataka, Madhya Pradesh, Puducherry, Rajasthan, West Bengal, etc.)

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Foreword
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JAYPEE

Contents

Basic Sciences of Anatomy, Physiology Related to Genetics—I

Systemic Diseases in Pediatrics: Respiratory, Cardiology, CVS, Neurology, Hematology, Nephrology, Rheumatology, Immunology, Metabolic, Gastroenterology, Growth and Development, Congenital and Acquired Disorders of Ear, Nose, Throat and Joints, Endocrine System, and Miscellaneous Diseases—III

Paper—III

Paper—IV

MD (Pediatrics) Examination, Summer 2020

Basic Sciences of Anatomy, Physiology Related to Genetics—I

Total duration: 3 hr **Total marks: 100**

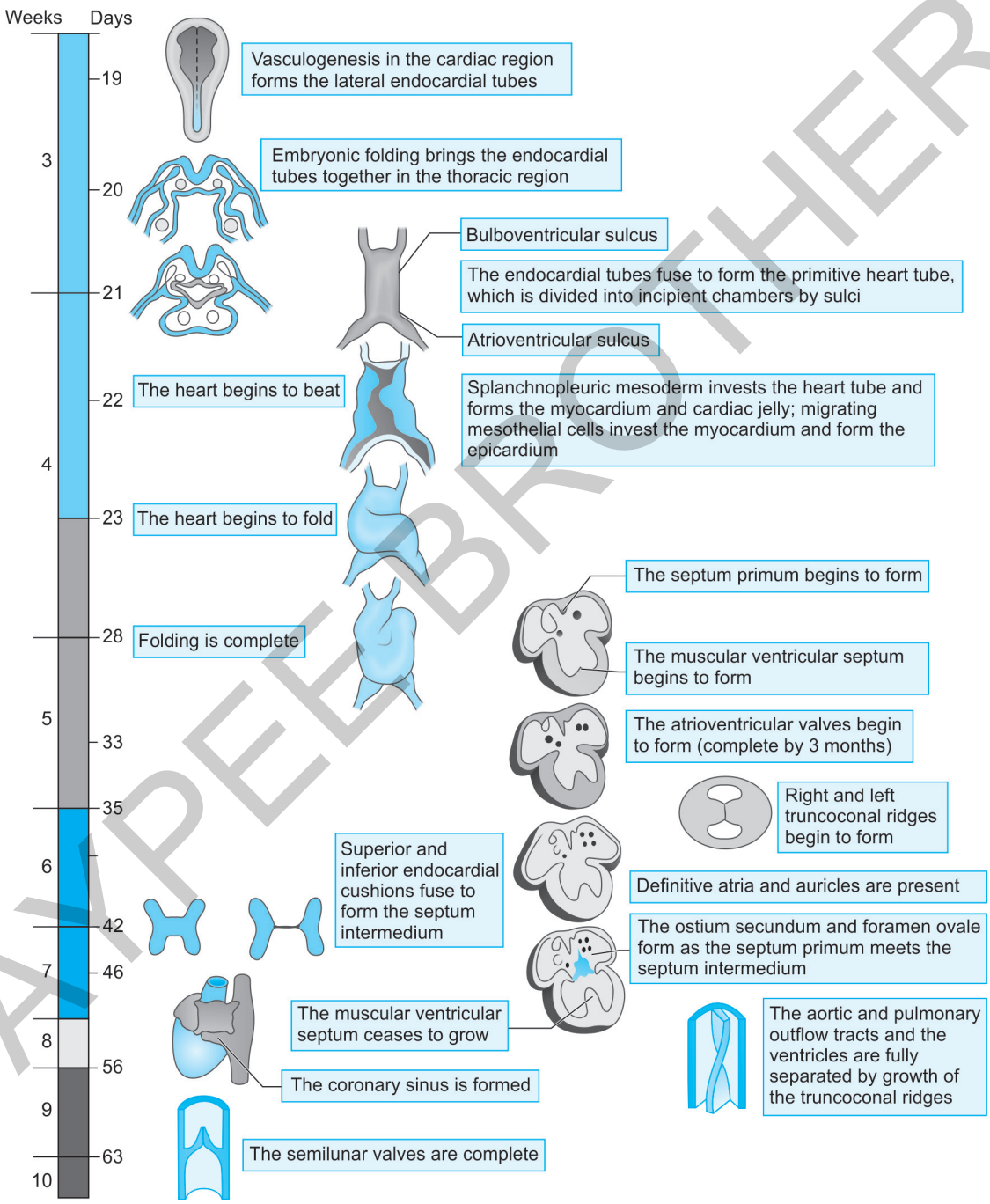
LAQ

1. Describe the development of fetal heart in details. Describe the transition from fetal to neonatal circulation. Add note on interventional cardiac catheterization.

Interventional Cardiac Catheterization

- Catheter treatment is the standard of practice for most cases of *isolated pulmonary or aortic valve stenosis as well as for recoarctation of the aorta.*
- A special catheter with a *sausage-shaped balloon* at the distal end is passed through the obstructed valve. Quick filling of the balloon with a mixture of contrast material and saline solution leads to tearing of the stenotic valve tissue, mostly at the site of inappropriately fused raphe.
- *Complication*: Creation of valvular insufficiency.
- *Balloon angioplasty* is the procedure of choice for cases with restenosis of coarctation of the aorta after earlier surgery.
- *Other applications* of the balloon angioplasty technique include:
  - Amelioration of mitral stenosis
  - Dilation of surgical conduits (e.g., RV-PA conduits)
  - Relief of branch pulmonary artery (PA) narrowing
  - Dilation of systemic or pulmonary venous obstructions
  - Long-used balloon atrial septostomy (Rashkind procedure) for transposition of the great arteries.
- Closure of a small *patent ductus arteriosus* (PDA) is routinely done with catheter-delivered coils, whereas a larger PDA can be closed with a variety of sandwich-type devices.
- Closure of *anomalous vascular connections* (coronary fistulas, venovenous collaterals in cyanotic heart lesions) can also be achieved using coils.
- *Secundum ASDs* can be closed with a double-disk occluder device.

- Interventional catheterization techniques are being adapted for use in the *fetus* with lesions, e.g., aortic stenosis to prevent their progression to more complex lesions, e.g., hypoplastic left heart syndrome (HLHS). In these procedures, after giving appropriate anesthesia, a needle is passed through the maternal abdominal wall, the uterine wall, and the fetal chest wall and directly into the fetal left ventricle. A coronary angioplasty balloon catheter is passed through the needle and across the stenotic aortic valve, which is then dilated. With the restoration of normal LV blood flow, normal LV growth potential is nearly restored.

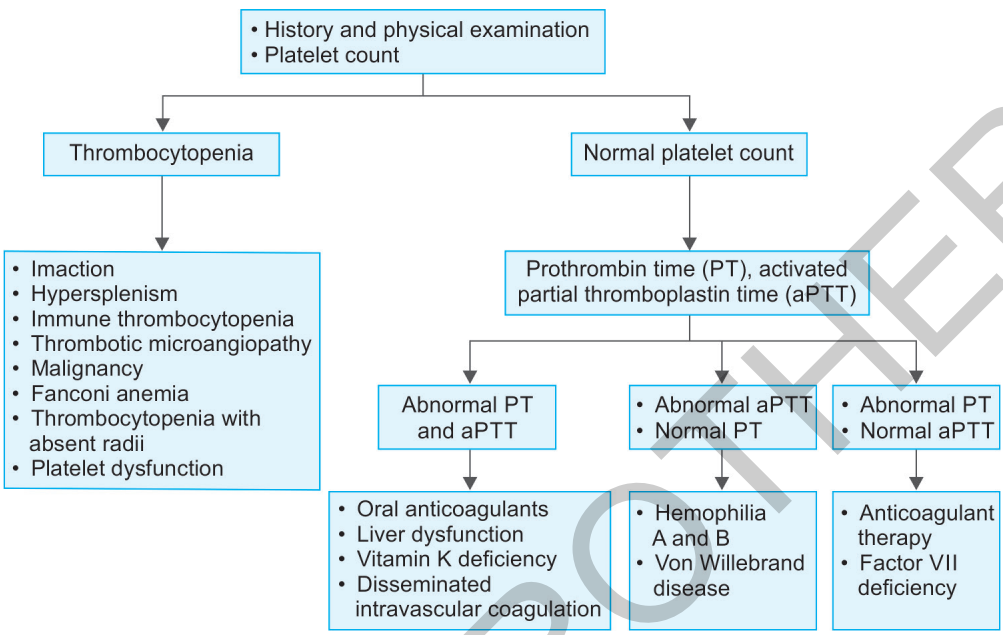


Development of heart. Timeline formation of the heart.

See DCH Summer 2018 I 3b (Page 138)

2. Discuss the physiology of hemostasis. Discuss the evaluation of child with bleeding/coagulation disorder.

See MD Summer 2014 I 2 (Page 241)



Evaluation of a child with bleeding/coagulation disorder.

SAQ

3. Any five out of six.

a. Gene therapy.

Definition

- Gene therapy is the introduction of a gene sequence into a cell with the aim of modifying the cell's behavior in a clinically relevant fashion.
- It may be used in several ways, e.g., to correct a genetic mutation (as for cystic fibrosis), to kill a cell (as for cancer) or to modify susceptibility (as for coronary artery disease).
- The gene may be introduced using a virus (usually a retrovirus or adenovirus) or by means of lipid or receptor targeting.
- Gene delivery to somatic cell to treat disease is ethical, and gene therapy should take place alongside other forms of medical treatment.

Gene Therapy Process

- In gene therapy, a normal gene is inserted into the genome to replace an abnormal gene responsible for causing a certain disease.
- Stem cells targeted in various diseases include blood (adenosine deaminase deficiency), bone marrow (Fanconi anemia), respiratory epithelium (α1-antitrypsin deficiency), tumor, liver (familial hypercholesterolemia), skin fibroblasts (hemophilia B), synovial membrane (rheumatoid arthritis), etc.

- A molecular carrier called a "*vector*" is used to release the gene, which needs to be:
  - Very specific
  - Display efficiency in the release of ≥1 genes of the sizes necessary for clinical applications
  - Not be recognized by the immune system
  - Be purified in large quantities and high concentrations so that it can be produced and made available on a large scale.
- Once the vector is inserted into the patient, it cannot induce allergic reactions or inflammatory process. It should:
  - Increase the normal functions
  - Correct deficiencies
  - Inhibit deleterious activities
  - Be safe not only for the patient, but also for the environment and for the professionals who manipulate it
  - Be capable to express the gene, in general, for the patient's entire life.
- *Limitations:* The presence of viral genetic material in the plasmid can induce an acute immune response, besides a possible oncogenic transformation.
- There are two main *approaches for genetic modifications* of the cells:
  1. Virus-mediated (Retrovirus, Lentivirus, Herpes virus, Adenovirus, Plasmid)
  2. Via physical mechanisms, from preparations obtained by advanced nanotechnology techniques. There are polymers that form networks that capture a gene and release its load when they penetrate the cells, e.g., DNA micro-injections, cationic polymers, cationic liposomes, and particle bombardment.

Gene Therapy Protocols

- The specific body cells that require therapy are to be identified and accessible.
- A way to effectively distribute the gene copies to the cells should be available, and the disorders and their genetic bonds should be completely understood.
- The target cell type of gene therapy is subdivided into two large groups: Gene therapy of the germline and gene therapy of somatic cells.
- In germline gene therapy, the stem cells, e.g., with the sperm and egg, are modified by the introduction of functional genes, which are integrated into the genome. The modifications are hereditary and pass on to subsequent generations. Theoretically, this approach must be highly effective in the fight against genetic and hereditary conditions.
- Somatic cell gene therapy is when therapeutic genes are given to an individual's somatic cells. Any modification and any effects are restricted only to that individual and are not inherited by future generations.

Disease	***Objective***
Adenosine deaminase deficiency	Substitution of the adenosine deaminase deficiency
α1-antitrypsin deficiency	Substitution of α1-antitrypsin
AIDS	Inactivation of the HIV-presenting Ag
Cancer	• Improvement of immune function • Tumor removal • Chemoprotection • Stem cell marking
Cystic fibrosis	Enzymatic substitution
Familial hypercholesterolemia	Substitution of low-density lipoprotein receptors
Fanconi anemia	Complement C gene release
Gaucher disease	Glucocerebrosidase substitution
Hemophilia B	Factor IX substitution
Rheumatoid arthritis	Cytokine release

Ethical issues: A large part of the scientific community approves genetic therapy in somatic cells, especially in cases of severe disorders, e.g., cystic fibrosis and Duchenne muscular dystrophy. Although, debate exists on various issues related to the misuse of gene therapy.

b. Hypokalemia.

Definition

It is defined as reduced serum K levels (i.e., <3.5 mEq/L).

Causes

- *Spurious*: High WBC count
- *Transcellular shifts:* Alkalemia, insulin, α-adrenergic agonists, drugs/toxins (theophylline, Ba, toluene, CsCl, hydroxychloroquine), hypokalemic periodic paralysis, thyrotoxic period paralysis, refeeding syndrome
- *Reduced intake:* Anorexia nervosa
- *Extrarenal losses:* Diarrhea, laxative abuse, sweating, Na polystyrene sulfonate (Kayexalate) or clay ingestion
- *Renal losses:*
  - *With metabolic acidosis:* Distal renal tubular acidosis (RTA), proximal renal tubular acidosis, uretero-sigmoidostomy, diabetic ketoacidosis
  - *Without specific acid–base disturbance:* Tubular toxins (amphotericin, cisplatin, aminoglycosides), interstitial nephritis, diuretic phase of acute tubular necrosis, postobstructive diuresis, hypomagnesemia, high urine anions (e.g., penicillin or penicillin derivatives)
  - *With metabolic alkalosis:*
    - *Low urine Cl^-:* Emesis or nasogastric suction, Cl^--losing diarrhea, cystic fibrosis, low-Cl^- formula, posthypercapnia, previous loop or thiazide diuretic use
    - *High urine Cl^- and normal BP:* Gitelman syndrome, Bartter syndrome, AD hypoparathyroidism, loop and thiazide diuretics
    - *High urine Cl^- and high BP:* Adrenal adenoma or hyperplasia, glucocorticoid-remediable aldosteronism, renovascular disease, renin-secreting tumor, 17β-hydroxylase deficiency, 11β-hydroxylase deficiency, Cushing syndrome, 11β-hydroxysteroid dehydrogenase deficiency
  - *Liddle syndrome*

Clinical Features

- The heart and skeletal muscle are especially vulnerable to hypokalemia. ECG changes include a flattened T wave, a depressed ST segment, and the appearance of a U wave, which is located between the T wave (if still visible) and the P wave. Ventricular fibrillation and torsades de pointes may occur. Hypokalemia makes the heart especially susceptible to digitalis-induced arrhythmias, e.g., supraventricular tachycardia, ventricular tachycardia, and heart block.
- Muscle weakness and cramps may occur. Paralysis can occur if K levels <2.5 mEq/L. It mostly begins in the legs and involves the arms. Respiratory paralysis may need mechanical ventilation. Some patients have rhabdomyolysis; the risk rises with exercise.
- Hypokalemia reduces gastrointestinal motility, leading to constipation. At K levels <2.5 mEq/L, an ileus may occur.
- It affects bladder function, and may cause urinary retention.
- It causes polyuria and polydipsia by affecting urinary concentrating ability, which results in nephrogenic diabetes insipidus.
- It stimulates renal NH_3 production, an effect that is clinically significant if hepatic failure is present, as the liver cannot metabolize the NH_3. Consequently, it may worsen hepatic encephalopathy.
- Chronic hypokalemia may lead to kidney damage, e.g., interstitial nephritis and renal cysts.

Diagnosis

- Child's diet, gastrointestinal losses, and medications history is taken.
- The presence of hypertension suggests excess mineralocorticoids. Concomitant electrolyte abnormalities are helpful clues.

- Hypokalemia with metabolic acidosis are mostly seen in diarrhea and distal and proximal RTA.
- A concurrent metabolic alkalosis is seen in emesis or nasogastric losses, aldosterone excess, use of diuretics, and Bartter and Gitelman syndromes.
- If a clear etiology is not apparent, the measurement of urinary K distinguishes between renal and extrarenal losses. The kidneys should conserve K in the presence of extrarenal losses. Urinary K losses can be assessed with a 24 hours urine collection, a spot K creatinine ratio, a fractional excretion of K, or calculation of the transtubular K gradient (TTKG):

  $$TTKG = (urine\ K/plasma\ K) \times (plasma\ osmolality/urine\ osmolality)$$

  Urine osmolality must be more than serum osmolality for the result of this calculation to be valid. A TTKG >4 in the presence of hypokalemia suggests excessive urinary losses of K.

Treatment

- Factors affecting the treatment are the K level, clinical symptoms, renal function, the presence of transcellular shifts of K, ongoing losses, and the patient's ability to tolerate oral K.
- Severe, symptomatic hypokalemia needs aggressive treatment. Supplementation is more cautious if renal function is poor doe to the kidney's limited ability to excrete excessive K.
- Serum K level does not always give an accurate estimation of the total body K deficit as there may be shifts of K from the intracellular space to the plasma. Clinically, such shifts occur most commonly with metabolic acidosis and the insulin deficiency of diabetic ketoacidosis; the serum K measurement underestimates the degree of total body K depletion. When these problems are corrected, K moves into the intracellular space, so more K supplementation is required to correct the hypokalemia. Likewise, the presence of a transcellular shift of K into the cells indicates that the total body K depletion is less severe. In an isolated transcellular shift, as occurs in hypokalemic periodic paralysis, K supplementation is used cautiously, given the risk of hyperkalemia when the transcellular shift resolves.
- Patients who have ongoing losses of K need correction of the deficit and replacement of the ongoing losses.
- Due to the risk of hyperkalemia, IV K should be used very cautiously. Oral K is safer, albeit not as rapid in urgent situations. Oral dose: 2–4 mEq/kg/day with a maximum of 120–240 mEq/day in divided doses); IV dose: 0.5–1.0 mEq/kg, usually given over 1 hour. The adult maximum dose is 40 mEq. Conservative dosing is generally preferred.
- KCl is the usual choice for supplementation, although the presence of concurrent electrolyte abnormalities should be considered. Patients with acidosis and hypokalemia can receive K acetate or K citrate. If hypophosphatemia is present, then some of the K deficit can be replaced with K phosphate.
- It is sometimes possible to reduce ongoing losses of K. For patients with excessive urinary losses, K-sparing diuretics are effective, but they should be used cautiously in patients with kidney disease.
- If hypokalemia, metabolic alkalosis, and volume depletion are present (with stomach losses), then restoration of intravascular volume with adequate NaCl will reduce urinary K losses. Correction of associated hypomagnesemia is essential as it may cause hypokalemia. Disease-specific therapy is effective in many of the genetic tubular disorders.

c. Neural tube defect.

Definition

CNS starts as a neural tube and folds into the brain and spinal cord by a complex mechanism during early embryologic development. Failure of normal closure results in neural tube defects (NTDs).

Types of NTDs

- *Primary NTDs:* They constitute the majority of NTDs and occur due to primary failure of closure of the neural tube or disruption of an already closed neural tube between 18 and 25 day' gestation. The resulting abnormality manifests in two anatomic lesions: an exposed (open or aperta) neural placode along the midline of the back caudally and rostrally and the Arnold-Chiari II malformation (malformation of pons and medulla, with downward displacement of cerebellum, medulla, and 4th ventricle into the upper cervical region), with associated aqueductal stenosis and hydrocephalus.

- *Myelomeningocele:* It is the most common primary NTD. A saccular outpouching of neural elements (neural placode), mostly through a defect in the bone and the soft tissues of the posterior thoracic, sacral, or lumbar (~80% cases) regions are seen. Arachnoid is typically included in the sac (meningo), which contains visible neural structures (myelo), and the skin is discontinuous over the sac. Hydrocephalus, Chiari II malformation and cerebral cortical dysplasia are also seen in these patients.
- *Encephalocele:* This defect of anterior neural tube closure is an outpouching of dura with or without brain, noted in the occipital region, and less commonly in the frontal, parietal, or temporal regions.
- *Anencephaly:* In this defect, the cranial vault and posterior occipital bone are defective, and derivatives of the neural tube are exposed, including both brain and bony tissue. It may extends through the foramen magnum and involve the brainstem. It is not compatible with long-term survival. Rachischisis is a more severe form wherein the spine is also involved due to nonfusion of the majority of the primary neural tube.

- *Secondary NTDs:* 5% of all NTDs result from abnormal development of the lower sacral or coccygeal segments during secondary neurulation. This leads to defects primarily in the lumbosacral spinal region. These heterogeneous lesions are rarely associated with hydrocephalus or the Chiari II malformation, and the skin is typically intact over the defect.
  - *Meningocele:* It is a spinal fluid-filled sac causing an outpouching of skin and dura without involvement of the neural elements aside from a commonly associated dorsal band of neurovascular tissue adherent to the sac. It may be associated with bone and contiguous soft tissue abnormalities.
  - *Lipomeningocele:* It is a lipomatous mass usually in the lumbar or sacral region, occasionally off the midline, typically covered with full-thickness skin. Adipose tissue frequently extends through the defect into the spine and dura and adheres extensively to a distorted spinal cord or nerve roots.
  - *Filum lipoma, sacral agenesis/dysgenesis, diastematomyelia, myelocystocele,* all may have varying degrees of bony involvement. As these lesions may be inapparent on physical examination of the child, the term occulta is used to describe them.

Etiology

Factors implicated include:

- Folic acid deficiency
- Maternal ingestion of the anticonvulsants carbamazepine and valproic acid and folic acid antagonists, e.g., aminopterin and certain antimalarial drugs
- Maternal diabetes
- Disruptive influences, e.g., antenatal irradiation and maternal hyperthermia
- Positive family history
- Genetic and chromosomal disorders such as trisomies 13 and 18, triploidy, and Meckel syndrome.

Prevention

- Women of childbearing age who are capable of becoming pregnant should consume 0.4 mg/day of folic acid to reduce their risks of having a fetus affected with NTDs.
- Higher doses (4 mg/day) beginning 1 month before conception to 12 (wkGA) are recommended for women with prior affected offspring.

Diagnosis

Antenatal diagnosis: The combination of maternal serum α-fetoprotein (AFP) determinations, antenatal USG, rapid acquisition fetal MRI scans, and AFP and acetylcholinesterase determinations on amniotic fluid where indicated, is useful to make antenatal diagnosis and to distinguish from abdominal wall defects.

- Maternal serum AFP measurements of 2.5 multiples of the median (MoM) in the 2nd trimester (16–18 wkGA) have a high sensitivity for myelomeningocele.
- Karyotype may also be done at the time of amniocentesis to detect associated chromosomal abnormalities.
- USG diagnosis through direct visualization of the spinal defect or through indirect signs related to Arnold-Chiari malformation can be done. The Chiari malformation is seen as a flattened cerebellum called a "banana

sign" and a transient frontal bone anomaly called a "lemon sign." USG can also show the level of termination of the normal cord and placode.

- Antenatal MRI may define the defect more accurately.

Evaluation

- *History:* This includes:
  - Detailed family history about occurrence of NTDs and other congenital anomalies or malformation syndromes
  - Presence of risk factors.
- *Physical examination:*
  - *Back:* The defect is inspected and note is made if it is leaking CSF. A sterile nonlatex rubber glove is used when touching a leaking sac. The location, shape, and size of the defect and the thin "parchment-like" overlying skin, is noted. The sac may be deflated with a wrinkled appearance. The curvature of the spine and the presence of a bony gibbus underlying the defect is checked. For suspected closed lesions, presence of hemangioma, hairy patch, deep dimple, or sinus tract, if present, are documented; USG of the lower spine can show the level of the conus and presence of normal root movement.
  - *Head:* The head circumference is recorded and plotted daily until stable postoperatively. At birth, some infants will have macrocephaly due to hydrocephalus, and still, more will develop hydrocephalus after closure of the defect on the back. USG is useful to assess ventricular size. The intracranial pressure (ICP) is assessed with the baby sitting upright by palpating the anterior fontanel and tilting the head and torso forward until the midportion of the anterior fontanel is flat. The fontanels may be quite large and the calvarial bones widely separated.
  - *Eyes:* Abnormalities in conjugate movement of the eyes are common and include esotropias, esophorias, and CNVI paresis.
  - *Neurologic examination:* The child's spontaneous activity and response to sensory stimuli in all limbs is observed.
  - *Lower limbs:* Deformities (e.g., clubfeet) as well as muscle weakness and limited range of motion are looked for. The thigh positions and skinfolds are examined and the Ortolani and Barlow maneuvers are done for evidence of congenital dysplasia of the hips. Dislocation of the hips can also be diagnosed by USG. Deep tendon reflexes are examined.
  - *Bladder and kidneys:* The abdomen is palpated for evidence of bladder distension or kidney enlargement. The pattern of urination is observed and the infant's response to the Credé maneuver is checked to evaluate residual urine in the bladder.
  - *General neonate assessment:* All neonates with neural tube defects are evaluated for the presence of congenital heart disease (especially ventricular septal defect), renal malformation, and structural defects of the airway, gut, ribs, and hips. Other findings of associated chromosomal anomalies may be noted. An ophthalmologic examination and hearing evaluation is important.

Consultations

The care of an infant with a neural tube defect requires the coordinated efforts of a number of medical and surgical specialists, e.g., neurosurgery, neonatology, genetics, urology, orthopedics, physical therapy and social service.

Management

- *Fetal surgery:* In utero repair is associated with lower rates of ventriculoperitoneal (VP) shunting and consistent reversal of hindbrain herniation. Long-term effects remain uncertain. However, it is associated with high risk of complications during pregnancy including premature delivery and tearing of the uterine wall from the surgical scar.
- *Perinatal:* Cesarean section prior to the onset of labor is the preferred mode of delivery as it decreases the likelihood of rupturing the meningeal sac and is associated with improved neurologic outcome.

- *Preoperative management:*
  - *Care of placode:* The neonate is kept in the prone position with a sterile saline-moistened gauze sponge placed over the defect covered by plastic wrap to reduce bacterial contamination and tissue damage related to dehydration.
  - *Infectious disease:* IV antibiotics (Ampicillin and Gentamicin) are given to diminish the risk of meningitis, particularly due to group B streptococci.
  - *Fluids/Nutrition:* As insensible losses are minimized by covering the lesion with plastic wrap, standard maintenance fluids are generally appropriate.
  - *Urologic/Renal:* Clean intermittent catheterization is indicated to check postvoid residuals until urologic and renal function are assessed.
- *Surgical treatment:*
  - Infants whose defect is covered with skin and whose nervous system is therefore not at risk for bacterial contamination may undergo elective repair, typically within the 1st 6 months of life.
  - The initial neurosurgical treatment of an open meningo-myelocele includes closing the defect to prevent infection and reducing the raised ICP. The back should be closed within the 1st 24–48 hours of life if safely possible to reduce the risk of infection. If intracranial hypertension occurs, then ventricular puncture or continuous ventricular drainage are done.
  - If hydrocephalus is severe from birth, it can be treated at the same time as the back closure.
  - Endoscopic 3rd ventriculocisternostomy with choroid plexus cauterization (ETV-CPC) can be done.
- *Postoperative management:*
  - *Neurology:* Baby should be kept prone or side-lying until the wound heals. Head circumference should be measured daily, particularly in the baby who has not had shunt placement. MRI brain and spine should generally be done postoperatively.
  - *Nutrition:* Feeding difficulties are commonly associated with the Chiari II malformation. Growth and nutritional status should be watched closely as well as the baby's ability to suck and swallow.
  - *Urologic/Renal:* Monitoring for urine output and postvoid residue by USG is required.

Prognosis

- Most of the children with NTDs survive.
- Some children may have neurological complications (e.g., raised ICP, shunt infection, seizures, lower limb paralysis, developmental delay, learning disabilities, hearing/vision disturbances), urological complications (e.g., urinary bladder incontinence, urinary tract infection, growth retardation), orthopedic complications (e.g., lower limb contractures, kyphosis/scoliosis) and endocrinopathies (e.g., growth hormone deficiency).

d. Clinical assessment of acid–base disorders.

Appropriate compensation during simple acid–base disorders.

Disorder	*Expected compensation*
Metabolic acidosis	$PCO_2 = 1.5 \times [HCO_3^-] + 8 \pm 2$
Metabolic alkalosis	PCO_2 increases by 7 mm Hg for each 10 mEq/L increase in serum HCO_3^-
Respiratory acidosis	
Acute	HCO_3^- increases by 1 for each 10 mm Hg increase in PCO_2
Chronic	HCO_3^- increases by 3.5 for each 10 mm Hg increase in PCO_2
Respiratory alkalosis	
Acute	HCO_3^- falls by 2 for each 10 mm Hg decrease in PCO_2
Chronic	HCO_3^- falls by 4 for each 10 mm Hg decrease in PCO_2

Normal values of arterial blood gases.	
pH	7.35–7.45
HCO_3^-	20–28 mEq/L
PCO_2	35–45 mm Hg

Three-step process for interpreting acid–base disturbances.
In step 1, determine whether the ph is low (acidemia) or high (alkalemia).
In step 2, establish an explanation for the acidemia or alkalemia.
In step 3, calculate the expected compensation and determine whether a mixed disturbance is present.

Step 1	Acidemia or alkalemia											
	Acidemia						Alkalemia					
Step 2	Low $[HCO_3^-]$			High pCO_2			High $[HCO_3^-]$			Low pCO_2		
	Metabolic acidosis			Respiratory acidosis			Metabolic alkalosis			Respiratory alkalosis		
Step 3	Low pCO_2	Expected pCO_2	High pCO_2	Low HCO_3^-	Expected HCO_3^-	High HCO_3^-	Low pCO_2	Expected pCO_2	High pCO_2	Low HCO_3^-	Expected HCO_3^-	High HCO_3^-
	Mixed metabolic acidosis and respiratory alkalosis	Simple metabolic acidosis	Mixed metabolic acidosis and respiratory acidosis	Mixed respiratory acidosis and metabolic acidosis	Simple respiratory acidosis	Mixed respiratory acidosis and metabolic alkalosis	Mixed metabolic alkalosis and respiratory alkalosis	Simple metabolic alkalosis	Mixed metabolic alkalosis and respiratory acidosis	Mixed respiratory alkalosis and metabolic acidosis	Simple respiratory alkalosis	Mixed respiratory alkalosis and metabolic alkalosis

e. Progeria.

Hutchinson-Gilford progeria syndrome (HGPS), or progeria, is a rare, fatal, autosomal dominant (AD) segmental premature aging disease.

Etiology

- *Incidence:* 1 in 4 million live births.
- There is no gender, ethnic, or regional bias.
- Progeria is almost always a sporadic AD disease.
- It is caused by a single-base mutation in the *LMNA* gene, which results in the production of a mutant lamin A protein called progerin. Lamin A is an intermediate filament inner nuclear membrane protein. It is found in most differentiated cells of the body.
- Without progerin-specific treatment, patients with progeria develop premature progressive atherosclerosis. They die of cardiac failure, mostly between ages 5–20 years. Progerin is found in high concentration in skin and the vascular wall of normal older individuals compared to younger individuals, suggesting a role in normal aging.

Clinical Features

Children develop the appearance of accelerated aging, but both clinical and biologic overlaps with aging are segmental, or partial. Physical appearance changes dramatically each year that they age.

- *Dermatologic changes:*
  - Skin findings are variable in severity and include areas of discoloration, stippled pigmentation, tightened areas that can restrict movement, and areas of the trunk or legs where small (1–2 cm), soft, bulging skin is present.

- Although usually born with normal hair presence, cranial hair is lost within the 1st few years, leaving soft, downy, sparse immature hair on the scalp, no eyebrows, and scant eyelashes.
- Nail dystrophy occurs later in life.

- *Failure to thrive:*
  - Apparently normal fetal and early postnatal development is seen. Abnormalities in growth and body composition are readily apparent during infancy.
  - Severe failure to thrive, generalized lipoatrophy, wasting of limbs, circumoral cyanosis, and prominent veins around the scalp, neck, and trunk are evident.
  - Weight is usually normal at birth, but gradually decreases to <3rd percentile despite adequate caloric intake.
  - Patients reach an average final height of ~1 m and weight of ~15 kg. Head circumference is normal. The weight deficit is more severe as compared to the height deficit. It is associated with the loss of subcutaneous fat. This results in the emaciated appearance characteristic of progeria.
  - Loss of subcutaneous fat leads to high sensitivity to cold temperatures and foot discomfort caused by lack of fat cushioning.
  - Overt diabetes is very unusual in progeria, but ~30–40% of children have insulin resistance.
- *Ocular abnormalities:*
  - Tightened skin and a paucity of subcutaneous fat around the eyes are seen.
  - Hyperopia and signs of ocular surface disease from nocturnal lagophthalmos and exposure keratopathy like corneal ulceration and scarring may be seen. Photophobia is present.
- *Craniofacial and dental phenotypes:*
  - Craniofacial disproportion, with micrognathia and retrognathia caused by mandibular hypoplasia is present.
  - Oral and dental manifestations, e.g., hypodontia, delayed tooth eruption, severe dental crowding, ogival palatal arch, ankyloglossia, presence of median sagittal palatal fissure, and generalized gingival recession may be present.
- *Bone and cartilaginous abnormalities:*
  - Development of bone structure and density shows skeletal dysplasia which is not due to malnutrition.
  - Due to the facial disproportion, narrow nasal bridge and retrognathia intubation is extremely difficult, and fiberoptic intubation is recommended.
  - Acroosteolysis of the distal phalanges, distal clavicular resorption, and thin, tapered ribs are early signs of progeria (as early as 3 months of age).
  - A pyriform chest structure and small clavicles may cause reducible glenohumeral joint instability.
  - Spine and bony pelvis growth are normal.
  - Dysplastic growth of the femoral head and neck axis result in coxa valgus (i.e., straightening of the femoral head-neck axis >125°) and coxa magna, where the diameter of the femoral head is disproportionately large for the acetabulum, resulting in hip instability.
  - Contractures in multiple joints (e.g., fingers, elbows, hips, knees, ankles) may be seen at birth and may progress with age due to changes in the laxity of the surrounding soft tissue structures (joint capsule, ligament, skin).
- *Hearing:* Low-tone conductive hearing loss is pervasive in progeria and indicative of a stiff tympanic membrane and/or deficits in the middle ear bony and ligamentous structures.
- *Cardiovascular disease:*
  - ~80% of progeria deaths are caused by heart failure, possibly precipitated by events, e.g., superimposed respiratory infection or surgical intervention.
  - Hypertension, angina, cardiomegaly, metabolic syndrome, and congestive heart failure are common end-stage events.
  - Cerebrovascular arteriopathy and stroke may occur.
- *Sexual development:* Females with progeria can develop Tanner stage II secondary sexual characteristics, including signs of early breast development and sparse pubic hair. They do not achieve Tanner stage III. More than 50% of females experience spontaneous menarche at a median age of 14 years.

- *Normally functioning systems:* Liver, kidney, thyroid, immune, gastrointestinal, and neurologic systems (other than stroke related) remain intact. IQ is normal, possibly due to downregulation of progerin expression in the brain by a brain-specific micro-RNA, miRNA-9.

Laboratory Findings

- Clinical suspicion should be followed by *LMNA* genetic sequence testing.
- Serum leptin is below detectable levels (>90% cases) and insulin resistance (60% cases).
- Platelet count is often moderately high.
- High-density lipoprotein (HDL) cholesterol and adiponectin concentrations decrease with increasing age to values significantly below normal.
- Otherwise, lipid panels, high-sensitivity CRP, blood chemistries, liver and kidney function tests, endocrine test, and coagulation tests are generally normal.

Differential Diagnosis

Wiedmann–Rautenstrauch syndrome, Werner syndrome, Cockayne syndrome, Rothmund–Thomson syndrome, restrictive dermopathy, and Nestor–Guillermo progeria syndrome.

Treatment and Prognosis

- Patients develop a severe premature form of atherosclerosis. Before death, cardiac decline with left-sided hypertrophy, valvular regurgitation, and pulmonary edema develop; neurovascular decline with transient ischemic attacks (TIAs), strokes, and sometimes seizures can result in significant morbidity. Death occurs generally between ages 5 and 20 years, with a median life span of 14.5 years, resulting from heart failure, sometimes with superimposed respiratory infection; from head injury or trauma, including subdural hematoma; and rarely from stroke or complications from anesthesia during surgery.
- Growth hormone (0.05 mg/kg/day SC) results in high rate of weight gain and overall size, but still well below that seen in normal children. Low-dose aspirin therapy is recommended at 2 mg/kg/day.
- *Under research:*
  - *Lonafarnib:* Farnesyl transferase inhibitor
  - Everolimus (mTOR inhibitor).

f. Leukopenia.

- *Leukopenia* is a WBC count 2 SDs below an age-appropriate mean (<9,100/mm^3 in neonates, <6,000/mm^3 in children 1 month to 2 years age, and <4,000/mm^3 in children >2 years age).
- Evaluation requires a careful history, physical examination, and review of the CBC with differential.
- *Lymphopenia:*
  - It is a decline in total lymphocytes below the lower range of normal (1,000/mm^3 in older children and 4,500/mm^3 in infants).
  - Most often, it results transiently from viral (e.g., HIV), fungal, or parasitic infections.
  - If lymphopenia persists, multiple cell lines are deficient, or common transiently acquired etiologies are not found, Ig measurements, flow cytometry, and CD4 and CD8 T-lymphocyte subset quantification are warranted.
- *Neutropenia:*
  - It is "mild" when the absolute neutrophil count (ANC) are 1,000–1500/mm^3, "moderate" if 500–1,000/mm^3, and "severe" (with high risk for a life threatening infection) if <500/mm^3.
  - Evaluation of neutropenia in children involves a tiered approach including serial neutrophil counts, peripheral blood smear, withdrawal of a potential inciting medication, further laboratory testing (kidney and liver function tests, electrolytes, CRP, blood pH, Ig, screening for autoimmune or infectious etiologies), or bone marrow examination.
  - Patients are at high risk for *infectious complications*.
    - Most infections result from organisms that are normal flora (gram negative bacteria, *Candida albicans*, varicella, and *Pneumocystis*).

- Other exogenously acquired agents are *Pseudomonas* or *Aspergillus* species. *E. coli*, *Pseudomonas*, and *Klebsiella* species are the most common gram-negative organisms infecting immunocompromised children. Coagulase-negative staphylococci are the predominant gram-positive organisms that cause infection, especially in patients with central venous catheters (CVCs).
- Anaerobic infections are uncommon.
- *Candida* and *Aspergillus* species are the most common fungal infections.
- Most common viruses are HSV, VZV, CMV, EBV, and adenovirus. *Pneumocystis* and *Toxoplasma* represent the major protozoan infections in this group.
- The standard approach for neutropenic patients with fever and no focus of infection is combination therapy to cover gram-positive and gram-negative bacteria.
- Ceftazidime (or Piperacillin/Tazobactam) and Vancomycin are used as initial therapy (especially in patients with a CVC).
- Children with pneumonia or perirectal infections may require antibiotics that cover pathogens, e.g., *Pneumocystis* and *Clostridium*.
- Culturing from all central-line ports, as well as percutaneously ("peripheral blood culture") is useful. Additional tests include a CBC with differential, urine analysis with Gram stain and culture, and X-ray chest.
- A tracheal aspirate with a culture should be considered in patients who are tracheally intubated.
- Most simple catheter infections can be cleared with antibiotics without catheter removal. Despite appropriate antibiotics, many catheters must be removed to clear the infection.

- Treatment to stimulate neutrophil recovery should be considered. Recombinant human granulocyte colony-stimulating factor (rhGCSF or GCSF) (5–10 μg/kg SC) stimulates the production of neutrophils from committed progenitor cells in the marrow, and is often used for chemotherapy-related neutropenia. An improvement is generally noted in 10–14 day to an ANC >1,500/mm^3.
- *Autoimmune neutropenia:*
  - It is caused by the production of Ab against neutrophil Ag.
  - This entity is usually self-limited, with recovery over several months.
  - Appropriate antibiotics should be given to febrile, neutropenic patients, as noted previously.
  - Treatment with rhGCSF is usually reserved for active bacterial infections or for prophylaxis against recurrent infections. Alternative treatments with steroids (Prednisone, 1–2 mg/kg/day for 1 week) and IVIg (a single dose of 1 g/kg) hasten recovery of the ANC.
- *Severe congenital neutropenia (SCN):*
  - It is severe neutropenia (ANC <200/mm^3) from birth.
  - Omphalitis, recurrent cellulitis, and abscesses are common.
  - SCN is most commonly secondary to heterozygous mutations in the elastase-neutrophil expressed (ELANE) gene.
- *Congenital cyclical neutropenia:*
  - It is caused by a defect in stem cell development, with ELANE gene mutations in 80–100%.
  - The duration of each cycle is ~21 day.
  - The most common manifestations are oral ulcers, stomatitis, pharyngitis, tonsillitis, lymphadenitis, cellulitis, otitis media, and sinusitis.
  - Presentation usually occurs in early childhood.
  - Infectious episodes should be treated with appropriate antibiotics and rhGCSF (5 μg/kg daily SC until the WBC count is ≥10,000/mm^3).

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