BASIC NEONATOLOGY

Lecture Notes

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Part (1)

Declaration:

Resemblance of any question, picture or image to any other source, book or journal is merely coincidental. This lecture notes is not intended towards any commercial benefits or monetary compensation.

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Contents

This content including curriculum for undergraduate and postgraduate students

Introduction, Neonatal history taking and Physical Examination

The neonatal period: is defined as **the 1st 28 days after birth** and may be further subdivided into:

1. Very early neonatal period (birth to <24 hr),
2. Early neonatal period (birth to <7 days)
3. Late neonatal period (7 days to <28 days)

Until the mid-20th century, the primary care of newly born infants was provided by the obstetricians. In the mid-20th century, pediatricians began to take care of the newborn.

Dr. Julius Hess in Chicago at 1914 opened the first 24-bed premature care center and considered the father of Neonatology in the world.

The neonatal period is a highly vulnerable time for infants as they are completing many of the physiologic adjustments required for extrauterine existence. The major causes of neonatal mortality are prematurity/low birthweight (LBW) and congenital anomalies. Mortality is highest during the 1st 24 hr after birth.

Neonatal history taking

- Newborn are examined immediately after birth to check for major abnormalities and to ensure that the transition to extra uterine life is without difficulty
- Greet the mother and introduce yourself
- Tell the mother what you are going to do, encourage her to ask questions and listen to what she wants to say

Personal information: Name, sex, address, and phone number

Maternal obstetric history (to find out risk factors)

- Maternal age
- Number of previous pregnancy?
- Number children
- History of abortion, prematurity or neonatal deaths
- History of blood group sensitization

Maternal medial history

- Maternal diabetes, hypertension, or other relevant diseases
- Transplacently transmitted diseases or infectious diseases

Birth events

- Time and date of birth – delivery either vaginal or cesarean section
- Fever and vaginal bleeding or foul smelling water around the time of delivery
- Premature rupture of membrane and duration if present
- Was the labour or birth difficult or complicated?

- Fetal distress, prolonged labour, , abnormal position and presentation and any other complication
- Did the baby cry immediately after delivery? Did he need resuscitation at birth

Neonatal Physical Examination

Examining a newborn requires patience, gentleness, and procedural flexibility

The important points to remember during a neonatal examination are given below.

1. Identify the neonate correctly
2. Assemble all records and cleaned equipment
3. Examine preferably in the presence of mother
4. Examination should be gentle and methodical
4. Wash hands thoroughly with soap and water and dry with lean cloth air dry
5. Warming the hands and stethoscope before use decreases the likelihood of making the infant cry.
6. Before even touching the infant, observe and assess color, activity, posture, maturity, and respirations.
7. It is easier to listen to the heart and lungs first and feel the pulses when the infant is quiet.
8. Head-to-toe Examination: Each part of the body gives a clue to the illness

Types of neonatal physical examination

The examination is done in three stages with different objectives in each of them.

1. Fast examination in the labor room

to detect critical conditions and life threatening anomalies incompatible with life and this fast examination includes the following:

1. APGAR sore after birth at 1, 5 at 5 minutes is more important
2. Level of consciousness and activity Color
3.Vital signs (heart rate, respiratory rate and temperature)

After the end of quick examination the newborn will be considered as

1. Normal →Proceed to other lines of examination.
2. Abnormal →Admit e.g. to NICU

2. Detailed examination is carried out within 24 hours

to detect any deviations from the baseline. including the following:

1.Measurements (weight, length, and head circumference)
2.Regional examination(head, limbs, skin, back and genitalia)
3. Systemic examination (neurological, cardiac, chest and abdomen)
4.Special examination for peculiar neonatal problems as Prematurity (assessment of gestational age), Congenital anomalies and Birth injuries

3. Third examination is done at the time of discharge,

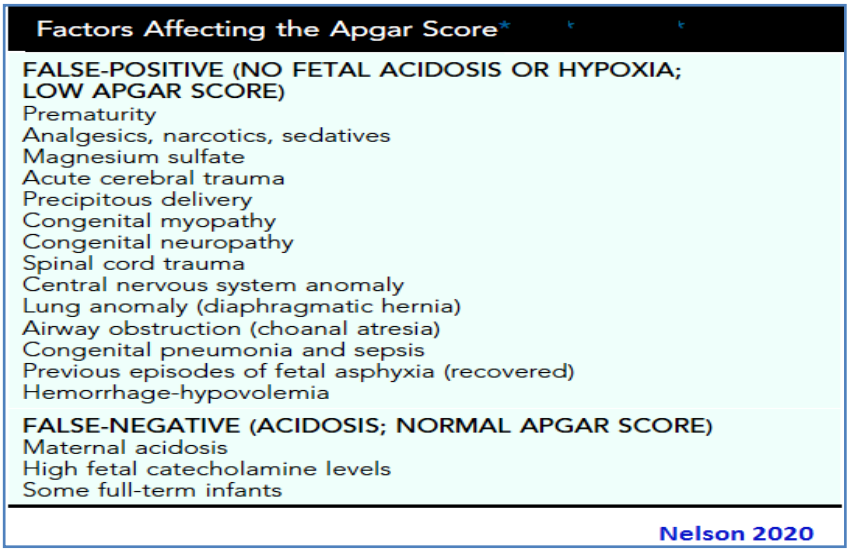
to detect any abnormality missed earlier or which might have appeared later

Apgar score

sign	0	1	2
Heart rate	Absent	Below 100	Above 100
Respiratory effort	Absent	Slow, irregular	Good, crying
Muscle tone	Limp	Some flexion	Good flexion
Response to catheter in nostril	No response	Some motion	Cough, sneezing
color	Blue, pale	Body pink, limb blue	All pink

It is a practical method to assess the condition of the newborn immediately after birth

1. The score assess 5 variables and each one takes a score of zero, one or two (total score 10)
2. The score is made at the following times:
3. At one minute to discover newborns who are depressed and are in need for resuscitation
4. At 5, 10, 15, 20 minutes to evaluate how resuscitation was successful (called **Expanded Apgar Score)**
5. Low score at 20 minutes is associated with high mortality and serious neurological sequelae



Interpretation of Apgar score:

1 - High score (10 – 8): good condition and needs routine care
2 - Moderate score (7 – 4): mild to moderate depression and needs usual resuscitative measures
4 - Low score (3 -0): severe depression and needs vigorous resuscitative measures. It strongly correlates with neonatal mortality.
5- Score <5 at 5 and 10 minutes increases the relative risk of cerebral palsy
6- A low 1-minute score does not correlate or predict the outcome of an infant.

It does not tell you if you need to resuscitate the infant. If an infant needs resuscitation, it should be started before the 1 minute of age score. The score also does not tell you what resuscitation steps are necessary and when to use them.

General Examination

Before disturbing a sleeping or a quiet infant, spend some time to assess his general appearance. Assess his state of arousal, cry, activity and color. This simple exercise gives invaluable amount of information about infant's well being

Level of consciousness

Normal newborn is conscious and active and responds to stimulation by crying or active movements

Disturbed consciousness as (lethargy – coma) indicate a serious cerebral lesion (hemorrhage) or severe sepsis
Poor or absent suckling indicate a serious illness as cerebral lesion (hemorrhage) or severe sepsis

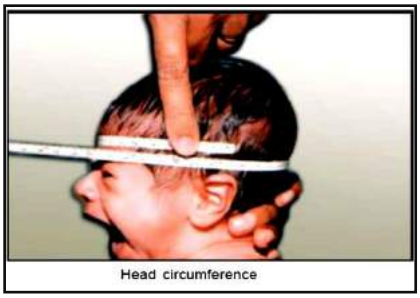
Posture

Posture reflects general neurological status and degree of maturity. Normal posture of a healthy neonate is that of universal flexion with head usually turned a little towards one side


Posture in a normal term baby

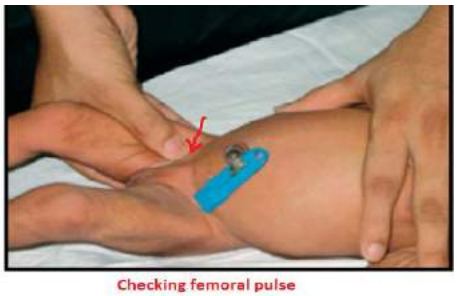
Measurements

Weight : 3.500 kg during the first 3-7 days the infant loses up to 10% of his birth weight and regain it by the 8th to 12th days
Length : Average 50 cm
Head circumference : Average 35 cm


Head circumference

Vital signs

Heart rate: 95 – 160 /minute, some infants, particularly those born postdates, may have resting heart rates as low as 80 bpm
Pulse best felt in the groin from the femoral artery
Tachycardia: heart rate ↑180/minute (hypoxia – heart failure etc…)
Bradycardia: heart rate ↓80/minute usually indicate hypoxia
Palpating the femoral pulse must always be noted so as not to assess coarctation


Checking femoral pulse


Checking axillary temperature

Respiratory rate: 30 -60 /minute
Tachypnea: respiratory rate ↑60 /minute ay caused by pulmonary, cardiac or metabolic condition.
Slow, shallow and irregular breathing: is usually associated with serious brain lesion as hypoxic ischemic encephalopathy (HIE)
Recurrent apnea: cession of respiration for more than 20 seconds and is significant when associated with bradycardia or cyanosis; it is common in premature infants
Periodic breathing is common in newborn short pauses (usually 5–10 seconds) are considered normal. **Oxygen saturation:** oxygen saturation <95% in a lower limb after the first day of life is abnormal **Temperature** of 36.5 – 37.4^{o}C
Temperature in the neonate is usually measured in the axilla

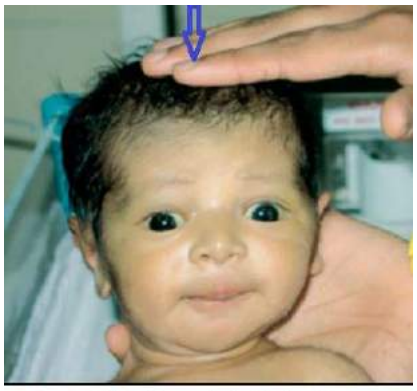
Fever: rectal temperature above 38.0^{o}C is caused by high environmental temperature or true fever (serious infection)
Hyperpyrexia: rectal temperature above 41. 0^{o}C is caused by overheating
Hypothermia: rectal temperature below 35.5^{o}C is caused by severe prematurity, cold exposure, bacterial sepsis
Blood pressure: Blood pressure is determined if a neonate appears ill or has a heart murmur
At birth 70/50 mmHg
Rising to 80/60 mmHg by the 4th day
A gradient between upper and lower extremity systolic pressure >10 mm Hg should be considered suspicious for coarctation or other anomalies of the aorta

Head

Examination of head should include the following points:

Superficial injuries-Scalp, defects, hair- Size-Shape-Localized swelling(caput-cephalhematoma) - Skull fractures-Sutures- Fontanelle-Craniotabes-Transillumination


Large head - Hydrocephalus


Checking anterior fontanel

Fontanelles

.Posterior fontanel: closed
.Anterior fontanel is opened and extremely variable in size(from 1 to 5 cm width)

Cranial bone

1.Craniotabes(softening of skull bones): Bone of the cranial vault is soft and connected by fibrous tissue so, if external pressure is applied → alternation of shape
2.Moulding (overriding of the cranial bones one upon the others) may be present

Caput succedaneum: is a diffuse edematous swelling of subcutaneous soft tissue of the scalp over the presenting part of the head presenting at birth. May extend over the middle line and may be associated with ecchymotic patches.The edema subsides spontaneously within the first few days

Cephalhematoma: is a subperiosteal hemorrhage that presents as a firm swelling limited to the surface of one cranial bone usually the parietal presenting hours after birth.

Abnormal features (mongolism)

Small head: (congenital microcephaly- congenital infection-chromosomal abnormalities)

Large head: mostly indicate hydrocephalus

Neck

Abnormalities are not common but include goiter, cystic hygroma, teratoma, hemangioma, lesions of the sternocleidomastoid muscle , webbing and clavicular fractures.

Face

Before labeling any subtle abnormality, the examiner should have a look at the parents and siblings look for (hypertelorism, cleft lip, nose anomalies and micrognathia

Eyes

Colopoma, Cataract, glaucoma or subconjunctival hemorrhage or discharge

Ears

Deafness, malformation, low set or periaurecular tag

Nose

Choanal atresia

Mouth

Mouth should be looked for size and symmetry. Inspection of inside of mouth is best done when child is crying. Pressing down on the chin can sometimes help. Mouth holds various normal variants and should be looked for. Use of tongue depressor is not recommended Look for cleft lip, cleft palate and oral moniliasis

Skin Following points should be noted in the examination of skin.

a. Color

Normal newborn varies from a pale pink (a sleep) to a deep red (crying), except for the possible normal cyanosis of the hands and feet (acrocyanosis).. Abnormal findings include:

Pallor: indicates (anemia – hypoxia – shock)

Central cyanosis: indicates (severe pulmonary disease – congenital cyanotic heart disease – serious brain lesion-polycythemia)

Plethora: it usually indicate polycythemia

Jaundice: it is a common problem which may be physiological or pathological

b.Texture: firm, loose, thickened (sclerema)

c. Superficial peeling of the skin in the

Normal pink looking baby

first week especially over the limbs

d. Vernix caseosa: white greasy ,waxy substance covering the skin to protect against amniotic fluids


Vernix caseosa

e. Lanugo hair: A fine and body hair. It presents mainly in the preterm. It may extent to term. It gradually disappears in the first month.

f. Dermal melanosis (Mongolian spots)

Flat ,blue-gray spots withskin texture, usually 2 to 8 cm wide, irregular in shape, with poorly distinguished edges, usually present at birth or soon after.


Mongolian spots

It usually lacated at the buttocks or lower back, and less commonly on the arms or trunk.

They fades slowly over the first few years

g. Neonatal urticaria: Papular lesions with erythematosus base on the trunk or extremities. It fades without treatment by 1 week

h. Milia: Inclusion cyst filled with debris, tiny white papules commonly seen on the face and scalp. It resolve spontaneously in the first weeks to months of life

i.Vascular abnormalities

1.Salmon patches(nevus simplex)

. Flat pink macular lesion found on forehead, upper eyelid

. Distended dermal capillaries that resolve by 1 year of age

2. Port wine (nevus flammeus)

. Flat mildly elevated reddish lesion mostly on face

. Associated with underlying hemangiomas in the region of 1st branch of trigeminal nerve. It may be associated with cortical lesions of the brain (Sturge Weber Syndrome)

Cavernous hemangioma

. Deep strawberry hemangioma→ platelets trapping.It requires: laser, surgery or drug therapy (steroid or alpha interferon)

j. Abrasions, eccchymosis

Breast engorgement

Incidence: at birth in both male and female infants with or without milk secretions

Prognosis: persist for several weeks, but may still present

Management: reassurance, never squeeze

Genitalia

Examination of genitalia should be a routine step in neonatal examination

Look for the following features in males: Length of penis (Stretched penile length under 2.5 cm is abnormal and requires evaluation) Position of urethral opening- Urinary stream- Rugosity of scrotum-Feel for both testes

- **Hypospadius and undescended** testes should be excluded.

-Scrotal swelling as congenital **hydrocele** is common

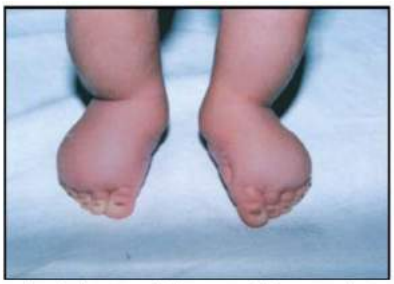
In term female babies labia majora completely cover the minora. Mucoid discharge, vaginal bleeding, hymeneal tags are common and require reassurance.

Ambiguous genitalia: A genitalia in which the sex cannot be determined is a medical

emergency

The anus should be checked carefully for patency, position, and size

Edema


Local edema over feet in a case of Turner syndrome

- Edema can be local or generalized. Physiological edema is commonly seen in preterm babies
- It appears by second day of life and disappears by end of first week

Causes of local edema:Caput - Superior vena cava syndrome - Turner syndrome - Vit E deficiency and congenital lymphedema

Causes of generalized edema:Physiologic - Anemia- Rh isoimmunization- Cardiac failure- Intrauterine infection-Congenital nephrosis - Over-hydration- SIADH - Renal causes

Limbs

Limbs should be examined for the shape, posture, symmetry and movements. Intrauterine position has greater influence on these parameters.

Look for birth trauma as Erb's palsy or fractures or congenital anomalies as talipus, polydactyly or syndactyly and hip examination

Joints

All newborns should be examined for the presence of developmental dysplasia of the hips

Back and spine

With the baby prone look for any midline abnormality such as swelling, dimple, tuft of hair, naevus or sinus.

Lymph nodes

Palpable lymph nodes are found in approximately one-third of normal neonates.

Gestational Age Assessment

Clinical assessment is based on changes in physical and neurologic characters with gestational age based on these changes many scoring systems have been described. One such system which is most widely used is **'New Ballard Scoring System'(see later)**

Systemic Examination (Neurological-Cardiac- Chest- Abdominal)

Neurological Examination

- Categorizing neurobehavioral observations into four systems **autonomic, motor, state, and responsiveness**
- Examination of the **neonatal autonomic** system includes evaluation of vital sign stability, neurocutaneous stability (pink color vs. mottling or cyanosis), gastrointestinal stability, and the presence or absence of jitteriness or myoclonic jerks.
-

- Assessment of the **motor system begins** with noting extremity and axial tone, particularly looking for asymmetries, such as those seen in brachial plexus injuries.
- Muscle tone (posture): a normal newborn has a posture of complete flexion of four limbs. Frog leg position indicate severe hypotonia
- **Neonatal reflexes(see later):** there are two types of reflexes; tendon reflexes(knee, ankles jerks) and Primitive reflexes (group of reflexes peculiar to neonatal period and early infancy) these reflexes are important for the following reasons:
  Evaluation of vision and hearing**:** optic blink and acoustic blink are useful in evaluation of vision and hearing of newborn
  Detection of focal lesions: asymmetric response is usually associated with a focal lesion
  Assessment of gestational age: the time of appearance of some reflexes can be useful in assessment of gestational age
  Persistence of some reflexes as Moro and Grasp reflexes above the age 4 months ay indicate cerebral palsy
  -**The six behavioral states** of the newborn include deep sleep, light sleep, drowsiness quiet alertness, active alertness (or fussing), and crying.
  -**The newborn's responsiveness** to the outside world can be observed. The ability to engage socially may be noted, including the ability to fi x on and follow a face and voice.

Cardiac Examination

Clinical presentation of neonatal cardiac disease

1.Central cyanosis
2.Heart sound, dysrrhythmias and Cardiac murmurs
3. Congestive heart failure
4.Apex to the right
5. Absent femoral pulsation

Apex beat: normally, the maximal intensity of the apex beat is in the 4th intercostal space just outside the mid-clavicular line. Apex beat to the right of the sternum **indicate Dextrocardia or a left sided pathology** pushing the heart to right as in pneumothorax
Cardiac murmurs: more than 90% of murmurs heard at birth are innocent transient murmurs
- Less than 10% of murmurs represent congenital heart disease
- Significant persistent murmurs necessities further evaluation including hest X ray, ECG and Echocardiography

Femoral pulsations: should be a routine step, a weak or absent pulsations should suggest coarctation of aorta

Chest examination

The thorax should be inspected for shape and symmetry and the clavicles should be palpated. **Rhythm of breathing**: a normal newborn has a regular breathing with no apneic spells. Apnea is present in prematurity and other pathological condition.
Pattern of breathing: A abnormalities includes respiratory distress (fast breathing, intercostal retraction and cyanosis) and respiratory depression (hypoventilation)
Stridor: the main causes are:
• Laryngomalacia
• Vocal cord paralysis
• Laryngeal webs
• Vascular ring
• Congenital subglotic stenosis
• Hypocalcemia
Chest auscultation: see before Look for (Shape- Bilateral expansion- Respiratory rate- Presence of retraction)

Abdominal examination

- The abdomen of a normal newborn is slightly distended and lax
- The liver may be normally palpated just below the costal margin
- Abdominal distension: observed in intestinal obstruction or septicemia
- Organomegaly: hepatoegaly and /or Splenomegaly should suggest congenital infection or metabolic diseases
- Scaphoid abdomen: should suggest diaphragmatic hernia
- Umbilical examination: umbilical sepsis, granuloma or hernia all are common problems that should be overlooked
  Main causes of **umbilical hernia** are
  • Normal Variant
  • Prematurity
  • Congenital hypothyroidism
  • Down's syndrome
  • Muopolysaccaridosis

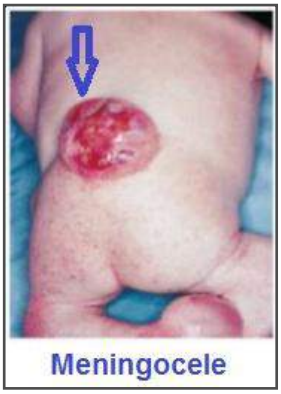
Special Examination

Congenital anomalies ''Head to toe'' examination is important for early detection of life threatening anomalies

- evident as abnormal features, limb defects or hernia
- Hidden as cardiac and renal anomalies
- Head anomalies: hydrocephalus microcephaly, encephalocele and abnormal features as Mongolism
- Limb anomalies: short limb, polydactyly, syndactyly or talipus
- Congenital hip dislocation: the hip and knee are flexed at right angles, and the thigh are abducted, during this maneuvere a dislocated femoral head will clunk back the

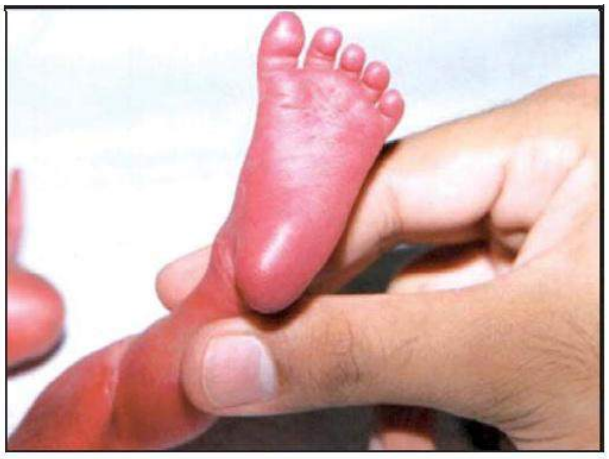
acetabulum (Ortolani maneuvere) this palpable clunk can be felt by the middle finger of each hand placed over each great trochanter

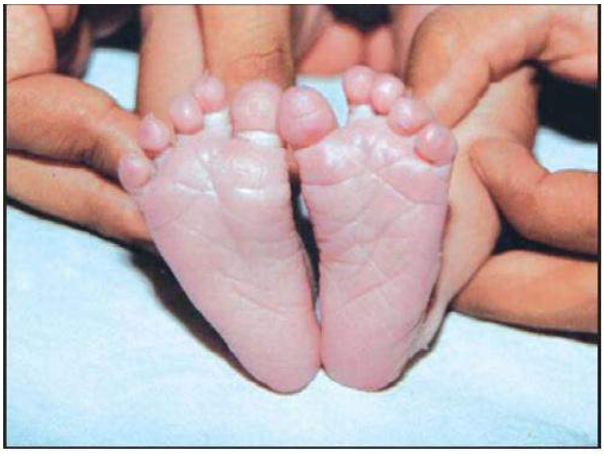
- Skin anomalies: birth marks, naevi and pilonidal sinus
- Back anomalies: meningocele and meningomyelocele
- Genital anomalies: undescended testes, hypospadius and hydrocele
- Hidden anomalies: congenital heart disease, respiratory anomalies (choanal atresia) gastrointestinal(diaphragmatic hernia, intestinal obstruction) and renal anomalies (congenital hydronephrosis)


Meningocele

Signs of prematurity

- Incomplete sole creases
- Underdeveloped genitalia
- Small breast nodules (less than 3 mm)
- Shapeless and pliable ear lobules
- Fine wooly scalp hair


Preterm baby-sole


Term sole

Neonatal Reflexes

Several transitory reflexes unique to the newborn period have been described and are exploited to examine the functional integrity and degree of maturity of the nervous system.these are primitive reflexes (brain stem and spinal cord centers). As cortical maturation proceeds, these reflexes gradually disappear. These reflexes are routinely tested in clinical examination

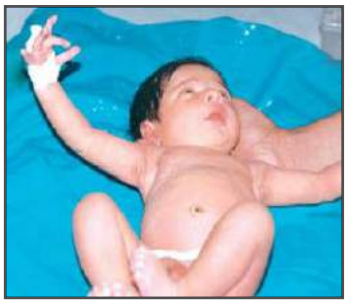
Moro's reflex

Methods:

-Raising the head of supine infant and allowing it to drop gently by 10° on to the examiner's hand supporting the shoulders

-Making a loud noise near the baby's ear

-Sudden withdrawal of the blankets from underneath the infant



The response: The responses are better seen in upper limbs than in lower

*Abduction of the shoulder and extension of the elbow

*The hands and fingers are held wide-open

*The arms are then moved as in embrace

*Vigorous cry follows

Normal response at birth indicate normal CNS

Abnormal response

Absence: Prematurity – intracranial birth injury – CNS depression

Asymmetrical response: Brachial palsy or fracture clavicle

Exaggerated: Hypoxic ischemic encephalopathy

Persistence after 6 months: Cerebral palsy or mental retardation

Suckling reflex

Method of Eliciting: Elicited by introducing clean finger into the mouth or better by putting the baby to breast.

Normal Response: Normal response is vigorous sucking. It is present from 28 weeks of gestation and disappears by 4 months.

Abnormal Response: Absence of sucking at birth or persistence beyond 7 months indicates developmental defect.

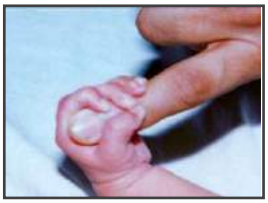
Rooting reflex

Method of Eliciting: By touching the corner of mouth lightly with finger tip or the lips upper or lower lip at midline

Response: Bottom lip is lowered on the same side and tongue moves towards the point of stimulating as finger slides away, head turns to follow it. It is present from 28 weeks but well elicited after 32 weeks. Sometimes it may not be elicited immediately after feeding. It disappears by 4 months in a wake state.

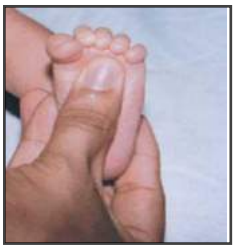
Abnormal Response: Absence at birth or persistence beyond 7 months indicates developmental defect.

Swallowing Reflex



Method: It is elicited by putting the baby to breast.
Normal Response: Rhythmical swallowing movements will be felt and seen at neck. It is present at birth and disappears by 6-9 months.
Abnormal Response: Decreased or absent in general neurological depression, hypotonia, immaturity and bulbar palsy.

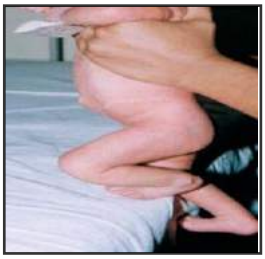
Palmar Grasp



Method: Elicited by applying pressure with index finger over ulnar aspect of palm. Normal **Response**: Infant grasps finger tightly. It is present at 28 weeks, but becomes strong by 32 weeks. At 37 weeks it becomes so strong, the infant can be lifted off the bed
Abnormal Response: Exaggerated following severe bilateral cerebral injury.

Plantar Grasp

Method: It is elicited by pressing a finger against balls of the infant's foot. Normal **Response**: Plantar flexion of toes. It is present at birth and disappears by 6-9 months.
Abnormal Response: Absent in spinal cord defects and asymmetrical in CNS defects.



Placing Reflex

Method: It is elicited by holding the infant upright so that dorsum of one foot touches the under surface of table edge.
Normal Response: Infant lifts the stimulated leg and places over the table.
Abnormal Response: Absent in depressed and anencephalic babies.


Stepping Reflex

Stepping

Method: Elicited by holding the baby upright with forward inclination and bringing the feet in contact with the surface
Normal Response: Is automatic walking. It is present at birth in full term babies and disappears by 6 weeks

Tonic Neck Reflex

This reflex differs from others in being less prominent in the newborn period but becomes marked at a few weeks of age
Method: Elicited by rotating the head slowly from midline position towards one side.
Normal Response: Consists of extension of upper limb on the side to which the face is rotated and flexion of the limb on the other side. Similar but variable of response is seen in lower limbs**.**

Abnormal Response: The TNR is an important indicator of neurological abnormality if the responses are excessive and obligatory. When unilateral, it indicates brain damage in the hemisphere opposite to the extended limbs.

Gallant's Reflex

Method: Elicited by ventrally suspending the baby and stroking with finger tip down the paravertebral area. **Normal Response**: It is swinging of pelvis towards the stimulated side.
Abnormal Response: This response may be useful as an aid in the localization of spinal cord lesions.


Gallant's Reflex

Babiniski reflex

Method: scratching the outer aspect of the feet
Response: dorsifliexion this reflex is normal in infant up to 2 years old (usually disappear by the age of 1 year)
Abnormal Response Persistence above 2 years of age → upper motor neuron disease


Babiniski reflex

Landau reflex

Method: the infant is held prone in a horizontal position
Response: the baby forms convex arc upwards with head, trunk and hips flexed and shoulders drawn back
Clinical significance
1- It appears at 3 months, and disappears at 9-12 months
2 – Delayed appearance suggests mental retardation or cerebral palsy

Pupillary reflex

Method: Exposure to bright light leads to pupillary constriction While exposure to dim light → pupillary dilatation **Clinical significance:** 1 – It appears at birth and persists 2 – It important for evaluation of vision

Neonatal Biochemical Screening

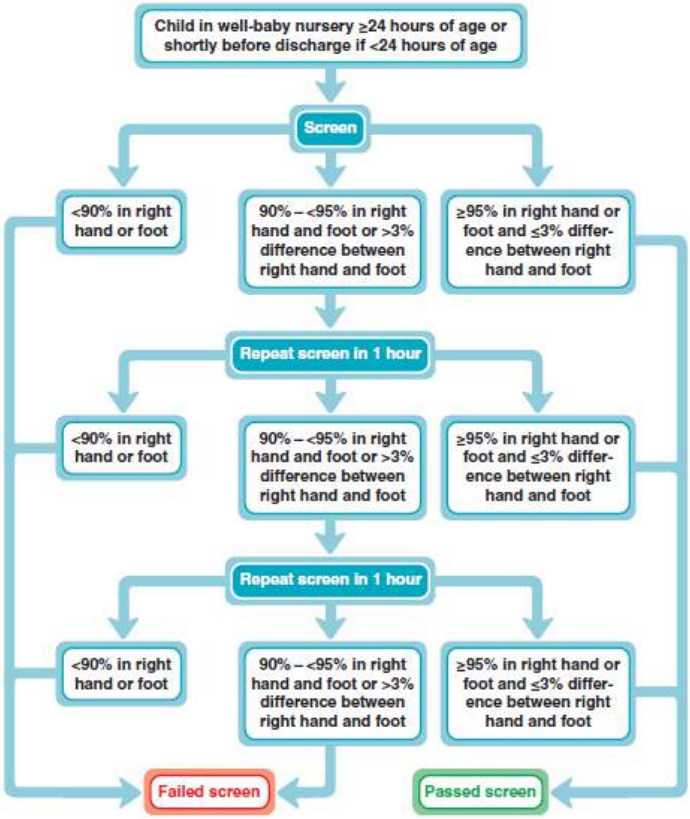
Definition: Simple and cheap tests to screen for many biochemical abnormalities

A. Maternal prenatal screening tests such as

1.Blood type, Rh, antibody screen.
2. Hemoglobin or hematocrit.
3. Rubella antibody.
4. HBsAg.

5. Serologic test for syphilis.
6. Human immunodeficiency virus (HIV).
7. Group B Streptococcus (GBS) culture..
8. Gonorrhea and Chlamydia cultures
9. Glucose tolerance

B. Pulse oximetry screening for all newborns between 24 and 48 hours of age (of pre- and postductal oxygen saturations) is most likely to help diagnose the following 12 CCHDs:



Screening algorithm for critical congenital heart disease using pulse oximetry.

Congenital heart disease is a common birth defect, occurring in approximately 1% of all newborns. CCHD, occurring in approximately 18 in 10,000 infants, is a life-threatening condition with significant morbidity and mortality in the newborn period. These conditions may require heart surgery or catheter-based intervention within the first year of life to prevent end organ damage or death. As of 2011, universal pulse oximetry screening is recommended for all newborns because low blood oxygen saturation may detect CCHD.

12 heart conditions that are detected by screening for CCHD with pulse oximetry include the following.

1. **7 most common critical lesions that present with hypoxemia**: Hypoplastic left heart syndrome, pulmonary atresia with intact ventricular septum, tetralogy of Fallot, total anomalous pulmonary venous return, transposition of the great arteries, tricuspid atresia, and truncus arteriosus.
2. **5 critical lesions that either are less common but present with hypoxia** or are morecommon and do not present with hypoxia): Coarctation of the aorta with patent

ductus arteriosus (PDA), double outlet right ventricle, Ebstein anomaly, interrupted aortic arch/aortic atresia, and single ventricle physiology.

C. Screening for neonatal sepsis risk

1. All newborns should be screened for the risk of perinatally acquired GBS disease Risk factors for early-onset neonatal sepsis include maternal GBS colonization in the genitourinary or gastrointestinal tract, gestational age <37 weeks, inadequate GBS prophylaxis, maternal intrapartum fever, rupture of membranes >18 hours, and signs of chorioamnionitis.

D. Cord blood screening for A blood type and direct Coombs, should be performed on any infant born to a mother who is Rh negative, has a positive antibody screen, or who has had a previous infant with Coombs-positive hemolytic anemia.

E. Newborn metabolic screen

Timing : After initiation of milk feeding between the 3rd and the 8th day (Routine collection of the specimen is between 24 and 72 hours of life), in some areas in the world, a second screen is routinely performed at 2 weeks of age.

Uses

1. Hypothyroidism 2. Galactosemia 3. Phenylketonuria 4. G6PD deficiency 5. Other conditions e.g. cystic fibrosis 6. Biotinidase deficiency. 7. Bilirubin screening before discharge from nursery 8. Glucose screening for infant of diabetic mothers 9. Group B streptococcal disease …..etc ast he number of this test increases yearly

F. Glucose screening

1. Infants should be fed early and frequently to prevent hypoglycemia.
2. Infants of diabetic mothers, infants who are SGA or LGA, and preterm infants should be screened for hypoglycemia in the immediate neonatal period

G. Bilirubin screening

1. Before discharge, all newborns should be screened for the risk of subsequent development of significant hyperbilirubinemia.
2. Risk factors for developing significant hyperbilirubinemia include hemolytic disease, prematurity, glucose-6- phosphate dehydrogenase (G6PD) deficiency, ethnicity (especially East Asian), presence of cephalohematoma or significant bruising, exclusive breastfeeding with weight loss, and a sibling history of phototherapy treatment.
3. Jaundice during the first 24 hours of life is considered pathologic and warrants a total serum bilirubin level.
4. The bilirubin result should be plotted and interpreted on an hour-specific nomogram to determine the need for phototherapy.
5. Parents should be given verbal and written information about newborn jaundice.

Hearing screening

Universal newborn hearing screening is recommended to detect hearing loss as early as possible.Neonatal intensive care unit (NICU) graduates are at high risk for developing hearing loss. When undetected, hearing loss can result in delays in language, communication, and cognitive development

The currently acceptable methods for physiologic hearing screening in newborns are **auditory brainstem response (ABR)** and **evoked otoacoustic emissions (EOAE).** A threshold of 35 dB has been established as a cutoff for an abnormal screen, which prompts further testing

A. Auditory brainstem responses (ABR)

measures the electroencephalographic waves generated by the auditory system in response to clicks through three electrodes placed on the infant's scalp.

B. EOAEs

This records acoustic "feedback" from the cochlea through the ossicles to the tympanic membrane and ear canal following a click or tone burst stimulus.

ABR is more recommended over the EOAE in high-risk infants including NICU patients . This is because the ABR tests the auditory pathway beyond the cochlea and picks up neural hearing loss including auditory dyssynchrony.

Infants who have **failed the screen in both ears** should have a diagnostic auditory brainstem response performed by a pediatric audiology specialist within 2 weeks of their initial test.

Infants with **unilateral abnormal** results should have follow-up testing within3 months The earlier habilitation starts, the better the child's chance of achieving age-appropriate language and communication skills

Degrees and Severity of Hearing Loss	Hearing Loss Range (dB HL)
normal	-10 to 15
slight	16 to 25
Mild	26 - 40 dB
Moderate	41 -55 dB
Moderately severe	56 to 70
Severe	71 - 90 dB
Profound	90 + dB

All infants should be monitored by their primary care providers for normal hearing and language development.

Infants who have risk factors for progressive or delayed-onset sensorineural and/or conductive hearing loss require continued surveillance even if the initial newborn screening results are normal.

Neonatal Resuscitation

Definition: Procedure applied to neonates who fail to establish respiration spontaneously.

With asphyxiation, the fetus develops **primary apnea,** during which spontaneous respirations can be induced by appropriate sensory stimuli such as drying.

If the asphyxial insult persists, the fetus develops deep gasping, followed by a period of **secondary apnea**, during which spontaneous respirations cannot be induced by sensory stimuli.

Death occurs **if secondary apnea is not reversed by ventilatory support** within several minutes. Because one can never be certain whether an apneic newborn has primary or secondary apnea, resuscitative efforts should proceed as though secondary apnea is present.

Normal transition at birth begins with lung expansion, generally requiring large negative intrathoracic pressures, followed by a cry (expiration against a partially closed glottis).

Umbilical cord clamping is accompanied by a rise in systemic blood pressure and stimulation of the sympathetic nervous system.

With the onset of respiration and lung expansion, pulmonary vascular resistance decreases, followed by a gradual transition (over minutes to hours) from fetal to adult circulation, with the closure of the foramen ovale and ductus arteriosus.

Goals of resuscitation:

1. To prevent hypoxic–ischemic tissue (brain, heart, kidney) injury
2. Minimizing immediate heat loss
3. Establishing normal respiration and lung expansion and fetal lung fluid is cleared
4. Increasing arterial PO2 by providing adequate alveolar ventilation.
5. Supporting adequate cardiac output.

General background

1. Approximately 10% of newborns require some resuscitation at birth and less than 1 % requires extensive resuscitation measures.
2. Every delivery should be attended by at least one person and at least two skilled persons should attend high risk deliveries
3. Thermal control should be of paramount concern and additional steps taken to ensure that the infant temperature remains normal during transition.
4. Most important and effective action in neonatal resuscitation is ventilating baby's lung
5. Exposure to oxygen at birth causes pulmonary arterioles to relax permitting a dramatic increase in pulmonary blood flow.
6. Mostly neonatal resuscitation can be anticipated
7. Preterm babies are at higher risk for needing resuscitation than babies

8. No additional steps are needed beyond drying and provision of warmth and initial stimulation in **most infant**.
9. Every hospital with a delivery suite should have a skilled resuscitation team and appropriate equipment available.
10. Cooperation between the obstetric, anesthesia, and pediatric staff is important.

Indications of resuscitation

The following antepartum and intrapartum events warrant the presence of a resuscitation team at delivery:

1- Evidence of non-reassuring fetal status including

a. Late decelerations, recurrent variable decelerations or bradycardia
b. Placental abruption, cord prolapse or history of decreased fetal movement

2 - Evidence of fetal disease or potentially serious conditions such as

a. Meconium staining of amniotic fluid
b.Prematurity, postmaturity, anticipated low or high birth weight
c.. Congenital anomalies
d.Hydrops fetalis
e. Multiple gestation

3 - Labor and delivery conditions including

a. Significant vaginal bleeding
b. Abnormal fetal presentation
c. Prolonged or unusual labor or possible shoulder dystocia

Steps for proper resuscitation

Ventilation of the lungs is the most critical action in neonatal resuscitation. PPV is indicated in newborns who are apneic, gasping, or have a heart rate <100 beats/min.

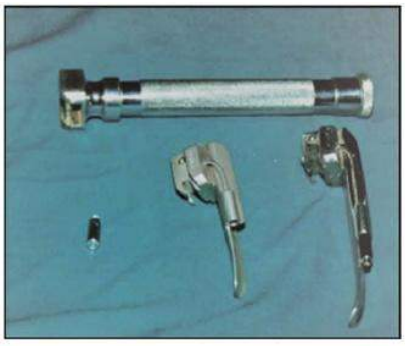
Prior to delivery

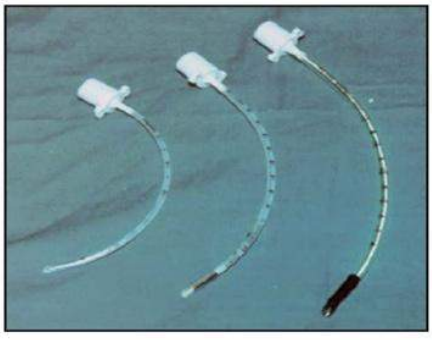
Antenatal counseling and equipment check.**Anticipate problems**

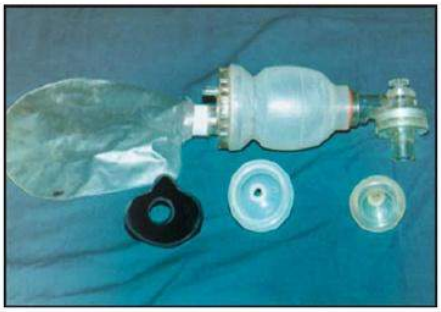
Adequate personnel: 2 persons if normal delivery is expected or 3 persons if a depressed infant is expected

Adequate equipments: Radiant warmer with procedure table or bed - Suction tubes - A blended oxygen source - -Flow-inflating bag-Face masks of appropriate sizes -Stethoscope with infant – or premature sized head

Pulse oximetry: The best defined data have been obtained using readings made at a "preductal" site **(i.e., the right upper extremity)** If the heart rate is difficult to detect, then a pulse oximetry that displays a heart rate or a 3-lead electrocardiogram (ECG) should be


Laryngoscope with straight blades


Endotracheal tubes


Bag and Mask

used. A 3-lead ECG may be more reliable than a pulse oximeter in cases of poor systemic perfusion.

End-tidal CO2 monitor

Transport incubator

Equipped emergency box or cart: Laryngoscope and extra batteries-Endotracheal tubes -Umbilical catheterization -Syringes, needles, T-connectors, and stopcocks

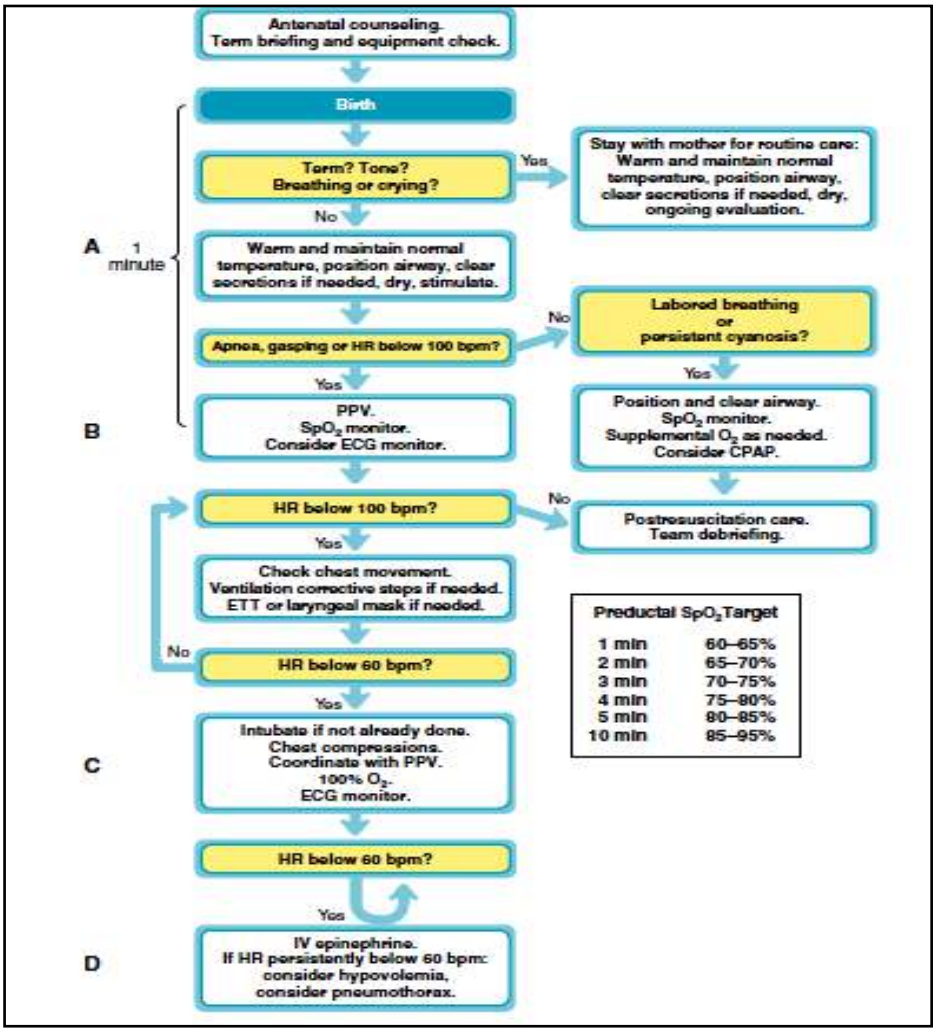
Medication(volume expanders, epinephrine, $NaCO_3$ and Naloxone)

During delivery

The team should be aware of the type and duration of anesthesia, extent of maternal bleeding, and newly recognized problems such as a nuchal cord or meconium in the amniotic fluid.

A. Immediately following delivery, begin a process of evaluation, decision, and action **(resuscitation)**

1. Place the newborn on the warming table.
2. Dry the infant completely and discard the wet linens, including those on which the infant is lying.
3. Place the infant with head in midline position, with slight neck extension.
4. Suction the mouth, oropharynx, and nares thoroughly with a suction bulb if there is obvious obstruction or the baby requires positive pressure ventilation.



(Algorithm for neonatal resuscitation)

Initial assessment: 3 questions

- Term gestation?
- Breathing or crying?
- Good muscle tone?

If yes: the baby should receive routine care: provide warmth, dry the baby, assure open airways then he should stay with the mother and ongoing evaluation

If any is no go to resuscitation according to the following algorithm

1- If the infant breathes spontaneously, heart rate is > 100 b/m, and colors becoming pink (Apgar score of 8 – 10), then he will need

1- keep warm and dry
2- Opening the airway: by proper neck position with head in midline position, with slight neck extension
3- Suctioning the airway: suction the mouth first, then nose
4- Stimulation appropriate form of tactile stimulation is gently rubbing the neck

2 – If the infant breathes spontaneously, heart rate is > 100 bpm, but the overall color appears cyanotic (Apgar score of 5-7) and labored breathing → free flow oxygen is indicated using an oxygen mask or tubing close to the infant nose and mouth

Reevaluate color, breathing and circulation in 30 seconds

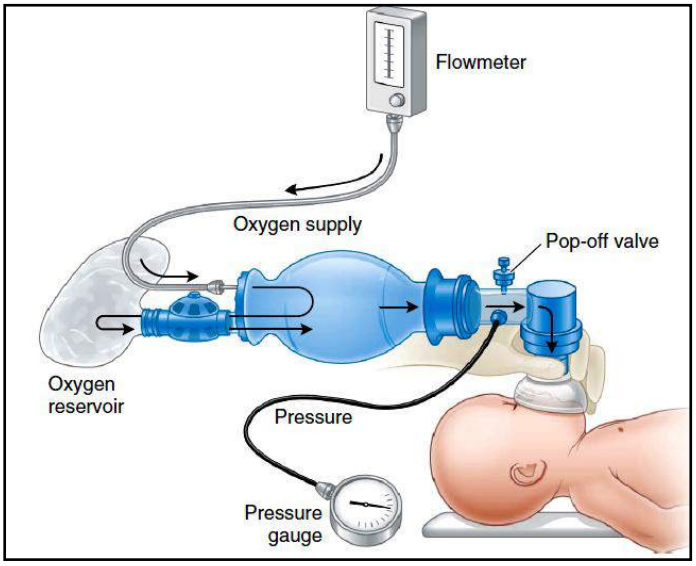
3- If apnea/gasping or heart rate less than 100 bpm even if breathing or persistent central cyanosis despite 100% free flow oxygen and consider CPAP

Positive pressure ventilation with bag and mask, SpO2 monitor and Consider ECG monitor.

Technique

1. Choose the size of the mask (covering mouth and nose not the eyes)
2. Recheck the position of the baby (slight extension of the neck)
3. Start ventilating at a rate of 60 breath /min.

Reevaluate after 30 seconds: HR if not improving: recheck the oxygen source, the bag, mask seal, position of baby and the presence of mouth

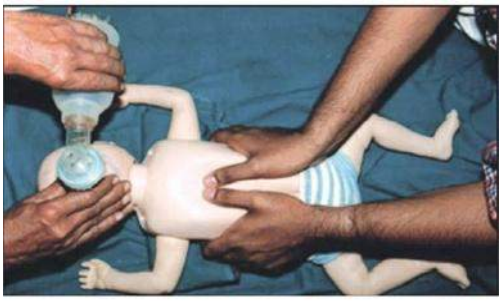


secretion, then:

1→If heart rate above 100 → stop PPV and reassess
2→If heart rate 60-100 → continue PPV with corrective step if needed, check chest movement and ETT and laryngeal mask if needed
3→If heart rate below 60 → intubate if not ready done, continue PPV and start chest compressions coordinate with PPV 100% O2.and ECG monitor.

Chest Compression

Rhythmic compressions of the sternum to compress the heart against the spine



Chest compression

Indications

1.Heart rate < 60 /min. after 15 seconds of positive pressure ventilation
2. Heart rate between 60 -80 /min. after 30 seconds of positive pressure ventilation

Importance

Compressing the heart against the spine, allowing blood to circulate to vital organs of the body

Method

- the baby placed on firm surface
- using the thumbs hands to depress the lower 1/3 of the sternum while the hands encircle the thorax **or** with the tip of the index and middle finger of one hand to compress the sternum while the other hand acts as support
- the depth of compression should be between 1 - 1.5 cm posteriorly
- rate is 90 compression and 30 ventilation in min
- continue chest compression till heart rate is greater than 60 bpm
- continue PPV at rate of 60 breath/min. till the HR > 100
- after30 seconds of coordinated chest compression and ventilation recheck heart rate
- If >60 bpm: stop compression and continue PPV at rate of 40-60/min
- If >100 bpm: stop compression and gradually stop PPV if the baby is breathing

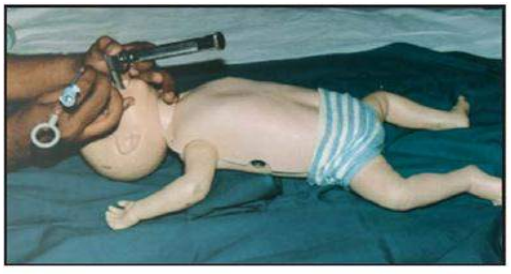
5- < 60: intubate the baby (if not done) and ensure route for epinephrine

Endotracheal intubation

For baby to breathe effectively, airway must be opened

Indications

1.Prolonged positive pressure ventilation
2.Tracheal suction
3.Expected diaphragmatic hernia
4.Ineffective bag and mask ventilation
5.Thick meconium in the amniotic fluid
6.Surfactant administration



Endotracheal intubation

Requirements

1.laryngoscope with different blades
2.ETT of different sizes and style

3.Suction device and adhesive tape
4.Bag mask and oxygen
Procedure : to be completed in 20 seconds
- Make sure ETT is correct
- Position of the infant on a flat surface with head in midline position and neck slightly extended - Stand at the head of the infant
- Stabilize the infant's head with the right hand slide the blade over the tongue allowing the tip to rest in the vallecula
- Lift the blade slightly by pulling the handle of the laryngoscope upwards moving the tongue out of the way and exposing the pharynx
- The glottis should be apparent with the two white vocal cords on either side
- Hold the ETT in your hand and introducing it to the Rt side of the mouth
- Once the cords are apart insert the tube and remove the laryngoscope
- Verify the position of the tube by watching for chest movement while applying bag ventilation
- If unsuccessful: Stop - Bag and mask ventilation - Then try again

Resuscitation medications

Indications: if heart rate less than 60/minute despite 30 second of adequate ventilation and chest compression
Route: IV, endotracheal or intrasseous
1. Epinephrine: indicated when the newborn infant remains bradycardic and profoundly hypoxemic despite being adequately ventilated through an endotracheal tube with 100% oxygen and receiving chest compressions**.** Epinephrine in a 0.1-mg/mL concentration (1:10,000) **is the only concentration that should be used in a neonatal resuscitation**.The volume given during resuscitation is 0.1–0.3 mL/ kg/dose IV or a 0.5–1 mL/kg/dose via endotracheal tube. **IV dosing is the preferred route** due to inconsistencies with administration and absorption via the ETT.
2. Volume expanders (saline or ringer) Indications: Hypovolaemia or baby not responding to resuscitation.**Action:** ↑ vascular volume and ↓ metabolic acidosis (by improving tissue perfusion).**Dose:** normal saline 10ml/kg over 5-10 minutes via umbilical vein.**Route:** IV
3. Naloxone: I**ndications**: respiratory depression. **Dose** and route: 0.1-0.2mg/kg IV. **Action**: narcotic antagonist
4. NaHCO3: Mostly not needed. Indications and This is due to a concern that CO2 is produced when sodium bicarbonate mixes with acid in the blood and that the excess CO2 may worsen acidosis in infants with impaired ventilation. In addition, rapid administration of sodium bicarbonate has been linked to intraventricular hemorrhage in preterm newborns. **Used in** : prolonged cardiac arrest. **Route:** IV. **Action:** increase vascular volume and decrease metabolic acidosis

The use of bicarbonate, naloxone, or vasopressors is not currently considered part of the acute resuscitation but can, under special circumstances, be used in the postresuscitation

Causes of failure of resuscitation

1.Delayed effective ventilation
2.Central apnea from brain insult

3.Upper airway obstruction
4.Lung pathology
5.Severe Hypovolaemia and shock

Withholding or withdrawing resuscitation

If there are no signs of life in an infant **after 10 minutes of aggressive resuscitative efforts,** with no evidence for other causes of newborn compromise, discontinuation of resuscitation efforts may be appropriate.

Contraindication of resuscitation

Neonatal resuscitation is not ethical and should not be offered in cases where there is no chance for survival. Examples of such cases include birth at <22 weeks' gestation, birth weight of 400 g. and some congenital malformations and chromosomal anomalies

Newborn Resuscitation Equipment Checklist	
Warm	□ Preheated warmer □ Warm towels or blankets □ Temperature sensor □ Plastic wrap or bag (<32 weeks) □ Chemical warming blanket (<32 weeks) □ Hat
Clear airway	□ Bulb syringe □ 10F or 12F suction catheter with 80–100 mm Hg wall suction □ Meconium aspirator
Auscultate/electrocardiogram (ECG)	□ Electronic cardiac monitor (ECG) and ECG leads
Ventilate	□Flowmeter set at 10 L/min □ Oxygen blender set at 21% if >35 weeks, 21%–30% if <35 weeks □ Positive-pressure device connected to a blender (positive endexpiratory pressure and peak inspiratory pressure set) □ Term and preterm masks □ 8F feeding tube and syringe □ Oral airway
Oxygenate	□ Equipment to give free-flow oxygen □ Pulse oximeter probe sensor and monitor □ Target oxygen saturation table
Intubate	□ Laryngoscope, size 0 and 1straight blades with bright light (size 00 optional) □ Stylet (optional) □ Endotracheal tubes (2.5, 3.0, and 3.5) □ End-tidal carbon dioxide detector □ Measuring tape and/or endotracheal tube insertion depth table □ Endotracheal tube securing device or waterproof tape and scissors □ Laryngeal mask airway, size 1, with 5-mL syringe
Medicate	□ 1 mg/10 mL (0.1 mg/mL) epinephrine □ Normal saline □ Code sheet for documentation □ Supplies for placing an emergency umbilical vein catheter and giving medications □ Intraosseous supplies (optional)
Data from American Academy of Pediatrics, American Heart Association, Weiner GM, et al: Textbook of Neonatal Resuscitation, 7th ed. Chicago, IL: American Heart Association and American Academy of Pediatrics Chicago; 2016.	

Classification of Newborns

Gestational age and birthweight classification help the neonatologist to categorize infants, guide treatment, and assess risks for morbidity and mortality. Neonates can be classified based on gestational age (preterm, late preterm, early term, full or late term, post term), birthweight (eg, extremely low birthweight, very low birthweight, low birthweight), and gestational age and birthweight combined (small for gestational age [SGA], appropriate for gestational age [AGA], large for gestational age [LGA]).

Classification According to gestational age (GA)

Gestation is the period of fetal development from the time of conception to birth. It is expressed in completed weeks (26-week and 4-day-old fetus is expressed as a 26-week fetus).
Neonates should be classified by GA as this generally correlates more closely with outcomes than birth weight does. Birth weight becomes significant if neonate is either SGA or LGA. Assessment is based on obstetric information and confirmed by modified Dubowitz (Ballard) examination for newborns.

Pre-term: infants are born before 37 completed weeks of gestation (258 days).
Subgroups of preterm infant include the following:
i. Extremely preterm infants are born <28 weeks (195 days).
ii. Early preterm infants are born <34 weeks (237 days).
iii. Late preterm infants are born between 34 0/7 and 36 6/7 weeks of gestation (238 to 258 days).
Term: between 37 and 41 6/7 weeks of gestation (259 to 293 days).
Early term infants are subgroup of term infants born between 37 0/7 and 38 6/7 weeks of gestation (259 to 272 days).
Full term 39 0/7 to 40 6/7 weeks
Late term 41 0/7 to 41 6/7 weeks
Post-term: infants are born after 42 weeks of gestation (295 days) or more.

According to birth weight

Although there is no universal agreement, the commonly accepted definitions are as follows:
A. Micro preemie**. <800 g.**
B. Extremely low birthweight (ELBW**). <1000 g.**
C. Very low birthweight **(VLBW). <1500 g**
D. Low birthweight **(LBW). < 2500 g. (*Moderate low birth weight*:** 1501 – 2500 gram)
2- ***Very low birth weight***: 1000-1500 gram
E. Normal birthweight **(NBW). From 2500 g. to 3990 g.**
F. High birthweight **(HBW). From 4000 g to 4500 g.**
G. Very high birthweight **(VHBW). >4500 g**.

According to birth weight in relation to gestational age

1. Small for gestational age: Birth weight less than the 10th percentile for gestational age or <2 standard deviations (SD) below the mean for the infant's GA. SGA is typically associated with maternal factors (eg, chronic disease, malnutrition, multiple gestation, high altitude, or conditions affecting the blood flow and oxygenation in the placenta [hypertension, preeclampsia, smoking]), placental factors (eg, infarction, previa, abruption, anatomic malformations), fetal factors (usually symmetric; birthweight, length, and head circumference all depressed the same), congenital infections (eg, TORCH [toxoplasmosis, other, rubella, cytomegalovirus, herpes simplex virus], chromosomal abnormalities, and congenital malformations (eg, dysmorphic syndromes and other congenital anomalies, fetal diabetes mellitus, familial causes, multiple gestation, constitutional).

IUGR (Intrauterine growth restriction (fetal growth restriction)) describes diminished growth velocity in the fetus as documented by at least two intrauterine growth assessments (e.g., a fetus that is "falling off" its own growth curve). fetus at <10th percentile weight for age or with a ponderal index <10% is sometimes used to classify an infant as IUGR.

2. Appropriate for gestational age: Birth weight between 10th and 90th percentile for gestational age

3. Large for gestational age: birth weight more than 90th percentile for gestational age or as 2 SDs above the mean for GA

Constitutionally small infants. Includes 70% of infants with a birthweight below the 10th percentile. They have no increased obstetrical or neonatal risks. They are constitutionally small, anatomically normal, well proportioned, and have normal development. They grow parallel to the lower percentiles throughout pregnancy. Mothers are usually slim, petite women.

Preterm Babies and Main Causes of Low Birth Weight Baby

Prematurity

Prematurity is the most common cause of neonatal mortality. Approximately 10% of all births are preterm.

Definition: a baby born before 37 weeks of gestations.

Etiology of prematurity:

is **unknown** in most cases. Preterm and/or LBW delivery is associated with the following conditions

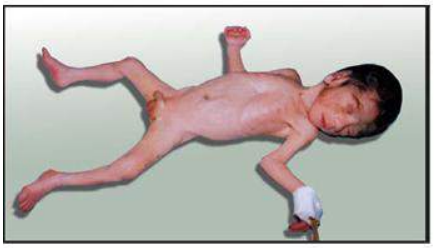
1-Obestetric causes: uterine anomalies- cervical incompetence-multiple pregnancy-placental separation-premature rupture of membranes and preeclampsia

2-Maternal: Acute or chronic disease or age younger than 16 or older than 35 years

3- Fetal: fetal hydrops, fetal distress, and erythroblastosis fetalis

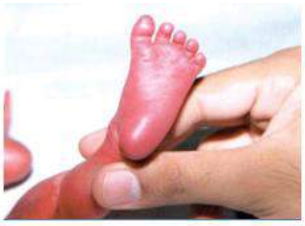
4- Multiple-gestation births

5- Others: trauma, iatrogenic and Low socioeconomic status (SES).


Frog like position

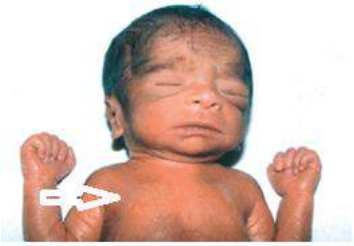
Features of prematurity

Frog like position, Incomplete sole creases, Underdeveloped genitalia(undescended testicles in male and widely separated labia majora not covering labia minor in female), Small breast nodules(less than 3 mm), Underdeveloped ear lobules with soft ear pinna, Fine woolly scalp hair ,excessive lanugo hair and dark red color skin


Incomplete sole creases

Complications of prematurity

Respiratory: Respiratory distress syndrome – Apnea - Recurrent aspiration - Bronchopulmonary dysplasia
Neurological: Perinatal depression- Intracranial hemorrhage - Periventricular leukomalacia – Kernictrus – Seizures
Cardiovascular : Patent ductus arteriosus -Hypotension - Bradycardia (with apnea) Cardiac dysfunction -
GIT: Necrotizing enterocolitis - Poor suckling and swallowing - Gastroesophogeal reflux disease
Hematological : Anemia of prematurity
Infections: Because of deficiencies in both humoral and cellular response, preterm infants are at greater risk for infection than are term infants


Small breast nodules

Metabolic complications: Hypoglycemia- hypocalcemia – hypomagnesaemia – Hypothermia – Hyperbilirubinemia – Osteopenia
Nutritional disorders
Temperature regulation. Preterm infants are especially susceptible to hypothermia; iatrogenic hyperthermia can also be a problem
Ophthalmological complications: Retinopathy of prematurity
Cutaneous complications
Renal : Hyponatremia – Hypernatremia – Hyperkalemia - Renal tubular acidosis- Renal glycosuria and Edema

Management of the preterm infant

1. Immediate postnatal management: Delivery in an appropriately equipped and staffed hospital is preferable.
2. Neonatal management
a. **Thermal** regulation should be directed toward achieving a neutral thermal zone; that is, environmental temperature sufficient to maintain body temperature with minimal oxygen consumption.
b. **Oxygen** therapy and assisted ventilation

c. **Fluid and electrolyte** therapy must account for relatively high insensible water loss while avoiding over hydration and maintaining normal glucose and plasma electrolyte concentrations.
d. **Nutrition** may be complicated by the inability of many preterm infants to tolerate enteral feedings, necessitating treatment with parenteral nutrition. When enteral feedings are tolerated, ineffective suck and swallow usually necessitate gavage feeding.
e. **Hyperbilirubinemia**, which is inevitable in less mature infants, can usually be managed effectively by careful monitoring of bilirubin levels and early use of phototherapy.
f. **Infection** may be the precipitant of preterm delivery. If an infant displays signs or symptoms that could be attributed to infection, the infant should be carefully evaluated for sepsis (e.g., physical exam, +/− CBC, +/− blood culture). There should be a low threshold for starting broad-spectrum antibiotics (e.g., ampicillin and gentamicin) until sepsis can be ruled out.
g**. Patent ductus arteriosus in preterm infants with birth weight >1,000 g often requires only conservative management with fluid restriction (usually 110 to 130 mL/kg/day) and supportive care.** Supportive care includes a neutral thermal environment, adequate oxygenation to minimize demands on left ventricular (LV) function, use of positive end-expiratory pressure (PEEP) to improve gas exchange in infants with respiratory compromise, and maintenance of the hematocrit at 35% to 40% to help increase pulmonary vascular resistance and reduce left-to right shunting. **In smaller infants, a prostaglandin antagonist such as indomethacin or ibuprofen may be necessary**. In the most symptomatic infants or those for whom medical therapy is either contraindicated or fails to close the ductus, surgical ligation may be necessary.
h**. Immunizations**. Diphtheria, tetanus toxoids, and acellular pertussis (DTaP) vaccine; inactivated poliovirus vaccine (IPV); multivalent pneumococcal conjugate vaccine (PCV); and Haemophilus influenzae type b (Hib) vaccine are given in full doses to preterm infants on the basis of their chronologic age (i.e., weeks after birth).

Long-term problems of preterm birth

1. Neurologic disability
a. Major handicaps (cerebral palsy, developmental delay)
b. Cognitive dysfunction (language disorders, learning disability, hyperactivity, attention deficits, behavior disorders)
c. Sensory impairments (hearing loss, visual impairment)
2. Retinopathy of prematurity
3. Chronic lung disease (CLD)
4. Poor growth. Preterm infants are at risk for a wide range of growth problems.
5. Increased rates of childhood illness and readmission to the hospital

Small for gestational age

Definition: birth weight below the 10^{th} percentile for gestational age

Etiology

1-Maternal: chronic diseases e,g, hypertension, heart diseases and collagen vascular disease.
2-Placental insufficiency e.g., pre-eclampsia, vascular malformation, multiple gestation

and placental infarction
3- Fetal causes: congenital infections, congenital anomalies, chromosomal disorders

Clinical picture

1- Measurements: weight, length and head circumference are below the 10th centile
. **Asymmetrical growth retardation**: due to factors that affect last part of pregnancy e.g. pre-eclampsia. The weight lies on a lower centile than that of the head.
. **Symmetrical growth retardation** occurs in early pregnancy e.g. congenital infections. Head circumference, length and weight, all decreased in a proportionate way
2- Skin: dry, loose, thick, decrease subcutaneous fat and malnourished appearance
3- Umbilical cord is thin
4- Ears, breast, and genitalia are mature
5 – Good muscle tone

Complications

Respiratory: Perinatal depression, meconium aspiration and pulmonary hemorrhage
Metabolic: hypoglycemia and hypothermia
Congenital infections are common
Congenital anomalies
Weight of 25000 gm or less is a common condition occurring in about 8% of all births

Main causes of low birthweight baby

- Prematurity (a baby born before 37 weeks of gestations)
  - Idiopathic
  - Antepartum hemorrhage
  - Premature rupture of membrane
  - Polyhydramnios
  - Fetal anomalies
- Dysmaturity (a full term baby who appears small for his gestational age and is asymmetric retardation caused by placental insufficiency)
  - Maternal chronic illness
  - multiple pregnancy
- Hypoplastic baby(a low birthweight baby caused by fetal problem and is symmetric retardation)
  - Chromosomal disorder
  - Congenital infection
  - Congenital anomalies

Large for Gestational Age

- **Definition**: birth weight above the 90th centile for gestational age or SDs above the mean for GA

- **Etiology:**

1- constitutional
2- Infant of diabetic mother
3- Hydrops fetalis
4- Some postterm infants
5. Beckwith-Wiedemann and other syndromes

Complications

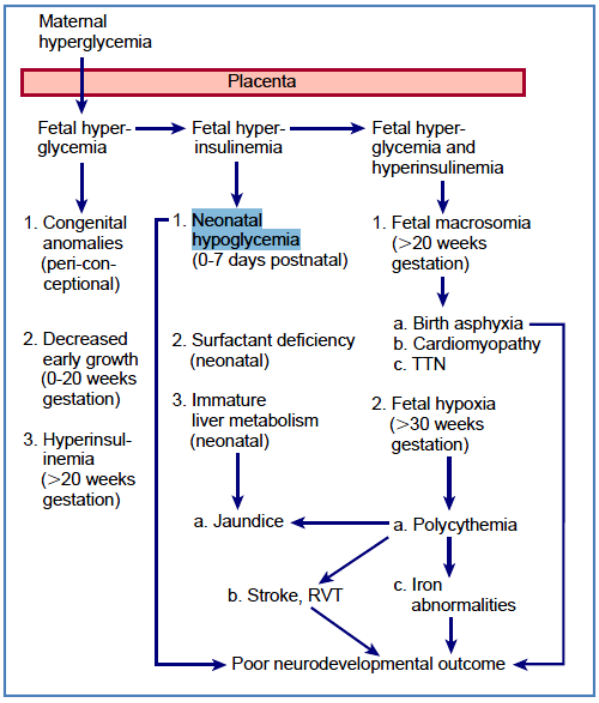
1- birth injuries
2- hypoglycemia
3- complications of infant of diabetic mothers
4- High neonatal mortality rate

Management

1- Look for evidence of birth trauma, including brachial plexus injury and Perinatal Depression
2- Allow the infant to feed early, and monitor the blood sugar level
3- Consider polycythemia

Infant of diabetic mother

- **Incidence:** 3% to 10% of pregnancies are complicated by abnormal glycemic control. The evaluation of the infant should begin before actual delivery.



- **Clinical features and complications of infant of diabetic mother**

Fetal problems

1- Malformations: cardiac malformations, neural tube defects, sacral agenesis,renal agenesis, and skeletal malformations.
2 - Macrosomia in 60% of infant of diabetic mother's → birth injury
3 - Intrauterine growth retardation in less than 5% of infants of diabetic mothers

Neonatal problems

1. Hypoglycemia resulting from hyperinsulinemia
2. Respiratory distress syndrome and transient tachypnea of the newborn
3. Hypocalcemia and Hypomagnesemia in 50% of case within 72 hours of birth

4. Polycythemia
5. Hyperbilirubinemia due to polycythemia and ineffective erythropoesis
6. Cardiomyopathy and heart failure
7. Hypoxic ischemic encephalopathy
8. Higher risk for delayed development
- 9. Higher risk for congenital malformations
10. Renal vein thrombosis

Investigations

1- Laboratory: CBC, blood glucose, calcium, bilirubin and magnesium
2- imaging: chest X ray, echocardiography and abdominal sonar

Management

1. Delivery should be in hospital
2 -supportive care should be given while a continuous evaluation of the infant is made.
3. After birth: monitoring for metabolic abnormalities especially hypoglycemia
- blood glucose should be done within 30 minutes of delivery, then at least 3 hourly for the first 48 hours
- start early feeding for asymptomatic infant
- if the infant is unable to tolerate oral feeding, glucose should be given by peripheral IV infusion at rate of 6- 8 mg/kg/minute
4. Careful monitoring of complications (NICU admission for unstable baby)
5.Every effort is made to involve the parents in infant care as early as possible

Neonatal Seizures

Definitions

Seizures: is defined clinically as a paroxysmal (transient) changes in neurological function (motor - sensory – experiential and autonomic) that is associated with an abnormal synchronous discharge of cortical neurons.

Epilepsy: is defined clinically as chronic condition characterized by 2 or more unprovoked seizures in a time frame of longer than 24 hr.

Key points

1. Seizures occur more frequently in the neonatal period than at any other time of life.
2. The exact basic mechanisms of neonatal seizures are unknown.
3. Incidence varies from 1 to 3.5 per 1,000 live births.
4. Most neonatal seizures are symptomatic due to underlying disorders.
5. Developmental immaturity in neonates influences many aspects of diagnosis, management and prognosis.
6. Clinical seizures pattern in neonates reflect the (reduced connectivity in the neonatal brain, with prominence of focal ectal characteristics and rarity of generalized patterns of clinical seizures.
7. The immature brain may be more susceptible developmental effect of anticonvulsant medication.
8. Many newborns may have more than one seizure type

Pathophysiology

The neurons within the central nervous system (CNS) undergo depolarization as a result of inward migration of sodium. Repolarization occurs via efflux of potassium. A seizure occurs when there is excessive depolarization, resultingin excessive synchronous electrical discharge. Possible reasons for excessive depolarization includes:

1. Failure of the sodium-potassium pump because of a disturbance in energy production.
2. Relative excess of excitatory versus inhibitory neurotransmitter
3. Alteration in the neuronal membrane, causing inhibition of sodium movement

Causes of Neonatal Seizures

Multiple possible etiologies may be identified in a neonate with seizures, such as HIE with hypoglycemia, hypocalcemia, and/or intracranial hemorrhage and each must be treated appropriately.

1.Hypoxic-ischemic injury

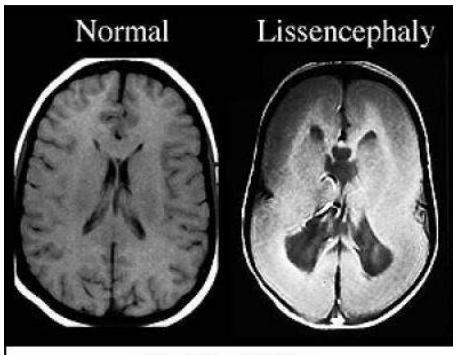
This is the most common cause of neonatal seizures, accounting for **over 50%of cases**

HEE can be global, as in perinatal asphyxia or focal (arterial infarction). Low Apgar score, suppuration of mental status, sometimes coma and hypotonia.Although the insult is global, the **seizures are usually focal** and may be multifocal and of **short duration** (<1 minute) but may be very frequent and refractory, especially in the first 24 hours.. In **focal ischemic lesion the infant appear** well and present with focal colonic seizures. In recent years, therapeutic hypothermia has become the standard of care in neonates with suspected hypoxic injury. Perinatal stroke is the second most common cause of seizures in the newborn period accounting for up to 20% of neonatal seizures. In focal ischemic lesions, such as middle cerebral artery stroke, the infant usually appears well and presents with focal clonic seizures.

2. Intracranial hemorrhage (ICHs):

Is responsible for 10 to 15 % of neonatal seizures.Subarachnoid hemorrhage is common in full term and may present with seizures in second day of life. These infants appear clinically well between seizures and have a very good outcome. Subdural hemorrhages are related to large infant size, breech delivery, and instrumentation. They are often associated with underlying cerebral contusions, which may be responsible for the seizures in some cases. Presenting seizures are usually focal and occur in the first few days of life. If large, subdural hematomas may require surgical treatment making diagnosis important. In the preterm infant, germinal matrix, intraventricular, and parenchymal hemorrhages are the prototypic neurologic complications of premature hypoxic injury.

3.CNS infections: Account for about 5% of neonatal seizures, congenital infection may present early (first 2 days). Postnatal sepsis complicated by meningitis the seizures occurring after the first 48 to 72 hours.



Lissencephaly

4.Malformation/structural lesions

Five percent of neonatal seizures are caused by cerebral dysgenesis Cerebral dysgenesis can cause seizure from the **first day of life**. Most common cerebral dysgenesis causing seizures are:
Hemimegalencephaly,lissencephaly and Polymicrogyria. Seizures are very refractory to medication. In general this infants are not encephalopathic interracially. Some Neurocutenous syndromes may present with neonatal seizures. Neuroimaging is primary in making these diagnoses

5.Acute metabolic disorders: These conditions are the focus of investigations in neonatal seizures and include Hypoglycemia,Hypocalcemia, Hypomagnesaemia andHyponatremia

a.Hypoglycemia: Definition is controversial, but responsible threshold for treatment are <40 mg/dl in the first 24 hours. And <50 mg/dl after 48 hours .Most hypoglycemic infants are asymptomatic but at any point, symptoms of neuroglycopenia should prompt immediate treatment. These are jitteriness/tremor, hypotonia, alteration of consciousness, poor feeding, apnea, and seizures.

b.Hypocalcemia: Hypocalcemia whole blood ionized calcium is the best measure of calcium status in ill infants. Hypocalcemia is considered present when iCa <4.4 mg/dl or <1.1mmol/L. **Early onset hypocalcemia occurs in first 3 days of life** and associated with
- prematurity - Infant of diabetic mother - Intrauterine growth retardation
- Perinatal asphyxia - Most are asymptomatic

Late onset hypocalcemia >7 days of life and associated with
- Hypoparathyroidism -Feeding of high phosphate formula
-DiGeorge syndrome - Some mitochondrial cytopathies - Hypomagnesemia

c.Hypomagnesemia: The most common cause is transient neonatal hypomagnesemia; hypomagnesemia must be corrected before hypocalcemia? Levels < 1.4mg/dl are considered low. Hypomagnesemia must be corrected before the hypocalcemia can be corrected as It causes parathyroid hormone resistance and so causes hypocalcemia.

d. Hyponatremia occurs because of improper fluid management or as a result of the syndrome of inappropriate antidiuretic hormone (SIADH).

e. Hypernatremia is seen with dehydration as a result of inadequate intake in breast-fed infants, excessive use of sodium bicarbonate, or incorrect dilution of concentrated formula.

6.Inborn error of metabolism

Inborn error of metabolism as a group causes 1 % of cases of seizures in the newborn. In these disorders infants initially appear well due to benefits of placental clearance of toxins until birth and only become encephalopathic and have seizures after 2 to 3 days. Biochemical markers for these disorders are hypoglycemia, metabolic acidosis, hyperammonemia and alternation in amino acids or organic acid profile

7.Pyridoxine dependency

Although rare, is an important cause of neonatal seizures as treatment available. Seizures present early, sometime in utero and infants are irritable. A test dose of pyridoxine 100 mg IV, with EEG and cardio respiratory monitoring resulting in immediate seizures cessation and resolution oh EEG abnormalities is diagnostic. 3 days trial of oral pyridoxine (30mg/kg/day) is recommended for non responders

8.Epilepsy syndromes: is a disorders that manifests as one or more specific seizure types and has a specific age of onset and a specific prognosis. These syndromes are rare, together accounting for about 1% of cases of seizures in the newborn period.

1.Benign familial neonatal convulsions :occur in otherwise well infants on day 2 to 3 of life, may be focal clonic or tonic, seizures resolve after a variable period, usually within 6 months and developmental outcome is normal

2.Benign infantile neonatal seizures (fifth day fits) Present suddenly on days 4 to 6 of life **and** often with frequent seizures leading to status epilepticus **.**Seizures are initially focal clonic often with apnea. Seizures usually cease within 2 weeks.

3.Early Myoclonic epilepsy (EME) often in the first few days of life with focal motor seizures and myoclonus and usually affects the face and limbs.. The seizures are very refractory to medication**.** EEG is characterized by a burst suppression**.** This syndrome is often associated with underlying metabolic disorders

4.Early infantile epileptic encephalopathy (Ohtahara syndrome) is associated with very refractory epilepsy**.** Characterized with early onset of tonic spasm, with focal motor seizures**.** Burst suppression and chaotic epileptiform pattern known as hypsarrhythmia on EEG

5.Malignant migrating partial seizures in infancy (Coppola syndrome)

May present from the first to the tenth month of life. ***Alternating focal*** motor seizures may occur, the etiology is unknowing.

9. Other high-risk subpopulations

a. Extracorporeal membrane oxygenation (ECMO) due to the high risk of cerebral injury during the transition to ECMO.
b. Congenital heart disease. Neonates that undergo surgery for congenital heart disease are known to be at risk for seizure

Diagnosis of neonatal seizures

Early diagnosis is important to allow:

1. Identification and treatment of underlying disorders
2. Treatment to prevent additional seizures and seizure-related systemic effects such as hypoxemia and hypertension
3. Treatment of seizures to prevent seizure- related excitotoxic neuronal injury.

Diagnosis of seizures in the neonate requires knowledge of:

1. The clinical patterns
2. Electrographic seizures at this age and confirmation with EEG.

Common clinical seizure patterns:

1. Focal clonic seizures: are more common in full-term infants
. This pattern may occur **unilaterally**, sequentially in different limbs, or simultaneously but asynchronously
. The movement is rhythmic biphasic with a **fast contraction** phase and a **slower relaxation**. Jerking 1-4 times /second
. Face, upper or lower limbs, eyes, or trunk may be involved.
2. Focal tonic seizures: occur primarily in premature infants.
. Patterns include a sustained posture of a single limb or trunk.
. Tonic horizontal eye and head deviation or asymptomatic tonic truncal postures.
. Only 30% of cases show EEG finding
3. Myoclonic seizures: are seen in both full-term and premature infants
. Rapid isolated jerking of muscles
. These are characterized by rapid movement usually of **flexion.**
. Generalized myoclonus, usually involving both upper limbs and less commonly the lower limbs (usually associated with an EEG seizure pattern).
4. Autonomic seizures (subtle): are more common in premature.
. This is the most common symptomatic pattern. Autonomic events such as apnea are associated with tachycardia rather than bradycardia and/or pupillary dilatation. These are often also associated with hypertension. In ***premature infants***, a wider range of clinical behaviors can be associated with electrographic patterns; for instance, self-limited short periods of otherwise unexplained (tachycardia – tachypnoea- and other autonomic changes may represents seizure in preterm infant, as may chewing, sucking, cycling movement. Staring, blinking, lip smacking

Notation of the seizure pattern When seizures are observed, they should be described in detail, including the site of onset, spread, nature, duration, and level of consciousness. Recognition of subtle seizures requires special attention.

EEG diagnosis

Continuous electroencephalogram (cEEG), defined as >3 hours of monitoring, is considered the gold standard for the diagnosis of neonatal seizures. cEEG is particularly important given the high proportion of neonatal seizures that are subclinical (studies suggest up to 80% of neonatal seizures are electrographic only) and would go undetected without continuous monitoring due to electroclinical uncoupling or dissociation. Many neonatal intensive care units (NICUs) rely on both routine EEG and amplitude-integrated electroencephalogram (aiEEG) to evaluate cerebral function in neonates.

A. Routine neonatal EEG recording, typically of 1 hour duration, allows assessment of

- Background activity
- Developmental maturity.
- Sometimes epileptogenic potential
- Routine recording is useful for prognostication.
- A typical clinical event may not be captured in such a short time

B. Prolonged EEG recording (hour-days) is helpful to capture a clinical event.

EEG usually demonstrates a rhythmic focal correlate associated with clinical event.

C. Amplitude-integrated EEG (aEEG) is a bedside technique increasingly used by neonatologist.The background EEG activity from a limited number of electrodes (2-4). One minute of EEG is thus represented by I mm of aEEG. This technique allows the neonatologist to continually assess the background EEG characteristics, and thereby judge the severity of encephalopathy.

Differential diagnosis of Neonatal Seizures

1. Jitteriness (benign tremors): Symmetrical rapid movements of the hands and feet, Stimulus sensitive, high frequency, low amplitude, and oscillatory not jerking movement. Activated and exacerbated by arousal. No associated abnormal eye movements or autonomic change and decrease with flexion of the extremity and gentle restraint.

2. Benign neonatal sleep myoclonus: occurs in term, healthy, thriving neonate. May be present from birth to 3 months, Bilateral, unilateral or Multifocal jerking during active sleep, Not stimulus related. Commonly involves the upper trunk and most common entity misdiagnosed as seizure in the neonate

3. Apnea of prematurity: Apnea and bradycardia in preterm neonate

Investigation of Neonatal Seizures

The approach to investigation should be individualized with an emphasis on early identification of correctable disorders through the following:

1. the **detailed history** of the pregnancy, labor and subsequent course

2. **EEG** monitoring of seizures
3. **General metabolic screening** (glucose, calcium, magnesium, electrolytes and blood gases)and error of metabolism screening(ammonia, lactate and amino acids in urine)
4. Assessment for **evidence of sepsis** (CBC, blood culture, CRP, ESR CSF analysis and Culture and TORCH screening)
5. **Neuroimaging** (ultrasound CT and MRI)

Management of Neonatal Seizures

1. Immediate management

A. airway opening
B. breathing: oxygen therapy to correct hypoxia
C. circulation: IV line and fluids (ringer or saline)

2. Correction of the cause

3. Control of convulsions with anticonvulsant

Correction of metabolic abnormalities

Hypoglycemia Dextrose 10%, 2–3 mL/kg IV
Hypocalcemia Calcium gluconate, 5% (50 mg/mL), 100–200 mg/kg IV 10% (100 mg/mL) 50–100 mg/kg IV if inadequate time for dilation
Hypomagnesemia Magnesium sulphate, 12.5% (125 mg/mL) 50–100 mg/kg IV
Hyponatremia Furosemide 1 mg/kg IV 3% NaCl 1–3 mL/kg over 15 to 30 minutes
Anti convulsants: Start an anticonvulsant if
1. Seizure lasting > 5minutes
2. Brief but frequent seizures > 3 /hour
3. Prolonged desaturations
4. Hemodynamic instabilityle

1.When anticonvulsant treatment is indicated Phenobarbital is the first drug
2.Other first line options include benzodiazepines (diazepam, lorazepam), phenytoin, liveteracetam and toperamite
3.No difference of efficacy between Phenobarbital and phenytoin

Phenobarbital: Affect GABA receptors to enhance GAPA-related inhibition. Alternation in acid-base balance in the newborn may affect efficacy of the drug. Its half-life is long , from 100 to 300 hours or longer in premature infants. An initial intravenous loading dose of 20 mg/kg may be followed by increments 5 to 10 mg/kg IV to a total of 40mg/kg with a higher doses associated with improved efficacy.
Phenytoin: Acts by blockade of voltage-dependent sodium channels, phenytoin is a weak acid and is poorly soluble in water. IV loading dose of 20 mg/kg at no greater than 1mg/kg /minute to avoid cardiac arrhythmia and hypotension. Maintenance dose between 2 to 3 mg/kg in 2 to 4 doses
Benzodiazepines (Diazepam – Lorazepam – Midazolam): Onset of action is

within minutes, diazepam may be more effective as a continuous infusion. Diazepam dose is 0.3 mg/kg IV an infusion. Lorazepam dose is 0.05 to 0.1 mg/kg. Midazolam is a short acting benzodiazepine that has been used as a continuous IV infusion (0.1-0.4mg/kg/hour) after an intial loading dose
(0.15mg/kg)

Levetiracetam

- The use of levetiracetam in the treatment of neonatal seizures continues to increase
- Why?
- Benign side effects and limited interactions
- dose
- Loading doses vary from 10 to 20 mg/kg
- Maintenance doses vary from 10 to 80 mg/ kg

Anticonvulsant for refractory cases

Topiramate. Topiramate is often used adjunctively after the acute phase of neonatal seizure for continued refractory neonatal seizures. Topiramate is thought to have neuroprotective properties. Studies of topiramate in human neonates are lacking.
Lidocaine has been used, mostly in Europe, as an IV infusion of 4 mg/kg/hour with decreasing doses over 4 to 5 days. This drug has a narrow therapeutic range and may induce seizures at higher levels.
DeVivo syndrome (glucose transporter deficiency). Treatment is **a ketogenic diet**.

Orally administered anticonvulsants that have been used adjunctively:

Carbamazepine (10 mg/kg initially followed by 15 to 20 mg/kg/day)
Valproic acid (three of six neonates developed hyperammonemia).

Explaination the poor efficacy of traditionally used GABA-ergic antiepileptic agents (Phenobarbital, benzodiazepines)

In some regions of the neonatal brain, GABA may temporarily act as an excitatory neurotransmitter. These developmental features may underlie the neonate's tendency to frequently recurrent seizures and may explain the poor efficacy of traditionally used GABA-ergic antiepileptic agents (phenobarbital, benzodiazepines

Prognosis of Neonatal Seizures

Mortality 20% totally and 10% in full term. Long term sequelae including cerebral palsy and intellectual disabilities still occur at a higher rate 30%to35

Clinical indicator for good outcome include

1. normal neonatal neurological examination
2. normal or mildly abnormal neonatal EEG background activity
3. normal Neuroimaging or abnormality limited to extraparynchymal

Hypoxic Ischemic Encephalopathy

Hypoxemia: decreased arterial **concentration** of oxygen.
Hypoxia: decreased **oxygenation** to cells or organs.
Ischemia: The reduction or cessation of **blood flow** to an organ.
Asphyxia: The state in which placental or pulmonary gas exchange is compromised or ceases altogether.
Neonatal encephalopathy. is a clinical and not an etiologic term that describes an abnormal neurobehavioral state consisting of an altered level of consciousness (including hyperalert state) and usually other signs of brainstem and/or motor dysfunction.

Causes of Neonatal Encephalopathy

1. Hypoxic ischemic encephalopathy
2. Perinatal stroke
3. Kernicterus
4. Metabolic derangements (inborn errors of metabolism, hypoglycemia)
5. Intracranial hemorrhage
6. Sinovenous thrombosis
7. Infection
8. Maternal toxins

Hypoxic-Ischemic Encephalopathy: is abnormal neurologic behavior in the neonatal period a rising as a result of a hypoxic-ischemic event as evidenced by neuroimaging (head ultrasonography [HUS], magnetic resonance imaging [MRI], computed tomography [CT]) or pathologic (postmortem) abnormalities.
Perinatal asphyxia: Is a condition during the first and second stages of labour in which impaired gas exchanges leads to fetal acidosis, hypoxemia and hypercarbia.

Incidence of Hypoxic-Ischemic Encephalopathy

Occurs in 1-6 per 1000 live term births in developed countries, approximately 20-30% of infants with HIE die in the neonatal period, and 33-50% of survivors are left with permanent neurodevelopmental abnormalities (cerebral palsy, mental retardation)

Etiology of Hypoxic-Ischemic Encephalopathy

Most cases of HIE follow a significant hypoxic event immediately before or during labour or delivery

Risk factors of perinatal asphyxia include the following:

1. Impairment of maternal oxygenation
2. Decreased blood flow from mother to placenta
3. Decreased blood flow from placenta to fetus
4. Impaired gas exchange across the placenta or at the fetal tissue level
5. Increased fetal O2 requirement

1. Maternal factors: Cardiac arrest, Asphyxiation, Severe anaphylaxis,Status epilepticus , Hypovolemic shock, Ruptured uterus

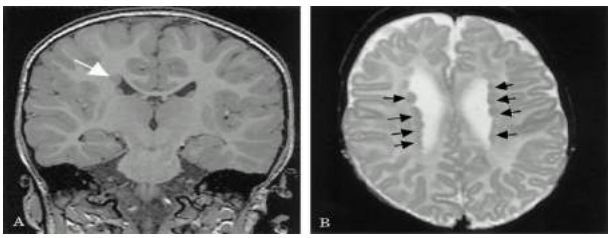
2. Uteroplacental factors: Placental abruption, Cord prolapse, Uterine rupture, Hyper stimulation with oxytocic agents

3. Fetal factors: Fetomaternal hemorrhage, Twin to twin transfusion, severe isoimmune hemolytic disease Cardiac arrhythmia, intrauterine growth retardation (IUGR)

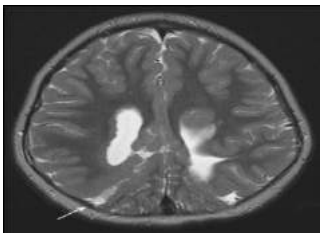
Pathophysiology

Gestational age plays an important role in the susceptibility of CNS structures

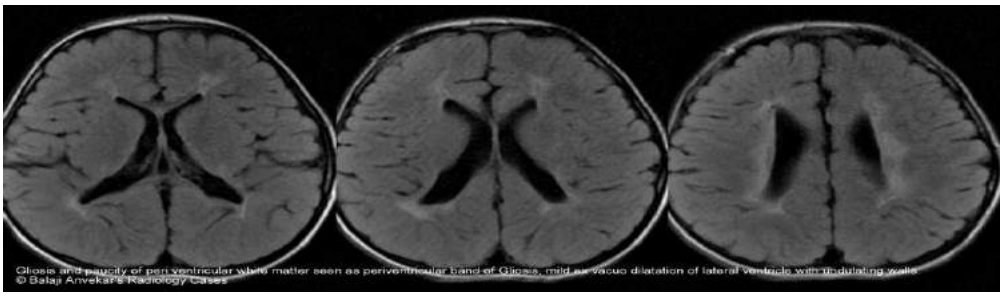
1. **< 20 weeks**: Insult leads to neuronal heterotopia or polymicrogyria
2. **26-36 weeks**: Insult affects white matter, leading to periventricular leukomalacia
3. **Term**: Insult affects primarily gray matter



Heterotropia



Microgyria



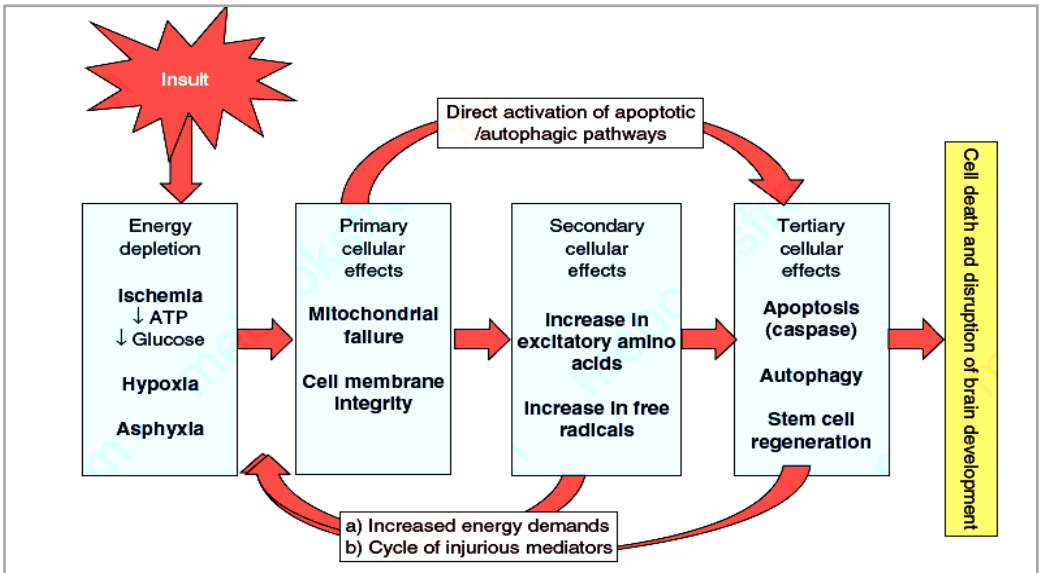
Per ventricular leukomalacia

Acute HIE leads to primary and secondary events:

1. Primary neuronal damage: cytotoxic changes due to failure of microcirculation → inhibition of energy-producing molecular processes → ATPase membrane pump failure → cytotoxic edema and free radical formation → compromised cellular integrity .This results in immediate necrotic cell death, from which the brain metabolism may be able to recover. Necrosis occurs after cellular membrane breakdown (from lack of ATP) results in the leakage of cellular contents, resulting in inflammation and necrotic cell death.

2. If the injury is sufficiently severe, after a brief period of attempted recovery, the brain may enter a phase of secondary energy failure. Secondary neuronal damage: May extend up to 72 hours or more after the acute insult and results in an inflammatory response and cell necrosis or apoptosis (fueled by reperfusion) due to Glutamate, an excitatory amino acid, accumulation in the extracellular space due to increased production, as well as decreased reuptake by damaged cells

a. Immediate neuronal death (necrosis) can occur due to intracellular osmotic overload of Na+ and Ca2+ from ion pump failure
b. Delayed neuronal death (apoptosis) occurs secondary to uncontrolled activation of enzymes and second messenger systems within the cell (e.g., Ca2+-dependent lipases, proteases, and caspases), perturbation of mitochondrial respiratory electron chain transport, generation of free radicals and leukotrienes, generation of nitric oxide (NO) through NO synthase, and depletion of energy stores.
c. Reperfusion of previously ischemic tissue may cause further injury because it can promote the formation of excess reactive oxygen species (e.g., superoxide, hydrogen peroxide, hydroxyl, singlet oxygen), which can overwhelm the endogenous scavenger mechanisms, thereby causing damage to cellular lipids, proteins, and nucleic acids as well as to the blood-brain barrier. This may result in an influx of neutrophils that, along with activated microglia, release injurious cytokines (e.g., interleukin 1-β and tumor necrosis factor α).



Mechanisms and neuropathologies associated with hypoxic-ischemic brain injury (Neonatal Neorology)

Diagnosis

Abnormal findings on the neurologic exam in the first few days after birth is the single most useful predictor that brain insult has occurred in the perinatal period. The diagnosis of neonatal encephalopathy includes a number of etiologies in addition to perinatal hypoxia-ischemia. Asphyxia may be suspected and HIE reasonably included in the differential diagnosis when there is:

1. Prolonged (>1 hour) antenatal acidosis
2. Fetal HR <60 beats per minute
3. Apgar score ≤3 at ≥10 minutes
4. Need for positive pressure ventilation for >1 minute or first cry delayed >5 minutes
5. Seizures within 12 to 24 hours of birth
6. Burst suppression or suppressed background pattern on EEG or amplitude-integrated electroencephalogram (aEEG)

Essential Criteria for Diagnosis of HIE:

1. Metabolic or mixed acidosis cord pH <7 or base deficit of >12)
2.Early onset of encephalopathy
3. Multisystem organ dysfunction
4. Five (5) min APGAR < 4

Clinical presentation and differential diagnosis.

HIE should be suspected in encephalopathic newborns with a history of fetal and/or neonatal distress and laboratory evidence of asphyxia.

Neurologic signs: The clinical spectrum of HIE is described as mild, moderate, or severe according to Sarnat stages.

Sarnat and Sarnat Stages of Hypoxic-Ischemic Encephalopathy			
Stage	**Stage 1 (Mild)**	**Stage 2 (Moderate)**	**Stage 3 (Severe)**
Level of consciousness	irritable	Lethargic	Stuporous, comatose
Neuromuscular control	Uninhibited, overreactive	Diminished spontaneous movement	Diminished or absent spontaneous movement
Muscle tone	normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive, disinhibited	Decreased or absent
Segmental myoclonus	Present or absent	Present	Absent
Complex reflexes	Normal	Suppressed	Absent
Suck	Weak	Weak or absent	Absent
Moro	Strong	Weak	Absent
Oculovestibular	Normal	Overactive	Weak or absent
Tonic neck	Slight	Strong	Absent
Autonomic function:	Generalized sympathetic	Generalized parasympathetic	Both systems depressed
Pupils	Mydriasis	Miosis	Midposition, often unequal; poor light reflex
Respirations	Spontaneous	Spontaneous; occasional apnea	Periodic; apnea
Heart rate	Tachycardia	Bradycardia	Variable
Bronchial and salivary secretions	Sparse	Profuse	Variable
Gastrointestinal motility	Normal or decreased	Increased, diarrhea	Variable
Seizures	None	Common focal or multifocal (6-24 hours of age)	Uncommon (excluding decerebration)
Electroencephalographic findings	Normal	Early: generalized low voltage, slowing (continuous delta and theta) Later: periodic pattern (awake); seizures focal	Early: periodic pattern with isopotential phases Later: totally isopotential

		or multifocal; 1.0-1.5 Hz spike and wave	
Duration of symptoms	<24 hours	2-14 days	Hours to weeks
Outcome	About 100% normal	80% normal; abnormal if symptoms more than 5-7 days	About 50% die; remainder with severe sequelae

A. Encephalopathy. Newborns with HIE must have abnormal consciousness by definition, whether mild, moderate, or severe. The background pattern detected by EEG or aEEG is useful for determining the severity of encephalopathy.
B. Brainstem and cranial nerve abnormalities. Newborns with HIE may have brainstem dysfunction, which may manifest as abnormal or absent brainstem reflexes, including pupillary, corneal, oculocephalic, cough, and gag reflexes. Newborns may show facial weakness (usually symmetric) and have a weak or absent suck and swallow with poor feeding. They can have apnea or abnormal respiratory patterns.
C. Motor abnormalities. With greater severity of encephalopathy, there is generally greater hypotonia, weakness, and abnormal posture with lack of flexor tone, which is usually symmetric.
D. Seizures occur in up to 50% of newborns with HIE and usually start within 24 hours after the HI insult. Seizures indicate that the severity of encephalopathy is moderate or severe, not mild. **After severe birth asphyxia, infants may have motor automatisms characterized by oral-buccal-lingual movements, rotary limb activities (rowing, pedaling, and swimming), tonic posturing, or myoclonus**.
E. Increased intracranial pressure (ICP) resulting from diffuse cerebral edema in HIE often reflects extensive cerebral necrosis rather than swelling of intact cells and indicates a poor prognosis. Treatment to reduce ICP does not affect outcome.
Multiorgan dysfunction. Other organ systems in addition to the brain usually exhibit evidence of asphyxial damage. In a minority of cases (<15%), the brain may be the only organ exhibiting dysfunction following asphyxia.
A. The kidney is the most common organ to be affected in the setting of perinatal asphyxia. The proximal tubule of the kidney is especially affected by decreased perfusion, leading to acute tubular necrosis (ATN) with oliguria and a rise in serum creatinine (Cr).
B. Cardiac dysfunction is caused by transient myocardial ischemia. Echocardiographic findings include decreased left ventricular contractility, especially of posterior wall; elevated ventricular end-diastolic pressures; tricuspid insufficiency; and pulmonary hypertension. In severely asphyxiated newborns, dysfunction more commonly affects the right ventricle. **A fixed HR may indicate severe brainstem injury**.
C. Pulmonary effects include increased pulmonary vascular resistance leading to PPHN, pulmonary hemorrhage, pulmonary edema due to cardiac dysfunction, meconium aspiration and Hypoxemic respiratory failure (HRF)

NB. Hypoxemic respiratory failure (HRF) in neonates is commonly due to hypoventilation, impaired diffusion and/or ventilation-perfusion mismatch and is often associated with persistent pulmonary hypertension of the newborn (PPHN) and right-to-left shunt.

Management of HRF includes gentle respiratory support with permissive hypercapnia, permissive hypoxemia (SpO2 in low to mid-90s) and surfactant replacement in cases with parenchymal lung disease, inhaled nitric oxide in patients with PPHN and if intractable despite medical therapy, extracorporeal membrane oxygenation (ECMO).

D. Hematologic effects include disseminated intravascular coagulation (DIC), poor production of clotting factors due to liver dysfunction, and poor production of platelets by the bone marrow.

E. Liver dysfunction may be manifested by isolated elevation of hepatocellular enzymes. More extensive damage may occur, leading to DIC, inadequate glycogen stores with resultant hypoglycemia, slowed metabolism,
or elimination of medications.

F. Gastrointestinal (GI) effects include an increased risk of bowel ischemia and necrotizing enterocolitis

Assessment Tools (Investigations)

1. Prenatal: fetal biophysiological profile. Doppler ultrasound (assess the cord blood flow)

2.Perinatal: Blood gas analysis and saturation (acidosis)

3.Postnatal:

a.Monitoring of ABG – saturation – blood glucose serum electrolytes - temperature - serum calcium

b.Renal function – bleeding profile and Liver function test

Neuroimaging

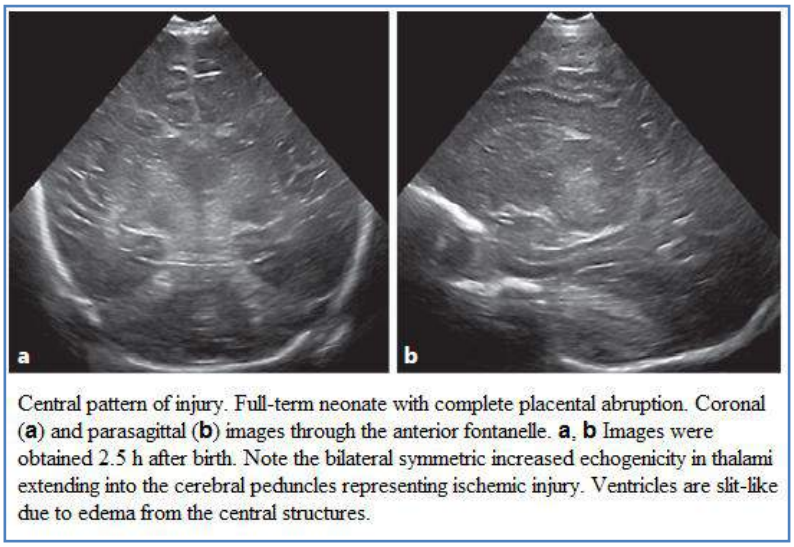
1. Cranial ultrasound

2.Amplitude-integrated EEG (a EEG)

a.When performed early, it may reflect dysfunction rather than permanent injury

b.Most useful in infants who have moderate to severe encephalopathy

c.Marginally abnormal or normal aEEG is very reassuring of good outcome



Central pattern of injury. Full-term neonate with complete placental abruption. Coronal (**a**) and parasagittal (**b**) images through the anterior fontanelle. **a**, **b** Images were obtained 2.5 h after birth. Note the bilateral symmetric increased echogenicity in thalami extending into the cerebral peduncles representing ischemic injury. Ventricles are slit-like due to edema from the central structures.

d.Severely abnormal aEEG in infants with moderate HIE raises the probability of death or severe disability from 25% to 75%

3. MRI: at 4 -14 days: bilateral abnormalities in basal ganglia and thalamus

4. Diffusion-weighted imaging (DWI) can show abnormalities within hours of an HI insult that may be useful in the diagnosis of neonatal HIE and an early indicator of possible brain injury.

5. **Proton magnetic resonance spectroscopy (MRS),** also called proton-MRS or H-MRS,1 measures the relative concentrations of various metabolites in tissue. Elevated lactate, decreased N-acetylaspartate (NAA), and alterations of the ratios of these two metabolites in relation to choline or creatine can indicate HIE and help with determining neurologic prognosis.

6. ECHO: to detect cardiac dysfunction and persistent pulmonary hypertension

Cardiac evaluation. An elevation of serum creatine kinase may indicate myocardial

injury. Cardiac troponin I (cTnI), cardiac troponin T (cTnT), and cardiac regulatory proteins are markers of myocardial damage

7. Lumbar Puncture
A lumbar puncture should be performed on any infant with HIE in whom the diagnosis is unclear. It is particularly important to rule out other potentially treatable intracranial disorders (e.g., early-onset meningitis) that may mimic the clinical features of HIE.

8. Renal evaluation. Blood urea nitrogen (BUN) and serum Cr may be elevated in perinatal asphyxia. Typically, elevation is noted 2 to 4 days after the insult.

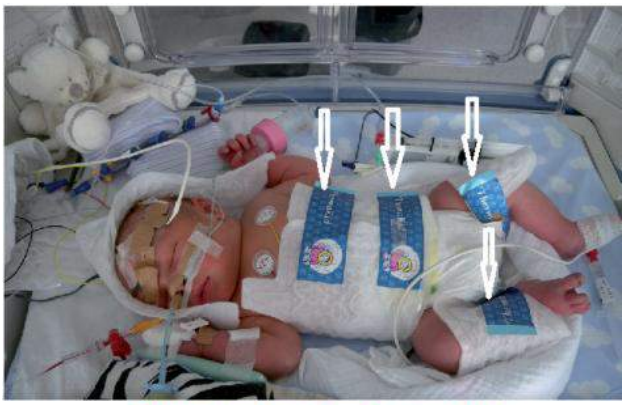
9. Neurologic markers of brain injury. Serum CK-BB may be increased in asphyxiated newborns within 12 hours of the insult. CK-BB is also expressed in placenta, lungs, GI tract, and kidneys. Other serum markers such as protein S-100, and urine markers have been measured in newborns with asphyxia and HIE.

Treatment of hypoxic ischemic encephalopathy:

The goal of therapies: is to prevent the onset or lessen the impact of secondary energy failure by decreasing cellular metabolism in the brain: Suppress cell death by decreasing proapoptotic proteins and increasing antiapoptotic proteins and neurotropic factors

1. Proper stabilization to minimize neuronal damage
2. Treatment of seizures by anticonvulsant
3. Treatment of hypotension by volume and inotropic support
4. Treatment of hypoglycemia and hypocalcemia
5. Therapeutic hypothermia
6. Treatment of complications

Management/monitoring: monitor systemic blood pressure, intracranial pressure (by feel of fontanel), and structural changes/damage (usually MRI)
Pharmacologically management: anticonvulsants (phenobarbitone, phenytoin); sedation, especially if ventilated and cooled (morphine, midazolam)
Hypovolaemia & hypotension may require management with volume expanders, blood transfusion and/or inotropes (improve cardiac contractility and cardiac output; therefore good for improving renal function as well)
Provide respiratory support if required (CPAP or ventilation)
Monitor respiratory status by observation and blood gases
Treat underlying pathology: ie. Sepsis (antibiotics), meconium aspiration/PPHN (ventilation/nitric oxide), poor or no respiratory drive due to CNS complications (ventilation)



Total body cooling using Criticool device

Therapeutic Hypothermia

a.Aim for body temperature to be 33 – 34 degrees
b.Treatment continues for 72hrs
c.Babies are rewarmed gradually over a 12 – 24hr period after this time
d.Supportive management continues throughout treatment
e. EEG monitoring is performed continuously
f. Blood tests are performed to monitor electrolytes, liver function, renal function etc
g.Reduces cerebral metabolism, prevents edema
h.Decreases energy utilization
i.Reduces/suppresses cytotoxic amino acid accumulation and nitric oxide
j.Inhibits platelet-activating factor, inflammatory cascade
k.Suppresses free radical activity, attenuates secondary neuronal damage,inhibits cell death and reduces extent of brain damage
l. Therapeutic hypothermia should only **start after the resuscitation** if clinically indicated as normothermia should be maintained during resuscitation in order to optimize the effect of epinephrine and avoid hypothermia-induced bradycardia.

New agents such as **erythropoietin, melatonin, xenon, and stem cells** that are undergoing preliminary evaluation in Phase I/II trials, but there are currently no data supporting the use of any agent besides therapeutic hypothermia for neuroprotection.

Outcomes

1. The location and extent of damage, and the immediate medical management, will determine the short and long term outcomes
2. It is possible to have no long term complications as a result of a brain injury at birth
3. Complications that can occur are delayed milestones, cerebral palsy or death

Jaundice and Hyperbilirubinemia in the Newborn

Jaundice: is yellowish discoloration of the skin and mucous membranes due to increased serum bilirubin level above normal (neonate appear jaundiced when serum bilirubin above 7mg/dl.)

Hyperbilirubinemia: is defined as a TB >95th percentile on the hour specific nomogram.

1. Jaundice identified prior to age 24 hours is a medical emergency and may result from excessive bilirubin production.
2. Approximately 85% of all term newborns and most preterm infants develop clinical jaundice. Also, 6.1% of well term newborns have a peak TB level >12.9 mg/dL. A TB level >15 mg/dL is found in 3% of normal term infants.
3. Jaundice usually becomes apparent in a cephalocaudal progression, starting on the face and progressing to the abdomen and then the feet, as serum levels increase.
4. It is the most common abnormal physical finding in neonatal period and is an important sign of disease, or functional disorder affecting hepatic, biliary or hematological system.

Bilirubin metabolism

A. Bilirubin production. Bilirubin is derived from the breakdown of heme containing proteins in the reticuloendothelial system.

1. Red blood cell (RBC) hemoglobin is the major heme-containing protein. Hemoglobin released from senescent RBCs in the reticuloendothelial system or from ineffective erythropoiesis accounts for 80% to 90% of bilirubin production. Breakdown of other heme-containing proteins such as cytochromes and catalase contributes the remaining 10% to 20% of bilirubin.

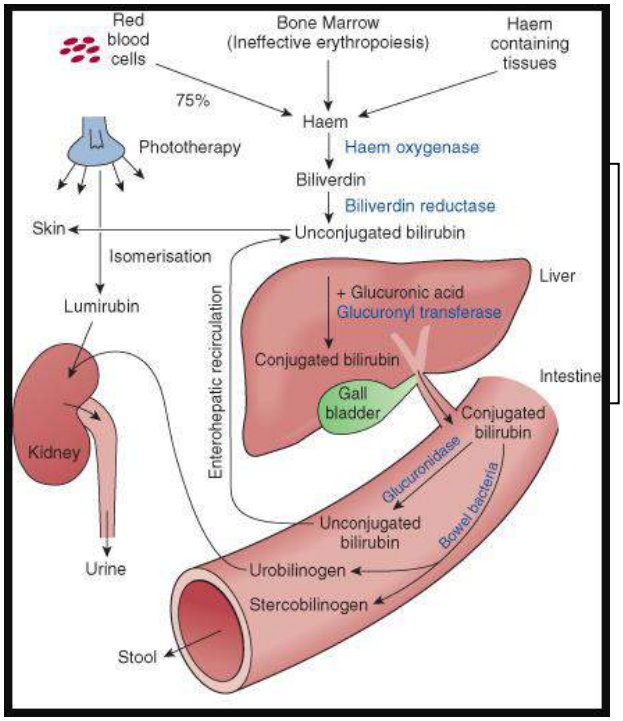
2. Bilirubin metabolism. The microsomal enzyme heme **oxygenas**e located in the liver, spleen, and nucleated cells oxidizes the heme ring from heme-containing proteins to biliverdin and carbon monoxide (CO). The enzyme biliverdin **reductase** reduces biliverdin to bilirubin. Because heme breakdown yields equimolar amounts of CO and biliverdin, the best indirect measure of bilirubin production is HbCO measurement.

B. Bilirubin clearance and excretion

1. Transport. Bilirubin is nonpolar, insoluble in water, and is transported to liver cells bound to serum **albumin**. Bilirubin bound to albumin does not usually enter the central nervous system (CNS) and is thought to be nontoxic. Displacement of bilirubin from albumin by acidosis, drugs, such as ceftriaxone, or by free fatty acids (FFAs) .

2. Hepatic uptake. Nonpolar, fat-soluble bilirubin (dissociated from albumin) crosses the hepatocyte plasma membrane and is bound mainly to **cytoplasmic ligandin** (Y protein) for transport to the smooth endoplasmic reticulum.

3. Conjugation. In hepatocytes, the enzyme **uridine diphosphogluconurate glucuronosyl transferase** (UGT1A1) catalyzes the conjugation of bilirubin with glucuronic acid, resulting in mostly bilirubin diglucuronides and some monoglucuronides that are more water-soluble than unconjugated bilirubin. Both forms of conjugated bilirubin are excreted into the bile canaliculi against a concentration gradient.



Inherited deficiencies and polymorphisms of the conjugating enzyme gene can cause severe hyperbilirubinemia in newborns. Polymorphisms in the UGT1A gene due to differences in the number of thymine adenine repeats in the promotor gene diminish the expression of the UGT1A1 enzyme and result in increased TB levels **(Gilbert syndrome).**

4. Excretion. Conjugated bilirubin is secreted into the bile and then excreted into the gastrointestinal (GI) tract where it is eliminated in the stool. Conjugated bilirubin is not reabsorbed from the bowel unless it is deconjugated by the intestinal enzyme **β glucuronidase**, present in the neonatal intestinal mucosa. Resorption of bilirubin from the GI tract and delivery back to the liver for reconjugation is called the **enterohepatic circulation**. Intestinal bacteria, present in adults but to a limited extent in newborns, can prevent enterohepatic circulation of bilirubin by reducing conjugated bilirubin to urobilin, which is not a substrate for β-glucuronidase.

5. Fetal bilirubin metabolism. Most unconjugated bilirubin formed by the fetus is cleared by the placenta into the maternal circulation. Formation of conjugated bilirubin is limited in the fetus because of decreased fetal hepatic blood flow, decreased hepatic ligandin, and decreased UGT1A1 activity. The small amount of conjugated bilirubin excreted into the fetal gut is usually hydrolyzed by β-glucuronidase and resorbed. Bilirubin is normally found in amniotic fluid by 12 weeks' gestation and is usually absent by 37 weeks' gestation. Increased amniotic fluid bilirubin is found in hemolytic disease of the newborn and in fetal intestinal obstruction below the bile ducts.

Classification of neonatal hyperbilirubinemia

1. Nonpathologic (Physiologic jaundice, Icterus Neonatorum or Normal jaundice)

Physiologic jaundice occurs in approximately 60% of term infants and 80% of preterm infants. The serum TB level of most newborn infants rises to >2 mg/dL in the first week

after birth. This level usually rises in full-term infants to a peak of **6 to 8 mg/dL by 3 to 5 days** of age and then falls. **A rise to 12 mg/dL is in the physiologic range**. In preterm infants, the peak may be 10 to 12 mg/dL on the fifth day after birth. **Levels <2 mg/dL may not be seen until 1 month of ag**e in both full-term and preterm infants.

Etiology:

A. Increased bilirubin production due to the following:
1. Increased RBC volume per kilogram and decreased RBC survival (90 days vs. 120 days) in infants compared to adults
2. Increased ineffective erythropoiesis and increased turnover of nonhemoglobin heme proteins

B. Defective uptake of bilirubin from plasma caused by decreased ligandin and binding of ligandin by other anions

C. Decreased clearance due to decreased UGT1A1 activity. In term infants at 7 days of age, UGT activity is approximately 1% that of adults and does not reach adult levels until at least 3 months of age.

D. Decreased hepatic excretion of bilirubin. Increased enterohepatic circulation caused by high levels of intestinal β-glucuronidase, preponderance of bilirubin monoglucuronide rather than diglucuronide, decreased intestinal bacteria, and decreased gut motility with poor evacuation of bilirubin-laden meconium

Diagnosis:

The diagnosis of physiologic jaundice in term or preterm infants can be established only by excluding known causes of jaundice on the basis of the history, clinical findings, and laboratory data

Exaggerated/severe physiologic jaundice can occur where higher bilirubin levels occur and the hyperbilirubinemia lasts longer (ie, 2 weeks). Some factors associated with this include prematurity, severe weight loss, maternal diabetes, induction of labor with oxytocin, bruising of the infant, and breast-feeding. These infants may require treatment.

2. Pathological jaundice

Suspect pathological jaundice in the following conditions:

(1) Jaundice appears in the 1st 24- hr after birth.
(2) Serum bilirubin is rising at a rate faster than 5 mg/dL/24 hr.
(3) Serum bilirubin is >12 mg/dL in a full-term infant (especially in the absence of risk factors) or 10-14 mg/dL in a preterm infant.
(4) Jaundice persists after 14 days after birth.
(5) Direct bilirubin fraction is >2 mg/dL at any time.
(6) Other factors suggesting a nonphysiologic cause of jaundice are family history of hemolytic disease, pallor, hepatomegaly, splenomegaly, failure of phototherapy to lower the bilirubin level, vomiting, lethargy, poor feeding, excessive weight loss, apnea, bradycardia, abnormal vital signs (including hypothermia), light-colored stools, dark urine positive for bilirubin, and signs of kernicterus

Pathological unconjugated hyperbilirubinemia may be caused or increased by:

1. Factors that increases the load of bilirubin to be metabolized by the liver (hemolytic anemias, polycythemia, bruising or internal hemorrhage, shortened red blood cell life as a

result of immaturity or transfusion of cells, increased enterohepatic circulation, infection)
2. Factors that damages or reduces the activity of the transferase enzyme or other related enzymes (genetic deficiency, hypoxia, infection, thyroid deficiency)
3. Factors that competes for or blocks the transferase enzyme (drugs and other substances requiring glucuronic acid conjugation)
4. Factors that leads to an absence or decreased amounts of the enzyme or to reduction of bilirubin uptake by liver cells (genetic defect, and prematurity)

A. Main causes of early onset neonatal jaundice (Jaundice appears during the first week)

<24 hrs	24 - 72 hrs	>72 hrs
(1)Hemolytic disease (2) Intrauterine infections (3) Crigler-Najjar syndrome (4) Lucey–Driscollsyndrome	1) Physiological (2) Sepsis (3) Polycythemia (4) Concealed hemorrhage	(1)Septicemia (2) Neonatal hepatitis syndrome (3) Breast milk jaundice (4) Metabolic diseases (5) Bowel obstructions

B. Main causes of late onset neonatal jaundice: Jaundice either appears after the first week or persists for more than 2 -3 weeks

1. Prolonged physiological jaundice (unconjugated)
2. Breast milk jaundice (unconjugated)
3. Crigler –Najjar syndrome and Gilbert disease (unconjugated)
4. Inspissated bile syndrome (conjugated or mixed)
5. Total parenteral nutrition (conjugated or mixed)
6. Extra hepatic biliary atresia (conjugated or mixed)
7.Metabolic liver diseases (conjugated or mixed)

Causes of Neonatal Hyperbilirubinemia

Overproduction	Undersecretion	Mixed	Uncertain mechanism
Fetomaternal blood group incompatibility (e.g., Rh, ABO) Hereditary spherocytosis (MCHC >36.0 g/dL), eliptocytosis, somatocytosis Nonspherocytic hemolytic anemias G6PD deficiency and drugs Pyruvate-kinase deficiency Other red cell enzyme deficiencies α Thalassemia δ–β Thalassemia Acquired hemolysis due to vitamin K, nitrofurantonin, sulfonamides, antimalarials, penicillin, oxytocin, bupivacaine, or infection **Extravascular blood** Petechiae Hematomas Pulmonary, cerebral, or occult hemorrhage	**Metabolic and endocrine conditions** Galactosemia Familial nonhemolytic jaundice types 1 and 2 (Crigler-Najjar syndrome) Gilbert disease Hypothyroidism Tyrosinosis Hypermethioninemia Drugs and hormones Novobiocin Pregnanediol Lucey-Driscoll syndrome Infants of diabetic mothers Prematurity Hypopituitarism and anencephaly **Obstructive disorders** Biliary atresia* Dubin-Johnson and Rotor syndrome* Choledochal cyst*	Sepsis Intrauterine infections Toxoplasmosis Rubella CID Herpes simplex Syphilis Hepatitis Respiratory distress syndrome Hypoxia-ischemia Infant of diabetic mother Severe erythroblastosis fetalis	Chinese, Japanese, Korean, and American Indian infants (see polymorphism discussion, section I.B.3.) Breast milk jaundice

Manual of Neonatal care

Discussion on the most common causes

Isoimmune Hemolytic disease due to Rh incompatibility

- Hemolytic disease of the newborn (HDN) is caused by the destruction of fetal/neonatal RBC by maternal IgG (immunoglobulin).
- 90% are caused by **D antigen** and other 10% are caused by antibodies that target the C and E antigens of the Rh locus, as well as antibodies to other RBC antigens, such as anti-Kell and anti-Duffy. Maternal sensitization to these antigens is not prevented by RhoGAM (anti-D) administration.

Hemolytic disease of the newborn is typically mild with the first pregnancy and becomes more clinically significant with each subsequent pregnancy.

Pathogenesis

-Sensitization of Rh-Ve mothers through blood transfusion, fetomaternal hemorrhage, amniocentesis, or abortion
- maternal immunoglobulin G Anti Rh antibodies are formed that cross the p;acenta causing hemolysis of fetal RBCS

Clinical picture:

- Symptoms in affected fetuses can range from mild anemia to hydrops fetalis due to severe anemia and high output cardiac failure.
- Affected neonates can have significant jaundice, as well as ongoing hemolytic anemia, respiratory distress, anemic heart failure, generalized edema, pleural effusion, low hemoglobin and hematocrit, a high reticulocyte count, and a positive direct Coombs test.

Hydrops fetalis .Note edema

ABO incompatibility between mother and fetus protects against sensitization of an Rh-negative mother, probably because maternal antibodies eliminate fetal RBCs from the maternal circulation before they can encounter antibody-forming lymphocytes

The severity of Rh incompatibility can predicted by:

A. Dilated umbilical vein
B. Degree of fetal liver enlargement
C. Amount of pericardial effusion

Prevention and treatment:

1. Anti-D gammaglobulin (RhoGAM) is given to Rh-negative mothers at 28 weeks' gestation and immediately after the delivery(within 72 hours) so that they clear Rh-positive fetal cells from their circulation before they generate anti-D antibodies.
2. Severe fetal anemia is treated with in utero transfusion.
3The goal of neonatal therapy is to control hyperbilirubinemia with phototherapy or exchange transfusion, as appropriate.
4. Anemia is treated with packed red blood cell transfusion, when necessary.
5. Careful follow-up of the hematocrit after discharge is important.

Isoimmune Hemolytic disease due to ABO incompatibility

-The cause is the reaction of maternal anti-A or anti-B antibodies to the A or B antigen on

the RBCs of the fetus or newborn
-Antibodies agglutinins against ABO system are naturally occurring.
- The hemolytic process begins in utero and is the result of active placental transport of maternal isoantibody.
- In type O mothers, isoa ntibody is predominantly 7S-IgG (immunoglobulin G) and is capable of crossing the placental membranes.

Why it occurs in type O mothers?
because these mothers of o type make anti-A or anti-B antibodies of the IgG class, which cross the placenta, whereas mothers of type A or B usually make anti-A or anti-B antibodies of the IgM class, which do not cross the placenta.

Characters

- More common but milder than Rh incompatibility
- Seen only in A or B infants born to O group mother
-It may be seen in the first born infant because the maternal antibodies are natural and **First-born infants have a 40–50% risk** for symptomatic disease.

Clinical picture

- Symptomatic ABO hemolytic disease occurs in **<1%** of all newborn infants but accounts for approximately two-thirds of observed cases of hemolytic disease in the newborn.The typical presentation is a type O mother with a type A or type B infant who **becomes jaundiced in the first 24 hours of life**. Mild hemolytic anemia with reticulocytosis, microspherocytosis.
- Exaggerated physiologic anemia may occur at 8–12 weeks of age, particularly when treatment during the neonatal period required phototherapy or exchange transfusion.

Diagnosis.

A. Blood type and Rh factor in the mother and the infant.
B. Reticulocyte count. In ABO hemolytic disease of the newborn, values range from 10 to 30%.
C. Direct Coombs test (direct antiglobulin test). Because there is very little antibody on the red blood cell (RBC), the direct Coombs test is often only **weakly positive at birth** and may become negative by 2–3 days of age
D. Blood smear. The blood smear typically demonstrates microspherocytes, polychromasia
E. Bilirubin levels (fractionated or total and direct
F. Additional laboratory studies. Supportive diagnostic studies may be indicated on an individual basis if the nature of the hemolytic process remains unclear.
1. Antibody identification (indirect Coombs test). The indirect Coombs test is more sensitive than the direct Coombs test.
2. Maternal IgG titer. The absence in the mother of elevated IgG titers against the infant's blood group tends to exclude a diagnosis of ABO incompatibility.

Management

Most infants with ABO incompatibility do not develop significant jaundice.
Approximately 10% of these infants with a positive direct Coombs test will need phototherapy

Breastfeeding jaundice and Breast milk jaundice

A distinction is made between breast milk jaundice, in which jaundice is thought to be due to factors in breast milk, and breastfeeding jaundice, typically seen when breastfeeding is not going well and intake is inadequate.

	Breast feeding jaundice	Breast milk jaundice
Incidence	5-10 % of newborn	2- 4 % of newborn
Etiology & pathogenesis	Decrease intake of breast milk leads to increased enterohepatic circulation	Due to unknown(substance in breast milk → blocks destruction of bilirubin
Day of appearance	Similar to physiological jaundice	4 to 7 days of age
Duration of jaundice	Less than 3 weeks	3 – 10 weeks. Bilirubin level may reach upto 20-30 mg/dl
Treatment	Adequate breast feeding	Not harmful
Aggravating factors	Dehydration	Nil

Neonatal Jaundice- Dr. Karuppiah

Breast feeding jaundice: Infants who are breast-fed have higher bilirubin levels after day 3 of life compared to formula-fed infants. The incidence of peak bilirubin levels above 12 mg/dL in breast-fed term infants is 12% to 13%. The main factor thought to be responsible for breastfeeding jaundice is a decreased intake of milk that leads to slower bilirubin elimination and increased enterohepatic circulation

- Phototherapy and Intravenous rehydration, may be indicated

Breast milk jaundice: By day 4, instead of the usual fall in the serum bilirubin level, the bilirubin level continues to rise and may reach 20 to 30 mg/dL by 14 days of age if no treatment is instituted. If breastfeeding is continued, the levels will stay elevated and then fall slowly at 2 weeks of age, returning to normal by **4 to 12** weeks of age. These infants show good weight gain, have normal liver function test (LFT) results, and show no evidence of hemolysis.

-Mothers with infants who have breast milk jaundice syndrome have a recurrence rate of 70% in future pregnancies

- The mechanism of true breast milk jaundice is unknown but is thought to be due to an unidentified factor (or factors) in breast milk interfering with bilirubin metabolism or The associated with Gilbert disease

- Breast-fed infants are more likely to have increased enterohepatic circulation because they ingest the ß-glucuronidase present in breast milk, they are slower to be colonized with intestinal bacteria that convert CB to urobilinoids, and they excrete less stool

- For very high levels of serum bilirubin, interruption of breastfeeding with formula supplementation for 24 hours can lower serum bilirubin levels quickly and confirm the

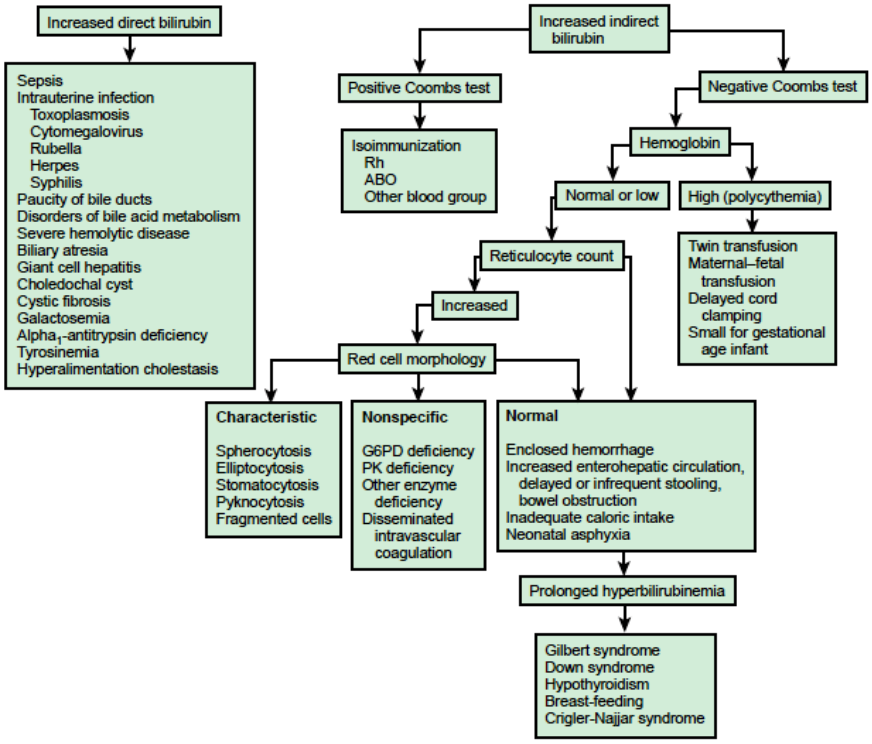
diagnosis

Increased enterohepatic circulation. Pathologic conditions leading to increased enterohepatic circulation include decreased enteral intake, including breastfeeding failure; breast milk jaundice; or impaired intestinal motility due to intestinal atresias, meconium ileus, or Hirschsprung disease.

Infection (eg, congenital syphilis, viral, or protozoal infections).

Assessment of neonatal hyperbilirubinemia

1. Differentiate between physiological and pathological jaundice
2. Differentiate between unconjugated and conjugated jaundice
3 Clinical evaluations: history and examination
4 investigations for unconjugated and conjugated jaundice



Schematic approach to the diagnosis of neonatal jaundice (Nelson 2020)

1. Differentiate between physiological and pathological jaundice

The following situations suggest pathological hyperbilirubinemia and require evaluation
1. Onset of jaundice before 24 hours of age
2. Any elevation of serum bilirubin that requires phototherapy
3. A rise in serum bilirubin levels of > 0.2 mg/dL/hour
4. Signs of underlying illness in any infant (vomiting, lethargy, poor feeding
5. Jaundice persisting after 8 days in a term infant or after 14 days in a premature infant

2. Differentiate between unconjugated and conjugated jaundice

3 Clinical evaluations: history and examination

A. History

1. A family history of jaundice, anemia, splenectomy, or early gallbladder disease suggests hereditary hemolytic anemia (e.g., spherocytosis, G6PD deficiency).
2. A family history of liver disease may suggest galactosemia, α1-antitrypsin deficiency, tyrosinosis, hypermethioninemia, Gilbert disease, Crigler-Najjar syndrome types I and II, or cystic fibrosis.
3. A sibling with jaundice or anemia may suggest blood group incompatibility, breast milk jaundice, or Lucey-Driscoll syndrome.
4. Maternal illness during pregnancy may suggest congenital viral infection or toxoplasmosis. Infants of diabetic mothers tend to develop hyperbilirubinemia or maternal drugs may interfere with bilirubin binding to albumin.
5. The labor and delivery history may show trauma associated with extravascular bleeding and hemolysis. 6. The infant's history may show delayed or infrequent stooling, which can be caused by poor caloric intake or intestinal obstruction and lead to increased enterohepatic circulation of bilirubin.
7. Breastfeeding may suggest Breastfeeding jaundice or breast milk jaundice

B. The physical examination

Jaundice progresses in a cephalocaudal direction. The highest bilirubin levels are typically associated with jaundice below the knees and in the hands. Visual inspection is not a reliable indicator of serum bilirubin levels. Jaundiced infants should be examined for the following physical findings:

1. **Prematurity.** Gestational age is an important predictor of risk for hyperbilirubinemia; this should be evaluated and documented for each newborn.
2. **Small-for-gestational-age (SGA),** which may be associated with polycythemia and in utero infections.
3. **Microcephaly**, which may be associated with in utero infections.
4. **Extravascular blood bruising,** cephalohematoma, or other enclosed hemorrhage.
5. **Pallor** associated with hemolytic anemia or extravascular blood loss.
6. **Petechiae** associated with congenital infection, sepsis, or erythroblastosis.
7. **Hepatosplenomegaly** associated with hemolytic anemia, congenital infection, or liver disease.
8. Omphalitis.
9. Chorioretinitis associated with congenital infection.
10. Evidence of **hypothyroidism**.

4 investigations for unconjugated and conjugated jaundice

The following tests are indicated when TSB is above the 95th percentile for age in hours at or near the threshold for initiation of phototherapy treatment.

1. Blood type, Rh, and antibody screen of the mother should have been done during pregnancy, and the antibody screen repeated at delivery.
2. Blood type, Rh, and direct Coombs test of the infant to test for isoimmune hemolytic disease.
3. Peripheral smear for RBC morphology and reticulocyte count to detect causes of Coombs-negative hemolytic disease (e.g., spherocytosis).
4. Hematocrit will detect polycythemia or suggest blood loss from occult hemorrhage.

5. Identification of antibody on infant's RBCs (if result of direct Coombs test is positive).
6. Direct bilirubin should be measured when bilirubin levels are at or above the 95th percentile or when the phototherapy threshold is approaching.
7. In prolonged jaundice, tests for liver disease, congenital infection, sepsis, metabolic defects, or hypothyroidism are indicated.
8. A G6PD screen may be helpful, especially in male infants

Management of unconjugated hyperbilirubinemia

1. Monitoring
2. Phototherapy
3. Exchange transfusion
4. Pharmacological therapy

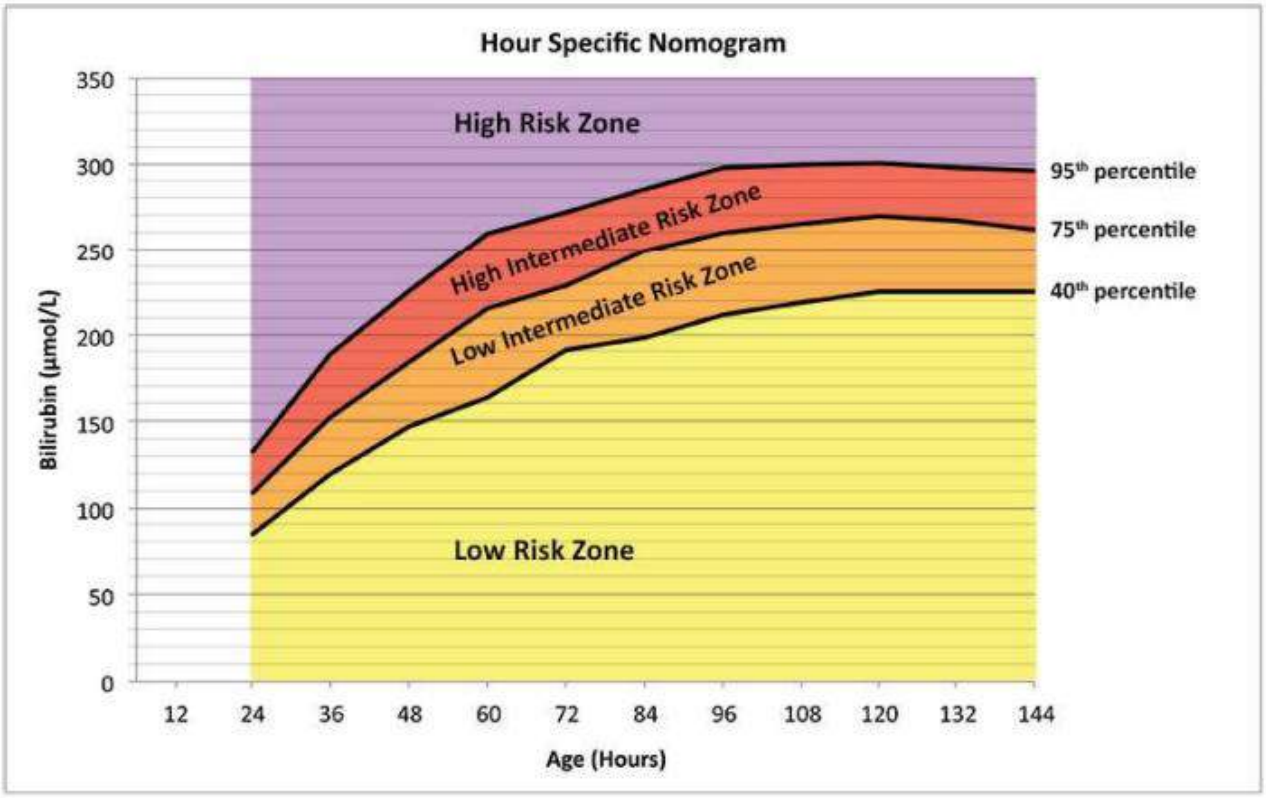
TcB measurements are not reliable in certain circumstances such as during or after phototherapy, after sunlight exposure, or at TB levels ≥15 mg/dL. TcB can overestimate TB in darkly pigmented infants and underestimate TB in light-skinned infants.

1. Intravenous immunoglobulin reduces the need for exchange transfusion in isoimmune hemolytic diseases
2. Phenobarbitone induce glucoronyl transferase enzyme used in **only Crigler Najjar type 2 only**

Management of unconjugated hyperbilirubinemia is clearly tied to the etiology when evaluating need for phototherapy or exchange transfusion, total bilirubin level should be used. Direct bilirubin is not subtracted from the total, except possibly if it constitutes >50% of total bilirubin

1. Monitoring

1. Screen serum bilirubin level or transcutaneous bilirubin of any neonates before discharge
2. TCB is not reliable during phototherapy treatment
3. Plot total serum bilirubin on an hour-spicific nomogram that identifies risk zone



2. Phototherapy

A. Principle

Bilirubin absorbs visible light with wave lengths of approximately 400 to 500 nm. Exposure of newborn to this light converts unconjugated bilirubin to non-toxic compounds that are easily excreted through urine and bile. Special blue lamps with a peak output at 425 to 475 nm are the most efficient for phototherapy

Photochemical reactions: when bilirubin absorbs light, three types of photochemical reactions occur 1. Photoisomerization 2. Structural isomerization 3. The slow process of photo-oxidation

B. Types

1- **Conventional** phototherapy
2- **Fibrooptic** blanket applied directly and can be used simultaneously with phototherapy has been shown to reduce bilirubin levels, although less effectively for term infants, likely due to limited skin exposure.
3- **Intensiv**e (Bilisphere 360) forms of light therapy

C. Indications

1. When the level of bilirubin may be hazardous to the infant (Bilirubin level higher than 15 mg/dl) and less than the level of exchange in healthy fullterm newborn
2. Before, after or in between exchange transfusion
3. Prophylactic in very low birth weight infants, hemolytic disease of the newborn or with severely bruised infants

If both direct and indirect bilirubin are high, exchange transfusion is probably safer than phototherapy because it is not known whether the bronze pigment is toxic.

D. Technique of conventional phototherapy

Effective phototherapy depends on the light spectrum, irradiance (energy output), distance from the infant (closer maximizes irradiance), and the extent of skin area exposure

1. Distence between the light source and baby: 45 cm
2. Maximum amount of skin exposed
3. Cover only eye and genitalia
4. If an incubator is used, there should be a 5- to 8-cm space between it and the lamp cover to prevent overheating.

E. Side effects

1. Skin : rash,erythema and Tanning of the skin of black infants.
2. Stool: loose
3. Dehydration and hyperthermia
4. D effective maternal – infant interaction
5. Damage of the retina
6. Low calcium levels have been described in preterm infants under phototherapy.
7. Mutations, sister chromatid exchange, and DNA strand breaks have been described in cell culture.

F. Contraindications

infants with direct hyperbilirubinemia caused by liver disease or obstructive jaundice, because indirect bilirubin levels are not usually high in these conditions and because phototherapy may lead to the “bronze baby” syndrome

It is contraindicated to put jaundiced infants under direct sunlight, as sunburn or hyperthermia may result.

G. Stopping

Phototherapy is stopped when the TSB is less than the level at which phototherapy was started. In a recent study of infants with non hemolytic hyperbilirubinemia, phototherapy was discontinued at mean bilirubin levels of 13 + 0.7 mg/dL in term and 10.7 + 1.2mg/dL in preterm infants.

3. Exchange transfusion

A. Mechanisms

Exchange transfusion removes partially hemolyzed and antibody- coated RBCs, as well as unattached antibodies, and replaces them with donor RBCs, lacking the sensitizing antigen. Within half an hour after the exchange, bilirubin levels return to 60% of preexchange levels due to hemolysis of antibody-coated RBCs sequestered in bone marrow or spleen and from senescent donor RBCs.

All infants should be under intensive phototherapy while decisions regarding exchange transfusion are being made.

B. Indications for exchange transfusion

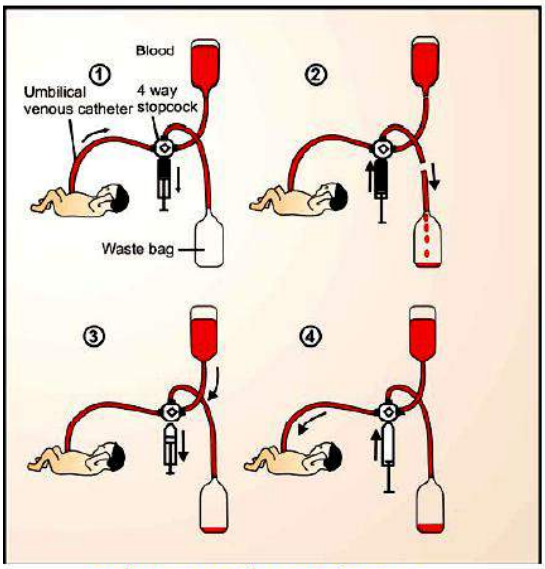
1. When phototherapy fails to prevent a rise in bilirubin to toxic levels
2. To correct anemia and improve heart failure in hydropic infants with hemolytic disease
3. To stop hemolysis and bilirubin production by removing antibody and sensitized RBCs
4. In hemolytic disease, immediate exchange transfusion is usually indicated if:
a. The cord bilirubin level is > 4.5 mg/dL and the cord hemoglobin level is under 11 g/dL.
b. The bilirubin level is rising >1 mg/dL/hour despite phototherapy
c. The hemoglobin level is between 11 and 13 g/dL, and the bilirubin level is rising >0.5 mg/dL/hour despite phototherapy.
d. The bilirubin level is 20 mg/dL, or it appears that it will reach 20 mg/dL
e. There is progression of anemia in the face of adequate control of bilirubin by other methods (e.g., phototherapy)
5. Repeat exchanges are done for the same indications as the initial exchange

C. Blood for exchange transfusion

1. fresh (<7 days old), irradiated, and reconstituted whole blood (hematocrit 45–50%) made from packed red blood cells (PRBCs) and fresh frozen plasma collected in citrate-phosphate-dextrose (CPD)
2. **In Rh hemolytic disease**, if blood is prepared before delivery, it should be type **O Rh-negative**, cross-matched against t**he mother**. If the blood is obtained after delivery, it also may be cross-matched against the infant
3. In ABO incompatibility, the blood should be type O Rh-negative or **Rh compatible with the mother and infant**, be cross-matched **against the mother and infant**, and have a low titer of naturally occurring anti-A or anti-B antibodies. Usually, type O cells are used with AB plasma to ensure that no anti-A or anti-B antibodies are present.
4. In other isoimmune hemolytic disease, the blood should **not contain the sensitizing antigen** and should be cross-matched against the mother
5. In nonimmune hyperbilirubinemia, blood is typed and **cross-matched against the plasma and red cells of the infant**
6. Exchange transfusion usually involves double the volume of the infant's blood and is known as a two-volume exchange.

D. Technique of exchange transfusion

1. Exchange transfusion is done with the infant under a servo-controlled radiant warmer and cardiac, blood pressure, and oxygen saturation monitoring in place. Equipment and personnel for resuscitation must be readily available, and an intravenous line should be in place for the administration of glucose and medication.
2. An assistant should be assigned to the infant to record volumes of blood, observe the infant, and check vital signs.
3. The blood should be warmed to 37°C
4. Sterile technique should be used
5. Exchanges by the push–pull technique through the umbilical vein



Exchange transfusion technique

6. Isovolumetric exchange transfusion
7. If it is not possible to insert the catheter in the umbilical vein, exchange transfusion can be accomplished through a central venous catheter placed through the antecubital fossa or into the femoral vein through the saphenous vein
8. After exchange transfusion, phototherapy is continued and bilirubin levels are measured every 4 hours.
9. When the exchange transfusion is fi nished, a silk purse-string suture should be placed around the vein; the tails of the suture material should be left.

E. Complications of exchange transfusions

1. Hypocalcemia and hypomagnesemia
2. Hypoglycemia.
3. Disturbance of Acid–base balance
4. Hyperkalemia.
5. Cardiovascular. Perforation of vessels, embolization (with air or clots), vasospasm, thrombosis, infarction, arrhythmias, volume overload, and arrest.
6. Bleeding. Thrombocytopenia, defi cient clotting factors
7. Infections
8. Hemolysis.
9. Graft-versus-host disease
10. Miscellaneous. Hypothermia, hyperthermia, and possibly necrotizing enterocolitis

4. Pharmacological therapy

1. Intravenous immunoglobulin reduces the need for exchange transfusion in isoimmune hemolytic diseases
2. Increasing bilirubin conjugation:Phenobarbitone used in only Crigler Najjar type 2 only as it induce glucoronyl transferase enzyme
3. Decreasing enterohepatic circulation: In breast-fed and formula-fed infants with bilirubins >15 mg/dL, oral agar significantly increases the efficiency and shortens the duration of phototherapy
4. Inhibiting bilirubin production: Metalloprotoporphyrins (e.g., tin and zinc protoporphyrins) these agents are still experimental and are not in routine use

Management of unconjugated hyperbilirubinemia in Infants with hemolytic disease

1. In Rh disease, start intensive phototherapy immediately. An exchange transfusion is performed if the bilirubin level is predicted to reach 20 mg/dL
2. High-dose intravenous immune globulin (IVIG) (500–1,000 mg/kg IV given over 2–4 hours) has been used to reduce bilirubin levels in infants with isoimmune hemolytic disease. Caution should be used when considering treatment with IVIG as there are emerging reports of increased incidence of **necrotizing enterocolitis** in term and late-preterm infants with hemolytic disease of the newborn and isoimmune neonatal thrombocytopenia who were treated with IVIG.
3. In ABO hemolytic disease, start intensive phototherapy if the bilirubin level exceeds 10 mg/dL at 12 hours, 12 mg/dL at 18 hours, 14 mg/dL at 24 hours, or 15 mg/dL at any time and perform an exchange transfusion if the bilirubin reaches 20 mg/dL.

4. Tin (Sn) porphyrin. This can decrease the production of bilirubin and reduce the need for exchange transfusion and duration of phototherapy. It is an inhibitor of heme oxygenase, which is the enzyme that allows the production of bilirubin from heme. The dose of Stannsoporfin is 6 µmol/kg intramuscularly as a single dose given within 24 hours of birth with severe hemolytic disease, and it is available via compassionate use protocol.
5. In hemolytic disease of other causes, treat as if it were Rh disease

Bilirubin toxicity

The level of bilirubin associated with toxicity in healthy term or preterm infants is **uncertain** and appears to vary among infants and in different clinical circumstances. Bilirubin enters the brain as free (unbound) bilirubin or as bilirubin bound to albumin in the **presence of a disrupted blood–brain barrier**.
Factors that disrupt the blood–brain barrier include **hyperosmolarity, asphyxia, and hypercarbia**
Free fatty acids and certain drugs interfere with bilirubin binding to albumin, although **acidosis** affects bilirubin solubility and its deposition into brain tissue.

Kernicterus: is a pathologic diagnosis and refers to yellow staining of the brain by bilirubin together with evidence of neuronal injury.

Brain Induced Neurological Dysfunction (BIND): the neurological complications of severe neonatal hyperbilirubinemia in the form of acute encephalopathy only or progression to chronic encephalopathy and permanent handicap

Acute bilirubin encephalopathy: is the clinical manifestation of bilirubin toxicity seen in the neonatal period. The clinical presentation of acute bilirubin encephalopathy can be divided into three phases:
1. Early phase. Hypotonia, lethargy, high-pitched cry, and poor suck.
2. Intermediate phase. Hypertonia of extensor muscles (with opisthotonus, rigidity, oculogyric crisis, and retrocollis), irritability, fever, and seizures. Many infants die in this phase. All infants who survive this phase develop chronic bilirubin encephalopathy (clinical diagnosis of kernicterus).
3. Advanced phase. Pronounced opisthotonus (although hypotonia replaces Hypertonia after approximately 1 week of age), shrill cry, apnea, seizures, coma, and death.

Risk Factors for Hyperbilirubinemia Neurotoxicity
Isoimmune hemolytic disease
G6PD deficiency
Asphyxia
Sepsis
Acidosis
Albumin less than 3.0 mg/dL
Manual of Neonatal Care 2018

Using Bilirubin/albumin ratio in conjunction with TSB can improve the accuracy of prediction of bilirubin-induced neurologic dysfunction and prevent unnecessary invasive therapy such as exchange transfusion in icteric neonates. B/A cutoff value for predicting acute BIND **is 8 mg/gm.**

Chronic bilirubin encephalopathy (post kernicteric cerebral palsy): is marked by athetosis, complete or partial sensorineural deafness (auditory neuropathy), limitation of upward gaze, dental dysplasia, and sometimes, intellectual deficits.

Management

1. Suspected or Established cases of BIND: Immediate exchange transfusion to prevent or minimize further brain damage
2. Auditory evoked potential for every infant to screen for hearing affection

Cholestasis (Direct or Conjugated Hyperbilirubinemia)

Definition: Conjugated hyperbilirubinemia is defined as a measure of direct reacting bilirubin of >1.0 mg/dL, if the total serum bilirubin (TSB) is ≤5.0 mg/dL, or more than 20% TSB.

1. It is due to failure to excrete conjugated bilirubin (CB) from the hepatocyte into the duodenum.
2. It may be associated with hepatomegaly, splenomegaly, pale stools, and dark urine.
3. Conjugated bilirubin (CB) is found in the urine, UCB is not.
4. Cholestasis means retention of CB, bile acids, and other components of bile
5. Evaluation of cholestasis in infants with jaundice at 2 weeks of age ensures prompt therapy of treatable disorders.
6. There is no physiologic conjugated hyperbilirubinemia.
7. Cholestasis is a medical emergency.

Pathophysiology

Normal bile production involves 2 main processes: bile acid uptake by the hepatocytes from the blood, and bile excretion into the biliary canaliculus. **Bile uptake from the blood is an active process** facilitated by 2 main receptors at the basolateral membranes, while bile secretion at the canalicular membrane is mediated largely by the **bile salt export pump**. In healthy newborns, the cellular processes that regulate bile flow are immature and do not function at the normal adult level, making them more susceptible to cholestasis.

Etiology (Differential diagnosis)

In the NICU, the most common causes of Cholestasis, are:

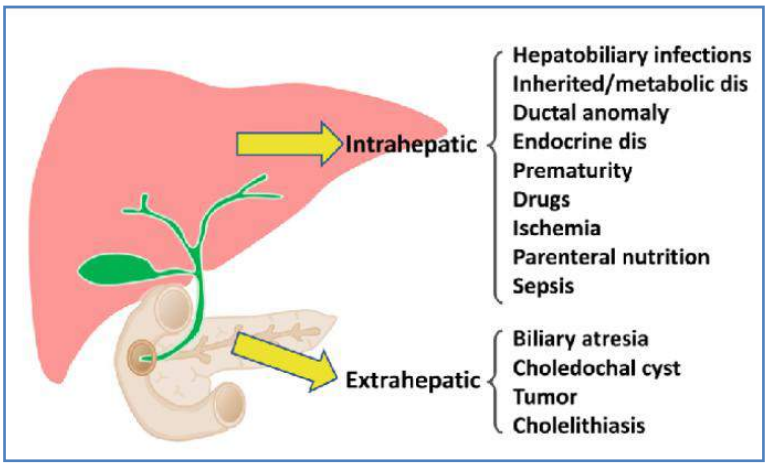
PN, idiopathic hepatitis, biliary atresia, α1-antitrypsin deficiency, intrauterine infection, choledochal cyst, galactosemia, and increased bilirubin load from hemolytic disease

1. Liver cell injury (normal bile ducts)

a. Toxic. Prolonged use of PN (generally greater than 2 weeks) in low birth weight infants is a major cause of elevated CB in the neonatal intensive care unit (NICU).

b. Infection.

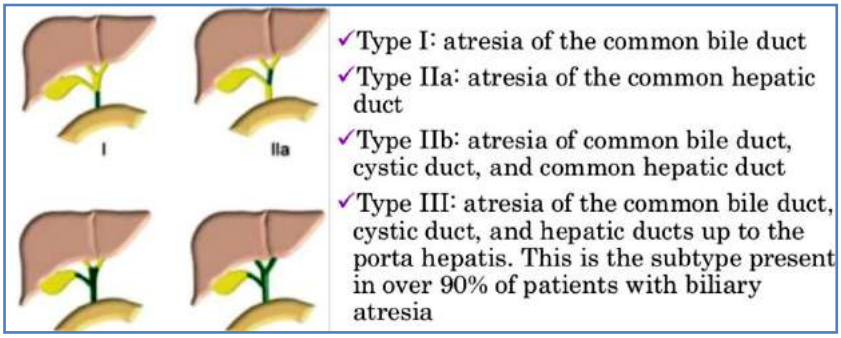
c. Metabolic. α1-antitrypsin deficiency, cystic fi brosis, galactosemia, tyrosinemia, hypermethionemia, fructosemia, storage diseases (Gaucher, Niemann- Pick, glycogenosis type IV, Wolmans), Rotor syndrome, Dubin-Johnson syndrome, Byler disease, Zellweger syndrome, idiopathic cirrhosis, porphyria, hemochromatosis, trisomy 18.



2. Excessive bilirubin load (inspissated bile syndrome) may be seen in any severe hemolytic disease

3. Bile flow obstruction (biliary atresia, extrahepatic or intrahepatic)..

A. Biliary atresia. The most common cause of cholestasis in term infants**, it remains the single most common reason for liver transplantation in children.** It is a progressive idiopathic inflammatory process that leads to chronic cholestasis and fibrosis of both the intrahepatic and extrahepatic bile ducts and subsequent biliary cirrhosis. It has a worldwide estimated incidence of 1 in 15,000 live births. There are 2 distinct phenotypes identified: **the embryonic or fetal form** is less common, associated with an earlier onset of cholestasis and multiple congenital anomalies, and the **perinatal or acquired form, occurring in 80% of cases**, without associated congenital anomalies. In the perinatal or acquired form, infants are presumed to have a normal and patent biliary system at birth that subsequently undergoes progressive inflammation and fibro obliteration due to a perinatal insult.



B. Genetic intrahepatic cholestasis. There are multiple forms of genetic intrahepatic cholestasis, each with different clinical features and variable clinical presentation and prognosis. **Some progressive familial forms** (formerly called progressive familial intrahepatic cholestasis [PFIC]) are potentially fatal; the syndromic paucity of intrahepatic bile ducts **(Alagille syndrome)** tends to have a more favorable prognosis.. These disorders, although individually rare, are collectively common.

1. Alagille syndrome(arteriohepatic dysplasia). It is a genetic disorder, transmitted as autosomal **dominant inheritance** with variable expression. Its major clinical features include a paucity of the intrahepatic bile ducts (chronic cholestasis), cardiovascular anomalies (peripheral pulmonic stenosis), skeletal abnormalities (butterfly vertebrae), ophthalmologic findings (posterior embryotoxon), and "typical facies" (facial shape of an inverted triangle, with broad forehead, deep-set eyes, mild hypertelorism, straight nose with flattened tip, prominent chin, and small, low-set, malformed ears). Long-term prognosis depends on severity and duration of cholestasis, severity of cardiovascular defect, and liver status as it relates to need for liver transplantation.

2.Progressive familial intrahepatic cholestasis (PFIC). A group of genetic disorders, with autosomal **recessive inheritance** and characterized by progressive intrahepatic cholestasis. Currently, 3 types of PFIC are recognized:

i. PFIC-1. Originally called **Byler disease**. It presents with conjugated hyperbilirubinemia early in life, typically within the first 3 months. Diarrhea, pancreatitis, and deficiency of fat-soluble vitamins are seen. Cirrhosis is seen by the first decade of life, and liver transplantation is usually needed by the second decade of life.

ii. PFIC-2. Caused by bile salt export pump (BSEP) deficiency, resulting in altered bile acid transport. It has a presentation similar to PFIC-1 with **no evidence of pancreatitis**. Serum g-glutamyl transpeptidase (γ -GTP) is not elevated despite cholestasis.

iii. PFIC-3. Due to multidrug resistance protein 3 (MDR3) deficiency, resulting in altered phospholipid transport into the canaliculus. It is clinically similar to PFIC-1 and PFIC-2, except that PFIC-3 has an elevated level of γ-GTP.

C. Inborn errors of metabolism In the neonatal period, several inborn metabolic disorders can result in hepatocellular injury that can give rise to a clinical syndrome of neonatal hepatitis. The most common metabolic disease that presents as cholestasis is α **1-antitrypsin deficiency**. Metabolic diseases that can present with rather fulminant liver dysfunction include **galactosemia, tyrosinemia, and hereditary fructose intolerance.** Hereditary fructose intolerance does not present in the neonatal period unless the infant was exposed to a fructose-containing diet.

Antitrypsin deficiency The most common inherited cause of neonatal hepatitis syndrome, with an incidence of 1 in 1600 to 1 in 2000 live births Clinical diagnosis is made by documenting low serum concentration of α 1-antitrypsin and identifying the phenotypic variant. There are several phenotypes; however, the homozygous Pi (protease inhibitor) ZZ is the most likely associated with neonatal liver disease and adult emphysema. Treatment is mostly supportive or liver transplantation if cirrhosis is progressive. Outcome is related to severity of neonatal liver disease; **50% of children are clinically normal by 10 years of age, 5–10% require liver transplantation, and in 20–30% of patients, cholestasis**

D. Idiopathic neonatal hepatitis A diagnosis given to neonatal hepatitis with liver histology showing giant cell multinucleated hepatocytes where no known infectious or metabolic cause has been found. Diagnosis is one of exclusion. Management is mostly supportive. Overall prognosis is difficult to estimate but generally good for infants whose liver disease resolves in the first year.

E. Inspissated bile The "inspissated bile syndrome" is the term traditionally used for conjugated hyperbilirubinemia resulting from severe jaundice associated with **hemolysis due to Rh or ABO incompatibility**, although a multifactorial cause cannot be entirely excluded. Intrahepatic cholestasis is found on liver biopsy, and cholestasis is probably related to **direct hepatocellular damage** produced by unconjugated hyperbilirubinemia. Prognosis is generally good.

F.Total parenteral nutrition (TPN)-related cholestasis The frequency, not necessarily the severity, of cholestasis is partly a function of the degree of prematurity. Cholestasis develops in >50% of infants with birthweight of <1000 g and <10% of term infants after prolonged hyperalimentation.

Clinical presentation Prolonged clinical jaundice is the main presenting complaint of conjugated hyperbilirubinemia, along with pale (acholic) stools and dark urine.

Diagnostic tests

A. Laboratory studies

1. Bilirubin levels (total and direct). The most important initial investigation in a persistently jaundiced infant is determining the fractionated serum bilirubin levels

2. Liver enzymes.

3. Prothrombin time and partial thromboplastin time. May be more reliable indicators of liver synthetic function.

4. f-Glutamyl transpeptidase (GGT). An enzyme in the biliary epithelium. Elevated levels are a very sensitive marker of biliary obstruction or inflammation. A normal level makes biliary atresia an unlikely diagnosis. Normal levels of GGT in the presence of cholestasis indicate failure of bile excretion at the canalicular level and can be seen in progressive familial hepatic cholestasis.

5. Complete blood count (CBC), C-reactive protein, blood and urine cultures.

6. Serum cholesterol, triglycerides, and albumin levels. Triglyceride and cholesterol levels may aid in nutritional management and assessment of liver failure. Albumin is a long-term indicator of hepatic function.

7. Ammonia levels. Should be checked if liver failure is suspected.

8. Serum glucose levels. Should be checked if the infant appears ill.

9. Urine testing for reducing substances. A simple screening test that should always be performed to screen for metabolic disease, especially for galactosemia.

10. TORCH titers and urine cultures for cytomegalovirus (CMV).

11. Other tests. More specific tests are indicated in the investigation of the specific

a. Urine organic acid and plasma amino acid. Screens for inborn errors of metabolism as a cause of neonatal liver dysfunction. High concentrations of tyrosine and methionine, and their metabolic derivatives, are seen in the urine in cases of tyrosinemia.

b. `1-Antitrypsin serum level. Decreased serum α 1-antitrypsin concentration and liver biopsy showing periodic acid–Schiff–positive cytoplasmic granules will reveal variable degrees of hepatic necrosis and fibrosis.

c. Sweat test. Done for confirmatory diagnosis of cystic fibrosis.

B. Imaging studies

1. Chest radiograph. Presence of cardiovascular or situs anomalies may be suggestive of biliary atresia. Skeletal abnormalities, such as butterfly vertebrae, may be consistent with a diagnosis of Alagille syndrome.

2. Ultrasonography. A simple and noninvasive test that should be done in all infants presenting with cholestasis **after a 4-hour fast**; a small or absent gallbladder is suggestive of biliary atresia, whereas the presence of a normal-looking gallbladder makes this diagnosis unlikely. Ultrasound is a sensitive method for recognizing other surgical causes of neonatal cholestasis, such as a choledochal cyst or structural abnormalities of the biliary tree.

3. Hepatobiliary scanning. Contrast agents are taken up by the liver and excreted into the bile; they are technetium labeled and provide a clear image of the biliary tree after intravenous injection.

4. Endoscopic retrograde cholangiopancreatography. Sensitivity and specificity are excellent. This procedure can be both diagnostic and therapeutic in cases of cholestasis caused by bile duct stones.

C. Other studies

1. Percutaneous liver biopsy. The single most definitive procedure in the evaluation

of neonatal cholestasis

2. Magnetic resonance cholangiopancreatography (MRCP). The few reports available to date regarding the use of MRCP in children are encouraging.

3. If the ultrasonography scans or fluid collections suggest extrahepatic obstruction disease, the baby will need an exploratory laparotomy, cholangiogram, and open liver biopsy to enable a definitive diagnosis

Management

A. Medical management. Few conditions causing neonatal cholestasis are treatable, and these conditions (ie, biliary atresia and choledochal cyst) need timely diagnosis and management. Medical treatment is mostly supportive and should be directed toward promoting growth and development and in treating the other complications of chronic cholestasis, **such as pruritus, malabsorption, nutritional deficiencies, and portal hypertension.** Management involves dietary manipulation and fat-soluble vitamin support.

1. Special formula. Elemental formula containing medium-chain triglycerides is preferable because it can be better absorbed regardless of luminal concentration of bile acids.

2. Medium-chain triglycerides (MCTs). Infants with cholestasis often require a diet that includes MCTs, which can be absorbed without the action of bile salts. Some formulas containing MCTs include Enfaport and Pregestimil. Breast-fed cholestatic infants should be given supplemental MCT.

3. Vitamin supplementation. Fat malabsorption interferes with maintenance of adequate levels of fat-soluble vitamins. Supplementation of vitamins A, D, E, and K is needed. Extra vitamin K supplementation may be necessary if a bleeding tendency develops.

4. Dietary restrictions. Removal of galactose and fructose from the diet may prevent the development of cirrhosis and other manifestations of galactosemia and hereditary fructose intolerance, respectively.

B. Pharmacologic management.

1. Ursodiol. A naturally occurring dihydroxy bile acid that appears to help cholestasis in 2 ways: substitution in the bile acid pool for more hydrophobic bile acids, and stimulation of bile flow. Recommended dose is 20 mg/kg/d in divided doses

2. Phenobarbital. Mode of action is to enhance bile acid synthesis, increase bile flow, and induce hepatic microsomal enzymes. Recommended dose is 3–5 mg/kg/d. Use is limited by its behavioral and sedative side effects.

3. Cholestyramine. Binds bile acids in the intestinal lumen, thereby decreasing enterohepatic circulation of bile acids, which leads to increased fecal excretion and increased hepatic synthesis of bile acids from cholesterol, which may lower serum cholesterol levels.

4. Rifampin. Effective in the management of pruritus due to cholestasis, but experience is very limited in neonates

C. Surgical management

1. Kasai procedure. Surgical procedure such as Kasai portoenterostomy should be done to establish biliary drainage in patients diagnosed with biliary atresia. **Optimal results are obtained if the procedure is done before 8 weeks of age**.

2. Liver transplantation. When end-stage liver disease is inevitable, liver transplantation is the last resort. Biliary atresia remains the most common indication for liver transplantation in the United States.

Neonatal Respiratory Distress

Respiratory distress is the most common neonatal emergency and main cause of admission to neonatal intensive care units. Hyaline membrane disease **(respiratory distress syndrome) is by far the most common cause** followed by neonatal pneumonia, transient tachypnea of newborn and meconium aspiration


Neonatal respiratory distress

An infant is said to be in respiratory distress if he has

1. Nasal flaring. One of the earliest signs of respiratory distress, nasal flaring may be present in intubated, ventilated patients as well.

2. Grunting. Commonly seen early in respiratory distress syndrome (RDS) and transient tachypnea, grunting is a physiologic response (partial closure of the glottis during expiration) to end-expiratory alveolar collapse. Grunting helps maintain functional residual capacity (FRC) through prolongation of expiration and therefore oxygenation.

3. Retractions. Intercostal, subcostal, and sternal retractions are present in conditions of decreased lung compliance or increased airway resistance and may persist during mechanical ventilation if support is inadequate.

4. Tachypnea. A respiratory rate >60/min implies the inability to generate an adequate tidal volume and may persist during mechanical ventilation.

5. Cyanosis. Central cyanosis indicates hypoxemia. Cyanosis is difficult to appreciate in the presence of anemia. Acrocyanosis is common shortly after birth and is not a reflection of hypoxemia.

6. Abnormal breath sounds. Inspiratory stridor, expiratory wheezing, and rales should be appreciable. Unfortunately, unilateral pneumothorax may escape detection on auscultation.

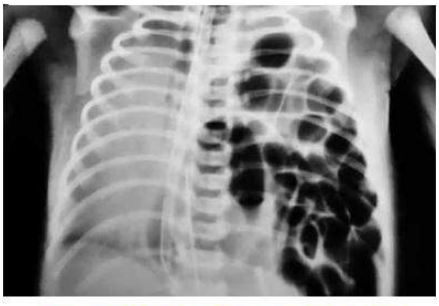
The absence of signs may be secondary to neurologic depression rather than absence of pulmonary disease.

Main causes of neonatal respiratory distress

Clinical evaluation should be combined with blood gas analysis to identify those in respiratory failure and those who in need for mechanical ventilation

1 – Pulmonary causes

a.Respiratory distress syndrome (hyaline membrane disease) :the most common in preterm
b. Transient tachypnea of newborn : the most common in fullterm
c. Meconium aspiration syndrome
d. Neonatal pneumonia
e. Persistent fetal circulation
f. Pulmonary hemorrhage


Congenital Diaphragmatic Hernia

g. Pulmonary air leak e.g.pnuemothorax
h. Diaphragmatic hernia
i. Bronchopulmonary dysplasia
j. Congenital lober emphysema
k. Pulmonary hypoplasia

2 – Extra pulmonary causes

a. Airway: Choanal atresia (bilateral) - Laryngomalacia - Tracheo-esophageal fistula - Pierre-Robin syndrome
b. Chest wall: Neonatal myasthenia - Thoracic dystrophy
c. Cardiac: Congestive heart failure- Congenital heart disease with heart failure - Persistent fetal circulation
d. Central: Cerebral Hypoxia (encephalopathy) - Intracranial hemorrhage (birth truma) - Meningitis
e. Metabolic: Hypothermia - Hyperthermia – Hypoglycemia- Severe metabolic acidosis - Renal tubular acidosis - Errors of metabolism
f. Hematological causes: Severe anemia - Polycythemia

Surgical causes of neonatal respiratory distress: 1. Pneumothorax and other air leaks 2. Tracheoesophageal fistula 3. Diaphragmatic hernia 4. Rib cage anomalies. 5. Choanal atresia

Grades of respiratory distress

- Grade 1(mild distress): rapid respiration above normal >60
- Grade 2(moderate distress): intercostal and Subcostal retraction
- Grade 3 (severe distress): expiratory grunting
- Grade 4 (advanced distress): central cyanosis and disturbed consciousness

Assessment of respiratory distress

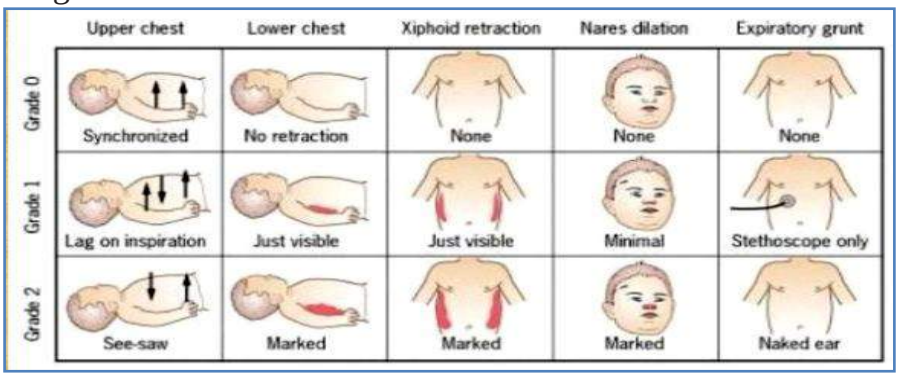
Usually assessed by a Downe's scoring system which is given below

Score	0	1	2
Respiratory rate/min	< 60	60-80	>80
Cyanosis	None	None with 40% FiO2	Needs > 40% FiO2
Retractions	None	Mild	Severe
Grunting	None	Minimal	Obvious
Air entry	Good	Decreased	Very poor

Score >6 indicates severe distress

Another Assessment score is **Respiratory severity score.** The respiratory

severity score (RSS) designed by Silverman and Andersen to quantify respiratory distress among neonates. The RSS is objective, easy to learn, quick to perform, and requires no expensive equipment. It is rated by giving scores from 0 to 2 from upper chest movement, lower chest retractions, xiphoid retractions, nares dilatation, and expiratory grunting.The RSS can be used for predicting the need for escalation of respiratory support and can help facilitate transfer decision making to higher resourced facilities**. Scores ≥5** have been the most useful cutoff point for transfer, although the sensitivity of the score is decreased in patients with a higher score.



The respiratory severity score (RSS)

Investigations of neonatal respiratory distress

- Chest X-ray: in all cases
- Blood gases: in all cases
- Hemoglobin and hematocrit value
- Sepsis screen: with suspected pneumonia
- Echocardiography: with suspected congenital heart disease
- All Pulmonary Function tests low.

General Management of neonatal respiratory distress

The initial approach to a neonate with respiratory distress, regardless of etiology, consists of:

1. Relieving cyanosis with supplemental oxygen and providing assisted ventilation, if needed. A neonate with obvious respiratory distress needs continuous monitoring with pulse oximetry to decide when intubation and mechanical ventilation are required.

2. Obtaining a chest radiograph to assist in diagnosis and to identify complications such as pneumothorax that may require urgent treatment.

3. Providing an appropriate **fluid management**.

4. Correction of any metabolic abnormalities (e.g., acidosis, hypoglycemia), if present.

5. Providing adequate nutrition. In general, infants with sustained RRs over 60 breaths per minute should not be fed orally; these infants should be maintained on gavage feedings.

6. Obtaining a blood culture and beginning antibiotic coverage with ampicillin and gentamicin while awaiting the results of the culture, in case of a preterm infant with respiratory distress or a term infant with respiratory distress that persists longer than four

to six (4-6) hours, or if sepsis or pneumonia is suspected by history or physical examination.

7. Providing an appropriate specific therapy that is directed at the underlying disorder.

8. Pharmacologic respiratory support

Numerous medications are available for improvement of respiration. They represent a broad range of therapeutics, of which the bronchodilators and anti-inflammatory drugs are the oldest and most common. The use of **mixtures of inhaled gases such as helium and nitric oxide is a recent form of treatment**. Sedatives and paralyzing agents remain controversial in neonatal respiratory management. Finally, surfactant replacement therapy has rapidly become a major adjunct in the care of preterm infants, and its use has expanded to disease states other than RDS (hyaline membrane disease), for which it was originally intended.

a. Bronchodilators (inhaled agents). Most of these drugs are sympathomimetic agents that stimulate β1-, β2-, or α-adrenergic receptors. They have both inotropic and chronotropic effects and provide bronchial smooth muscle and vascular relaxation. Albuterol is probably the most commonly used aerosolized bronchodilator. Two anticholinergic agents (atropine and ipratropium) are also used as inhaled bronchodilators for inhibition of acetylcholine at lung receptor sites and bronchial smooth muscle relaxation

b. Bronchodilators (systemic). Aminophylline (parenteral) and theophylline (enteral) are methylxanthines with considerable bronchial dilating action. Neonatal use includes bronchodilation and, more often, stimulation of respiratory efforts.

c. Steroid therapy. This has been used to treat or prevent chronic lung disease. Although steroid therapy results in significant short-term improvement in pulmonary function, long-term benefit remains unproved. The substantial adverse effects of steroid therapy with dexamethasone have led the American Academy of Pediatrics (AAP) and the Canadian Pediatric Society to issue a joint recommendation against the routine use of steroid therapy. Hydrocortisone may provide similar pulmonary benefits without the adverse neurodevelopmental effects of dexamethasone.

Use the mnemonic TRACHEA to help remember some of the causes of tachypnea in a newborn: T. transient tachypnea of the newborn; R, respiratory infections (pneumonia); A, aspiration syndromes (meconium, blood, or amniotic fluid); C, congenital malformations; H, hyaline membrane disease (now known as respiratory distress syndrome); E, edema; A, air leaks and acidosis.

Respiratory Distress Syndrome (RDS)

The Vermont Oxford Network definition for RDS requires that babies have:

1. An arterial oxygen tension (Pao2) <50 mm Hg and central cyanosis in room air, a requirement for supplemental oxygen to maintain Pao2>50 mm Hg, or a requirement for supplemental oxygen to maintain a pulse oximeter saturation over 85 %.

2. A characteristic chest radiographic appearance (uniform reticulogranular pattern to lung fields with or without low lung volumes and air bronchogram) **within the first 24 hours of life**.

It occurs principally in **premature babies** approximately 50% of infants with birth weight less than 1.5 kg develop RDS, depending on their gestational immaturity (only 5% in full term neonates) **due to deficient synthesis of surfactant by type2 alveolar cells** which results in massive diffuse alveolar atelectasis, edema, and cell injury. RDS causes 30% of all neonatal deaths. The incidence and severity of RDS are expected to decrease after the increase in use of antenatal steroids in recent years. After the introduction of exogenous surfactant, the survival from RDS is at >90%.

Pathophysiology: **Surfactant deficiency** is the primary cause of RDS, often complicated by **pliable chest wall**. Both factors lead to progressive atelectasis and failure to develop an effective functional residual capacity (FRC) resulting in:

1.alveolar collapse and reduced lung volume

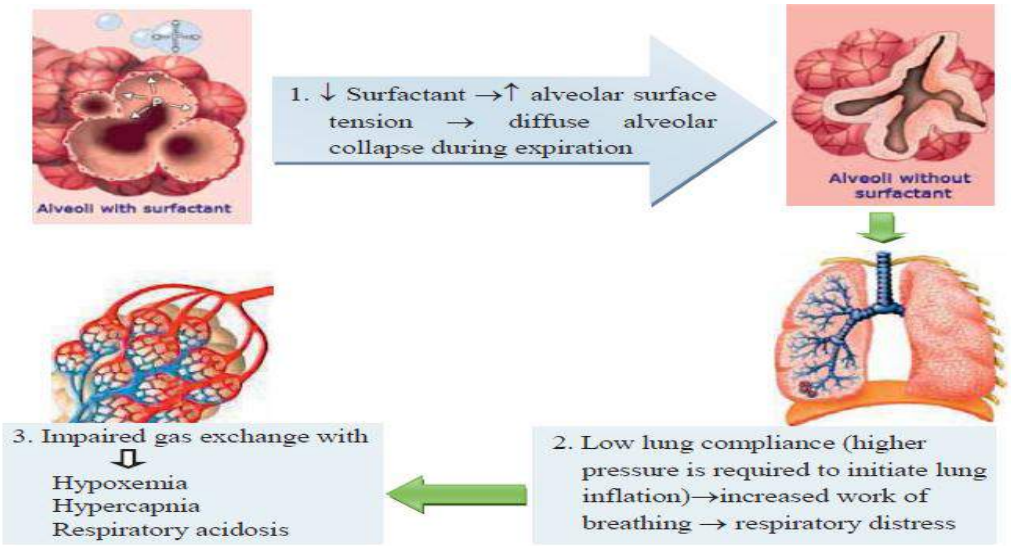
2.Peripheral tissue hypoxia which leads to metabolic acidosis

3.Respiratory acidosis also occurs due to alveolar hypoventilation

4.Combination of acidosis and hypoxemia reduces myocardial contractility

5.High pressures are needed to expand the lungs

6.Pulmonary hypertension with right left **shunting** will occur



(Diagram for Pathophysiology of RDS from Illustrated Baby Nelson)

Lung pathology: **Gross:** Deep purple, liver like consistency of the lung **Microscopic:** Collapsed alveoli are lined with acidophilic hyline membrane.

Lack of surfactant. In the absence of surfactant, the small airspaces collapse; each expiration results in progressive atelectasis. Exudative proteinaceous material and epithelial debris, resulting from progressive cellular damage, collect in the airway and directly decrease total lung capacity. In pathologic specimens, this material stains typically as eosinophilic hyaline membranes lining the alveolar spaces and extending into small airways.

Surfactant: is a surface-active material

a. Constituents: Phosphatidyl Choline (Lecithin), Phosphatidyl glycerol, Phosphatidyl inositrol and Surfactant proteins and cholesterol.

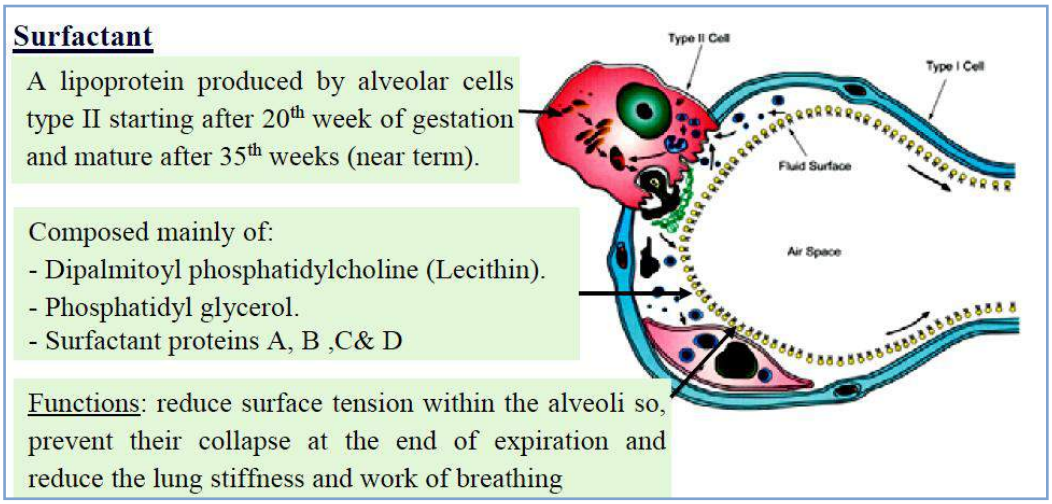
b. Production: alveolar cell type 2 (type 2 pneumatocyte). It produced from 22 – 24 weeks by pathway sensetive to changes in temperature and decreased by asphyxial insults in the perinatal period.

c. Maturation: 35 weeks of gestation by pathway resistant to alternations of PH and Hypoxia but is **delayed in the presence of fetal hyperinsulinemia**.The maturity of type II cells is **enhanced by the administration of antenatal corticosteroids** and by chronic intrauterine stress such as pregnancy-induced hypertension, intrauterine growth restriction, and twin gestation.

d.Stored in the characteristic lamellar bodies of type II pneumocytes

e.Function: *decrease surface tension of the fluid lining the alveoli preventing collapse in expiration, Enhanced fluid clearance and Host defense.*

f. Regulation of type 2 alveolar epithelial cells, maturation, and surfactant release are influenced by elevations of intracellular cAMP, cortisol, thyroid hormone, catecholamines, beta adrenoceptors and natriuretic peptide receptors.



(Diagram for surfactant production from Illustrated Baby Nelson)

f. **Surfactant therapy** is associated with pulmonary hemorrhage **but interestingly it is also used after hemorrhage** has occurred due inactivation of surfactant by blood.

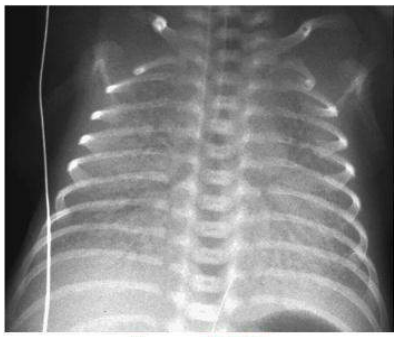
Factors that increase risk of RDS: Prematurity, Infant of diabetic mothers, Cesarean section, Asphyxia, Male sex and second born twins, Diaphragmatic hernia, the smaller of twins and Erythroblastosis fetalis.

Factors that decrease risk of RDS: Preeclaptic mothers, mothers taking steroids and premature rupture of membrane greater than 48 hour

Clinical picture of RDS

Within minutes after birth respiratory distress 4 grades occurs and in severe cases apnea and cyanosis. Chest examination: diminished air entry, bronchial breathing, crepitations and wheeze Shunting. The presence or absence of a cardiovascular shunt through a PDA or foramen ovale, or both, **may change the presentation or course of the disease process.**

Course: Natural course of RDS includes deterioration for first 48‑72 h followed by improvement due to synthesis of endogenous surfactant. With advent of exogenous surfactant, recovery could be faster with return of lung function within hours of its administration.



X ray of RDS

Complications of RDS

1.Barotraumas(Air leak): interstitial emphysema, pneumomediastinum ,pneumothorax and pneumopericardium

2.**PDA :**frequently complicates RDS; increasing left-to-right shunt may cause heart failure

3.**Infection** :may accompany RDS.

4. **Hemorrhage:** Pulmonary or intracranial

5.**Chronic complications**: Lober emphysema, bronchopulmonary dysplasia

Investigations of RDS

1. Chest x ray: A. Reticulo granular pattern. B. Air Bronchogram. C. Ground glass appearance D. White lung

2.Arterial blood gases: increase CO2, decrease O2 and decrease pH

3. Blood glucose, electrolytes and CBC

4. **Blood culture, CRP and ESR**

5.Amniotic fluid L / S ratio (prenatal diagnosis) the risk of RDS is very low **if the L/S ratio is >2**. With some exceptions as Perinatal asphyxia

6. Lamellar body counts in the amniotic fluid (prenatal diagnosis) A value of > 50,000 lamellar bodies/microliter predicts lung maturity

7. Echocardiography. A valuable diagnostic tool in the evaluation of an infant with hypoxemia and respiratory distress

Prevention of RDS

1. Intrapartum assessment of fetal well being

2. Antenatal corticosteroids: Dexamethasone or betamethasone **(betamethasone may be preferable because of potential neurotoxicity of dexamethasone)** at gestational 24 – 34 (48 hours before delivery) Contraindicated in Chorioamnionitis

3. Resuscitation and stabilization

4. Surfactant therapy (prophylactic) immediately after birth or within the first few hours

Treatment of RDS

1. Basic life support measures

a. Thermoregulation
b. Correction of acidosis, fluid and electrolyte balance
c. Prophylactic antibiotics until cultures appears

2. Monitoring

a. Heart rate, respiratory rate, arterial blood pressure and temperature
b. Oxygen saturation ABG, hemoglobin, electrolyte, calcium, glucose and albumin.

3. Correction of hypoxemia

a. In the delivery room: prophylactic nasal CPAP as CPAP treatment is recommended to be started from birth in all infants at risk of RDS, such as those born at <30 weeks' gestation. **Humidified high-flow nasal cannula system** also can be used.
b. In NICU: nasal CPAP or mechanical ventilation (intermittent or high frequency) in order to facilitate weaning. Caffeine should be routinely used for very preterm neonates with RDS to augment extubation.

Surfactant

4. Surfactant replacement therapy

The effect of surfactant therapy is better the earlier in the course of RDS it is given. Use of INSURE (INtubate–SURfactant–Extubate to CPAP) technique for early surfactant administration reduces the need for ventilation and improves survival.
a.Surfactant replacement is one of the best-studied therapies in neonates.
b. Natural or synthetic surfactant can be given via an endotracheal tube c.Natural (derived from animal lungs) surfactant preparations are better than synthetic (protein-free) at reducing pulmonary air leaks.
d. Multiple rescue doses result in greater improvements in oxygenation and ventilatory requirements, a decreased risk of pneumothorax and a trend toward improved survival.

Other babies that can be considered for surfactant therapy:
- Ventilated babies with meconium aspiration syndrome (may need to repeat dose after 6–8 hours).
- Term babies with pneumonia and less compliant lungs.

Procedure of surfactant admistration

Preparation

- Calculate dose of surfactant required and warm to room temperature.
- Ensure correct endotracheal tube (ETT) position.

Check ETT length at lips. Listen for bilateral air entry and look for chest movement. If in doubt, ensure ETT in trachea using laryngoscope and adjust to ensure bilateral equal air entry.

- Chest X-ray before first dose.
- Invert surfactant vial gently several times, without shaking, to re-suspend the material.
- Draw up required dose.

Instillation

- With baby supine, instill prescribed dose down ETT.
- Wait for recovery of air entry/chest movement and oxygenation between boluses.

Post-instillation care

- Do not suction ETT for first 6 hours after instillation (routine frequent suction is not indicated in surfactant-deficiency disease for 48 hours, can be done if there is signs of blockade of ETT).

- Be ready to adjust ventilator/oxygen settings in response to changes in chest movement, tidal volume and oxygen saturation.

Subsequent management

- If baby remains ventilated at **FiO2 >0.3** with a mean airway pressure of >7 cm H2O, give further dose of surfactant 6-12 hours after first dose.

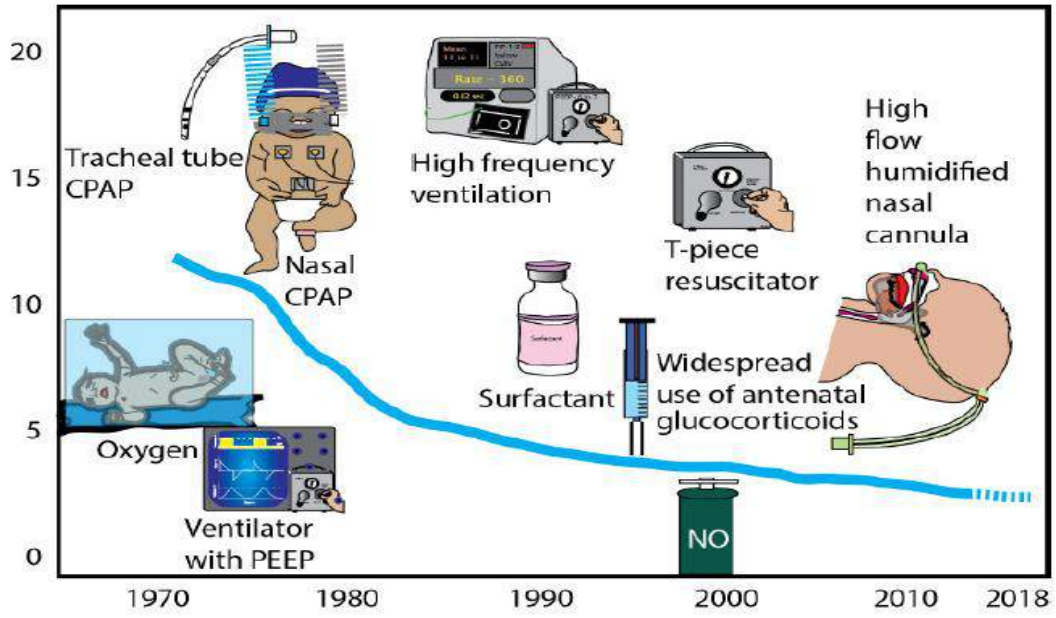
- Third dose should be given only at request of attending consultant.

5.Treatment after stabilization Noninvasive ventilation, Caffeine administration and Early optimized nutrition

6. Inhaled Nitric oxide or extracorporeal membrane oxygenation

Intrinsic NO comes from: L-arginine → Citrulline + NO

Inhaled NO → guanylate cyclase → GTP → GMP → **Relaxation**



Graph Showing Neonatal Mortality Rate and Various Innovations in Neonatal Respiratory

Outcome Although the survival of infants with RDS has improved greatly, the survival with or without respiratory and neurologic sequelae is highly dependent on birthweight and gestational age. Major morbidity (BPD/CLD, NEC, and severe IVH) and poor postnatal growth remain high for the smallest infants.

Transient Tachypnea of The Newborn

Definition: Transient tachypnea of the newborn (TTN) is a **benign self limited** respiratory distress syndrome of term and late preterm infants related to delayed clearance of lung liquid. Also known as RDS type II, Wet Lung Syndrome and Abbreviated as TTN, TTNB.

TTN is the most common cause of respiratory distress in **full term**. The distress appears shortly after birth and usually resolves within 3–5 days.Mainly affecting fullterm or late preterm infants born by caesarean section following uneventful delivery.

Incidence: It is the most common perinatal respiratory disorder, responsible for 40% of respiratory distress after birth.

Pathophysiology of TTN: To accommodate the transition to breathing air at birth, the lungs must switch from **a secratory mode**, which provides the fetal lung fluid required for normal lung growth and development in utero, to **an absorptive mode**. **Disruption or delay in clearance** of fetal lung fluid results in the transient pulmonary edema that characterizes TTN.

Risk factors for TTN:

1. Cesarean section with or without labour
2. Precipitous birth
3. Fluid overload in the mother, especially with oxytocin infusion
4. Breech delivery
5. Infant of a diabetic mother (2–3 times more common)

Clinical presentation of TTN: The lung liquid inhibits gas exchange, leading to an increased work of breathing. Tachypnea develops to compensate for that. Hypoxia develops because of poorly ventilated alveoli.

1. Respiratory distress appears within few hours **(first 6 hours)** after birth and is usually mild
2. Infants may have an **increased anteroposterior** diameter of the chest **"barrel chest"** due to hyperinflation
3. Rapid spontaneous improvement occurs within 24 -48 hours.
4. **Grunting, maximum respiratory rate >90/min, and an Fio2 >0.40 within 6 hours** of life were associated with an increase in risk of prolonged TTN/increased severity of TTN

Some clinicians differentiate transitional delay, TTN, and prolonged tachypnea.
A. Transitional delay. Tachypnea after birth for usually <6 hours (but can be for 2–12 hours). Grunting can occur after birth with transitional delay and usually subsides by 2 hours (93%).
B. Transient tachypnea of the newborn (TTN). Tachypnea that lasts from after birth usually <72 hours. It typically resolves by 12–24 hours.
C. Prolonged tachypnea of the newborn (PTTN). Some infants have prolonged tachypnea, lasting >72 hours

Diagnosis: TTN is a clinical diagnosis. It is based on clinical and radiologic findings.

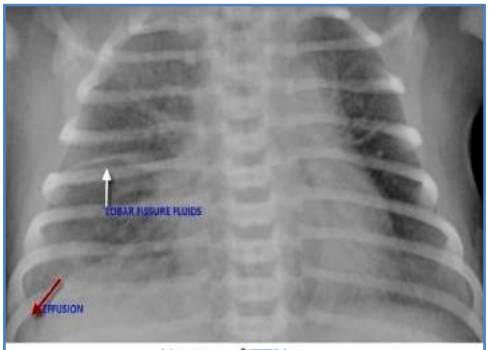
1.History and physical examination.

2.Radiographic evaluation: The chest radiograph of an infant with TTN is consistent with retained fetal lung fluid

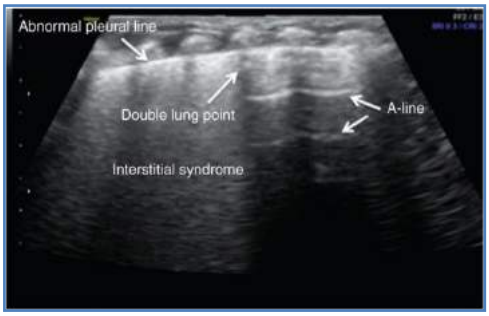
3. **Lung ultrasonography.** An ultrasound sign (" double lung point") was found to be diagnostic of TTN. Lung ultrasound shows a difference in lung echogenicity between the upper and lower lung areas.

4.Laboratory evaluation: A complete blood count (CBC) and appropriate cultures. An arterial blood gas

5. Other promising tests. Plasma **endothelin-1** levels may be higher in RDS compared with those in TTN. This test may prove useful in differentiating RDS from TTN. **Interleukin-6 (IL-6)** may distinguish proven and clinical sepsis from TTN. This may make it possible to avoid antibiotics in this group of infants. **Serum atrial natriuretic peptide** levels were lower for infants with TTN than normal infants in one study.



X - ray of TTN



Treatment of TTN

Prevention: An elective cesarean section (CS) scheduled at a gestational age (GA) of 39 weeks or later may decrease the frequency of TTN.

Treatment is mainly supportive with provision of supplemental oxygen, as needed. More severe cases may respond to continuous positive airway pressure (CPAP) to improve lung recruitment. Infants often undergo an evaluation for infection and are treated with antibiotics for 24 to 48 hours until blood cultures are negative.

Inhaled epinephrine. Infants with TTN have low levels of epinephrine, and epinephrine helps to mediate fetal lung fluid absorption. a2-Agonist salbutamol. Stimulation of β adrenergic receptors with salbutamol upregulates the activity of the sodium channels.

Diuretics are not recommended.Diuretics have been used in practice in some centers with the rationale of accelerating lung liquid absorption.

.**Prognosis:** Excellent. Recent studies have revealed that TTN is associated with the development of wheezing syndromes (bronchiolitis, acute bronchitis, chronic bronchitis, asthma, or prescription for asthma medication) in early childhood.

The chest radiograph of an infant with TTN

Prominent perihilar streaking (sunburst pattern) due to engorgement of periarterial lymphatics that participate in the clearance of alveolar fluid, Coarse; fluffy densities may reflect alveolar edema. Hyper aeration with widening of intercostal spaces, widened and fluid-filled interlobar fissure,. The radiographic findings in TTN usually improve by 12 to 18 hours and resolve by 48 to 72 hours

3 - Neonatal Pneumonia

The diagnosis of neonatal pneumonia is challenging. It is difficult to distinguish primary (occurring from birth) neonatal bacterial pneumonia clinically from sepsis with respiratory compromise, or radiographically from other causes of respiratory distress (hyaline membrane disease, retained fetal lung fluid, meconium aspiration, amniotic fluid aspiration).

Types and Pathogenesis:

1. True congenital pneumonia (acquired in utero)
2. Intrapartum pneumonia (acquired through the birth canal)
3. Postnatal pneumonia (acquired immediately after birth)

Etiology

A.Organism

1 .Bacteria : The causes of neonatal bacterial pneumonia are the same as for EOS, and antibiotic treatment is generally the same as for sepsis.
. Gram negative: E coli, Klebsiella and pseudomonas
. Gram positive: staph aurous, B beta hemolytic streptococci and listeria
. Chlamydia:

2 .Non bacterial: CMV, Toxoplasmosis

B.Routes of infection

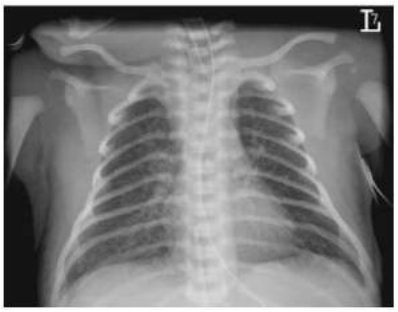
- Ascending transmission, from aspiration of infected or contaminated maternal fluids
- Hematogenous

C.Risk factors

1. Prolonged rupture of membranes 2. Prematurity 3. Chorioamnionitis 4. Meconium stained amniotic fluids 5. Fetal asphyxia 6. Indiscriminate use of broad spectrum antibiotics in obstetric ward and NICU

Clinical picture: Respiratory distress in the first few hours after birth

Differential diagnosis: from other causes of RD in the newborn



Investigations: X- ray patchy opacity of variable size and shape. Persistent focal opacifications on chest radiograph due tonneonatal pneumonia are uncommon, and their presence should prompt some consideration of noninfectious causes of focal lung opacification (such as congenital cystic lesions or pulmonary sequestration).

Treatment: Broad spectrum antibiotics until culture and sensitivity appear

Meconium Aspiration Syndrome

Aristotle, a philosopher-biologist (380‑323 BC) coined the term "meconium," as it resembled crude extract of Opium and the babies born through meconium-stained amniotic fluid (MSAF) were found depressed or sleepy

Meconium is the first intestinal discharge of the newborn infant. It is a sterile, thick, black-green, odorless material that results from the accumulation of debris in the fetal intestine during the third month of gestation. The components of meconium include water (72%–80%), desquamated cells from the intestine and skin, gastrointestinal mucin, lanugo hair, fatty material from the vernix caseosa, amniotic fluid, intestinal secretions, blood group–specific glycoproteins, bile, and drug metabolites.

Meconium first appears in fetal intestines between 10–16 weeks. .Increased amounts of motilin and parasympathetic innervation increases incidence of MSAF in postterm infants. .Fetal hypoxia, with the resultant intestinal ischemia, can induce intestinal hyperperistalsis and relaxation of anal sphincter leading to in utero passage of meconium.

The presence of meconium in the trachea can cause airway obstruction and, with aspiration below the vocal cords, further obstruction, air trapping, and an inflammatory response, all of which can result in severe respiratory distress. All infants with meconium-stained amniotic fluid do not develop meconium aspiration syndrome (MAS).

It mainly occurs in full term and pot-term newborn subjected to fetal distress with passage of meconium into amniotic fluid.The incidence of MSAF varies from 8–20% of all deliveries. Of infants born through an MSAF, 5% go on to develop MAS.

Pathophysiology MAS is a multifactorial disease and includes pulmonary and vascular components.

A. In utero passage of meconium. Fetal distress and vagal stimulation are 2 probable factors.

B. Aspiration of meconium. After intrauterine passage of meconium, deep irregular respiration or **gasping**, associated with fetal hypoxia either in utero or during labor and delivery, can cause aspiration of the MSAF. Before delivery, the progression of the aspirated meconium is usually impeded by the presence of the viscous liquid that normally fills the fetal lung and airways. Therefore, the distal progression occurs mostly after birth in conjunction with the reabsorption of lung fluid. Early consequences of meconium aspiration include airway obstruction, decreased lung compliance, and increased expiratory large airway resistance.

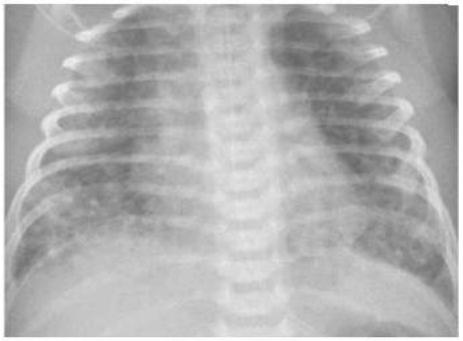
1. Airway obstruction. Thick MSAF can result in acute upper airway obstruction. As the

aspirated meconium progresses distally, total and partial airway obstruction may occur. Partial airway obstruction may result in a ball-valve phenomenon leading to air trapping and alveolar hyperexpansion. Total obstruction may lead to asymmetric areas of atelectasis, **resulting in hypoxia and increased pulmonary vascular resistance (PVR).**

2. Chemical pneumonitis. With release of Inflammatory mediators
4. Surfactant dysfunction. The free fatty acids in meconium stripping surfactant from the surface of the alveoli. Meconium also impacts surfactant production and clearance
5. Pulmonary hypertension. A third of infants with meconium aspiration develop persistent pulmonary hypertension of newborn (PPHN). Meconium aspiration alone may result in a delay of the normal decline of PVR. Additional increases in PVR are multifactorial. PVR increases as a direct result of alveolar hypoxia, acidosis, and lung hyperinflation.
Risk factors: Post term, acute hypoxia, chronic hypoxia and infection.
Clinical presentation: The presentation of an infant who has aspirated MSAF is variable, ranging from mild to profound respiratory distress.
A. General features
1. Infants with MAS often exhibit signs of **postmaturity**. Respiratory distress is evident at birth or in the transition period.

Meconium staining on the skin is proportional to the length of exposure and meconium concentration. Fifteen minutes of exposure to thick MSAF or 1 hour to lightly stained fluid will begin to stain the umbilical cord. Yellow staining of the newborn's nails requires 4–6 hours; staining of the vernix caseosa takes ~12 hours.

2. **The amniotic fluid.** The meconium present in amniotic fluid varies in appearance and viscosity, ranging from a thin green-stained fluid to a thick "pea soup" consistency. Although MAS can occur in the presence of thin MSAF, the majority of infants who develop MAS have a history of thick meconium-stained fluid.
B. Airway obstruction. Large amounts of thick meconium, if not removed, can result in an acute large airway obstruction. These infants may be apneic or have gasping respirations, cyanosis, and poor air exchange. Later, as the meconium is driven down to more distal airways, the smaller airways are affected, resulting in air trapping and scattered atelectasis.
C. Respiratory distress. The infant who has aspirated meconium into the distal airways but does not have total airway obstruction manifests signs of respiratory distress secondary to increased airway resistance, decreased compliance, and air trapping (ie, tachypnea, nasal flaring, intercostal retractions, increased anteroposterior (AP) diameter of the chest, and cyanosis). Some infants may have a delayed presentation, with only mild initial respiratory distress that worsens hours after delivery as atelectasis, surfactant inactivation, and chemical pneumonitis develop.
D. Other pulmonary abnormalities. If air trapping develops, there may be a noticeable increase in AP diameter of the chest. Auscultation often reveals decreased air exchange, rales, rhonchi, or wheezing.


Chest X - ray meconium aspiration

Air trapping can lead to air leak syndromes

Differential diagnosis

· TTN
· Aspiration of amniotic fluid/blood
· Pneumonia/Sepsis
· Diaphragmatic hernia

Investigations

1. X-ray chest: Areas of lung collapse, areas of hyperinflation and heterogeneous patchy infiltrates. Pneumothorax, pneumomediastinum, and sometimes pleural effusion may occur.
2. Other investigation of respiratory distress
3. Evaluation of PPHN using cardiac echocardiogram.

Complications

1.Collapse or emphysema
2. Pneumonia
3. Pneumothorax and pneumomediastinum
4. Pulmonary hypertension: one-third of infants with MAS develop pulmonary hypertension
5. Hypoxic ischemic encephalopathy
6. Secondary surfactant deficiency

Management

Prevention of MAS:

1. Early intervention when fetal hypoxia is noted.
2. Reducing post-term (≥41 weeks) deliveries.
3. Prevention of aspiration by proper oropharyngeal and nasopharyngeal suctioning of meconium from upper airway with large pore suction catheter for infants who are depressed or have respiratory distress. Aspiration of meconium in vigorous infants are not effective in preventing MAS.

1. General management: Immediate management at delivery room. The clinician should determine whether the infant is **vigorous, distressed or depressed.**
Vigorous infant has the following: heart rate >100 beats per minute, spontaneous respirations, and good tone (spontaneous movement or some degree of flexion).

1. If the infant appears vigorous, routine care should be provided, regardless of the consistency of the meconium.

2. If respiratory distress develops or the infant becomes depressed, the trachea should be intubated under direct laryngoscopy and intratracheal suctioning performed.

a. Maintain a neutral thermal environment.
b. Minimal handling protocol to avoid agitation.
c. Maintain adequate blood pressure and perfusion.
d. Correct any metabolic abnormalities such as hypoglycemia, hypocalcemia, or metabolic acidosis.

e. Sedation may be needed in infants on mechanical ventilation.

2. Respiratory management

a. Pulmonary toilet. If suctioning the trachea does not result in clearing of secretions. Chest physiotherapy every 30 minutes to 1 hour. Chest physiotherapy is contraindicated in labile infants when associated PPHN is suspected.

b. **Arterial blood gas levels.**

c. **Oxygen monitoring.** A pulse oximeter provides important information regarding the severity of the infant's respiratory status and also assists in preventing hypoxemia.

d. **Chest radiograph**. A chest radiograph should be obtained after delivery if the infant is in distress.

e. Antibiotic coverage.

f. Supplemental oxygen. A major goal is to prevent episodes of alveolar hypoxia leading to hypoxic pulmonary vasoconstriction and the development of PPHN.

g. Continuous positive airway pressure (CPAP). This can be used to improve oxygenation **if the Fio2 exceeds 40–50**%. If hyperinflation is present, use CPAP cautiously since it can make air trapping worse.

h. Mechanical ventilation or ECMO **.** Patients with severe disease or in severe, refractory respiratory failure

i. **Surfactant, nitric oxide and corticosteroids** may be used.

j. Treatment of complications: air leak, **PPHN** and Pulmonary sequelae

Prognosis: Complications are common and associated with significant mortality. MAS is associated with neurodevelopmental sequela, including global developmental delay, cerebral palsy, and autism, and therefore warrants long-term follow-up.

Persistent Pulmonary Hypertension (PPHN)

Definition: Persistent pulmonary hypertension of the newborn (PPHN) is a condition characterized by marked pulmonary hypertension resulting from elevated pulmonary vascular resistance (PVR) and altered pulmonary vasoreactivity, leading to right-to-left extrapulmonary shunting of blood across the foramen ovale and the ductus arteriosus, if it is patent. When this disorder is of unknown cause and is the primary cause of cardiopulmonary distress, it is often called **"idiopathic PPHN"** or persistent fetal circulation.

Gentle ventilation targeting PaCO2 between 50 to 60 mmHg and PaO2 between 50 and 80 mmHg while avoiding acidosis (pH > 7.25) appears to be rational approach.

Incidence: 2–6 per 1000 live births.

Normally, there are four phases to transition of PVR

1) **In utero phase**: PVR is higher than systemic vascular resistance.

2) **Immediate phase**: happens in the first minutes after birth

3) **Fast phase:** lasts 12–24 hours after birth.
4) **Final phase:** lasts for, on average, 6–8 weeks up to several months and is characterized by pulmonary vascular remodeling.

Causes of PPHN

1) Pulmonary vasoconstriction post natally, but normal pulmonary vascular development: acute perinatal hypoxia, meconium aspiration syndrome (MAS) Increased PVR is transitory and reversible, and prognosis is generally good.
2) Fixed decreased pulmonary arteriolar diameter: chronic hypoxia can stimulate thickening of smooth muscle layer in the intraacinar and alveolar arteries. Prognosis is poor.
3) Decreased cross-sectional area of pulmonary vascular bed: hypoplasia of alveoli and associated vasculature as in congenital diaphragmatic hernia (CDH), lung hypoplasia (idiopathic or associated with renal problems), thoracic dystrophies, or oligohydramnios due to prolonged rupture of membranes). Poor prognosis.
4) Functional obstruction of pulmonary blood flow: polycythemia, hyperfibrinogenemia. Usually good prognosis.

Clinical picture of PPHN

a. Respiratory distress and labile hypoxemia, often disproportionate to pulmonary parenchymal disease.
b. Right ventricular heave, single or closely split and loud S2, low-pitched systolic murmur.

Diagnosis of PPHN

a. Preductal oxygen saturations are higher than the postductal oxygen saturation (above 20 mmHg between a preductal (right radial artery) and a postductal (umbilical artery) samples)
b. Hyperoxia test: exposure to 100% oxygen for 5–10 minutes results in increase in Pao2 to >100 in PPHN but not so in cyanotic heart lesions.
c. Doppler Echocardiography
d. Chest x-ray may reveal opacities and hyperinflation in MAS or lobar opacities inpneumonia. Clear lung fields or only minor disease in the face of severe hypoxemia is strongly suggestive of PPHN, if cyanotic congenital heart disease has been ruled out.

Treatment of PPHN

A. Prevention: Adequate resuscitation and support from birth may presumably prevent or ameliorate, to some degree, PPHN when it may occur superimposed on a preexisting condition.
B. corrects shock, polycythemia, hypoglycemia, hypothermia, metabolic acidosis, and hypotension.
C. High ambient oxygen while avoiding hyperoxemia, and optimal mechanical ventilation.
D. Minimal handling. Because infants with PPHN are extremely labile with significant deterioration after seemingly “minor” stimuli, this aspect of care deserves special mention. Endotracheal tube suctioning, in particular, should be performed only if indicated and not as a matter of routine. Noise level and physical manipulation should be kept to a minimum.
E. Pressor agents. Some infants with PPHN have reduced cardiac output. In addition, increasing systemic blood pressure reduces the right-to-left shunt. Hence at least normal blood pressure should be maintained, and some recommend maintaining blood pressure of

≥40 mm Hg. Dopamine is the most commonly used drug for this purpose. Milrinone, a type 3 phosphodiesterase inhibitor, is also sometimes employed to improve cardiac output.

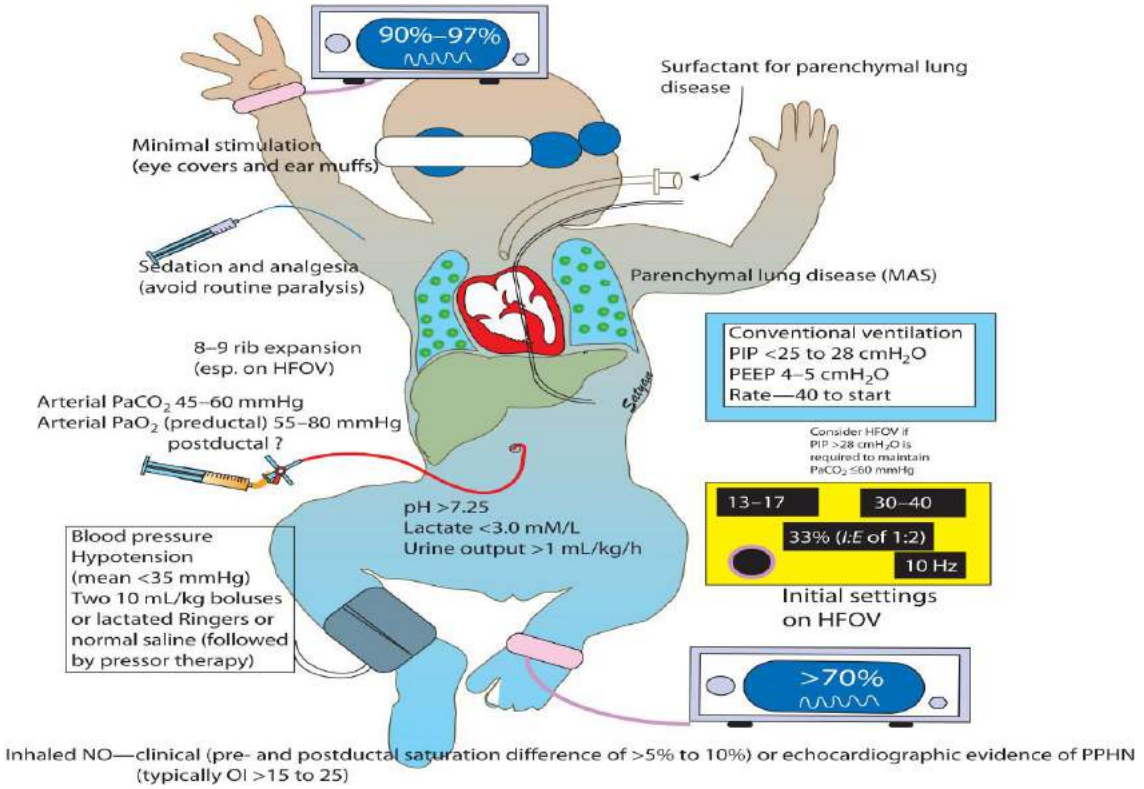
F.Extracorporeal membrane oxygenation (ECMO)

G. Specific pulmonary vasodilators:

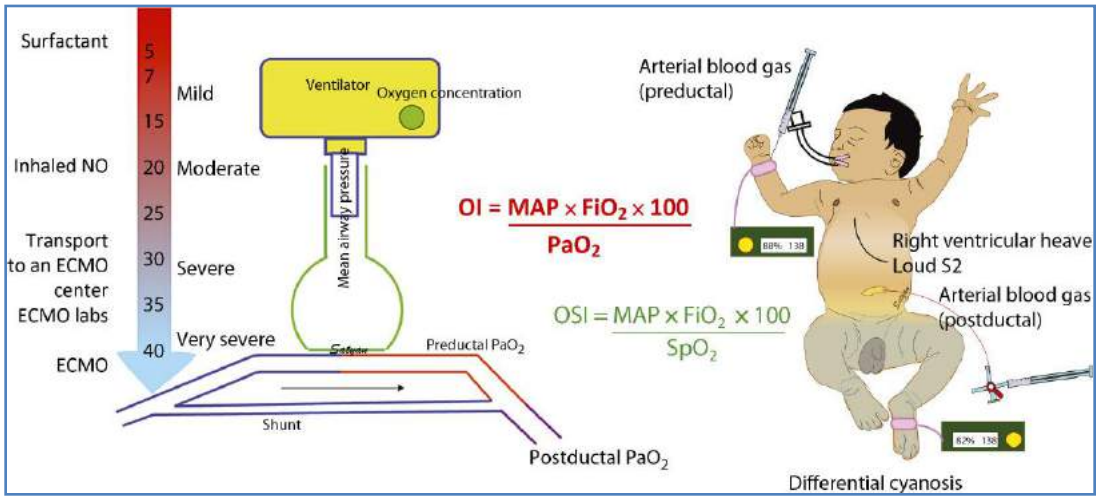
1) Inhaled nitric oxide (iNO)

2) Phosphodiesterase inhibitor(Sildenafil inhibits PDE5)

3) Endothelin receptor antagonists (bosentan)



Prognosis: The overall survival rate is >70–75%. There is, however, a marked difference in survival and long-term outcome according to the cause of the PPHN.



Clinical Features and Assessment of Severity of PPHN with Oxygenation Index (OI) and Oxygen Saturation Index (OSI).

Apnea

Apnea is defined as cessation of airflow

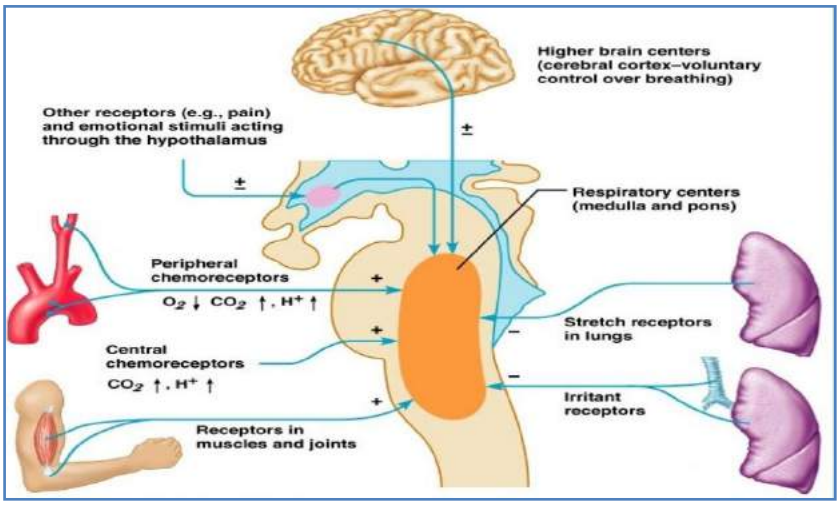
Apnea is pathological when absent airflow is prolonged (usually 20 second or more). Accompanied by bradycardia (heart rate < 100 beats/minute). . Hypoxemia that is detected clinically (cyanoses) or by oxygen saturation monitoring. Pallor or hypotonia and the infants may be unresponsive to tactile stimulation. Apnea in the first 24 hours is usually pathologic

Insignificant apnea: Shorter apnea <10 seconds without hypoxemia or bradycardia is due to immaturity and is not clinically important.

AOP is a diagnosis of exclusion; therefore, it is important to diagnose and treat any secondary cause.

Incidence

- All infants < 28 weeks gestational age have apnea
- As many as 25% of all premature infant who weight <1.800 gm (34 weeks gestational age) have at least one apneic spell.
- Apneic spells usually cease by 37 weeks gestational age



Regulation of Respiration

Etiology

A. Prematurity due to:

1- Developmental immaturity of respiratory center
2- Immaturity of peripheral chemoreceptor response resulting in **blunting response for CO2**
3- Impaired coordination of the Inspiratory muscles
4- Gastro esophageal reflux
5- Many inhibitory neurotransmitters

B. Secondary to

1.**Hypoxia:** hypoxic ischemic encephalopathy, RD. 2. **Hemorrhage:** intracranial hemorrhage. 3. **Metabolic disturbances** e.g. hypoglycemia, hypocalcemia, hypothermia

and hyperthermia. 4.**Meningitis:** septicemia and TORCH infections 5.**Maternal drugs** e.g. magnesium sulfate or Intrapartum sedatives. 6**. Gastroesophogeal reflux and aspiration.** 7**. Suction or endotracheal tube insertion.** 8**.Seizures.**

Common Causes of Apnea and Bradycardia According to Gestational Age:

Premature Infant	Full-Term Infant	All Ages
Apnea of prematurity PDA RDS Respiratory insufficiency of prematurity PV-IVH GER Anemia of prematurity Posthemorrhagic hydrocephalus	Cerebral infarction Polycythemia	Sepsis NEC Meningitis Aspiration GER Pneumonia Cardiac disorder Postextubation atelectasis Seizures Cold stress Asphyxia

GER, gastroesophageal reflux; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; PV-IVH, periventricular-intraventricular hemorrhage; RDS, respiratory distress syndrome.

Classification (pathogenesis)

1.**Central apnea**: occurs when Inspiratory efforts are absent.

2. Obstructive apnea: occurs when Inspiratory efforts are persist in the presence of airway obstruction

3. Mixed apnea: occurs when airway obstruction with inspiratory efforts precedes or follows central apnea. This is the most common type found in most premature infants (50%– 75%).

4. Periodic breathing. Three or more respiratory pauses lasting >3 seconds separated by normal respiratory intervals not >20 seconds and not associated with bradycardia. Periodic breathing can occur in 2–6% of healthy term neonates and in up to 25% of preterm infants.

5. Apnea of infancy (AOI). American Academy of Pediatrics (AAP) definition: "an unexplained episode of cessation of breathing for 20 seconds or longer or a shorter respiratory pause associated with bradycardia, cyanosis, pallor, and/or marked hypotonia" in an infant >37 weeks' gestational age.

6. Apnea of prematurity (AOP). Sudden absence of breathing that lasts at least 20 seconds or is associated with bradycardia or cyanosis (oxygen desaturation) in an infant <37 weeks' gestational age. It is most commonly central or mixed apnea. AOP is a developmental disorder usually of physiologic immaturity of respiratory control.

7. Persistent apnea. Apnea persists in a neonate ≥37 weeks postmenstrual age. It usually occur in infants born at <28 weeks' gestation.

8. Secondary causes of apnea. Apnea that has a specific cause (eg, sepsis, anemia, asphyxia, temperature instability, pneumonia, and others). Remember immaturity can worsen any apnea that is associated with a specific cause.

Presentation

Onset of apnea of prematurity .25% at first or second days of life and if it doesn't occur till 7 days of age, it is unlikely to occur.

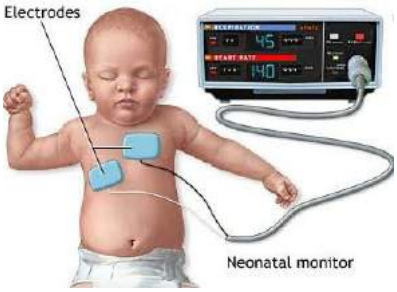
Clinical picture Apnea _cyanosis _bradycardia and if more than 45 second pallor and hypotonia occurs

Offset: apnea of prematurity usually stops when the baby reaches 37 weeks of gestations, however in premature baby less than 28 weeks apnea may persist beyond them
Apneic spells in full term infant is always abnormal→ search for a cause

Apnea at birth in the absence of drug depression or asphyxia is generally caused by irreversible structural abnormalities of the central nervous system (CNS).

Investigations: according to susceptible cause:

Complete blood count, cultures -Continuous oxygen saturation monitoring - arterial blood gas measurement- chest x-ray, Glucose, calcium, electrolytes Magnesium- screen for toxic substances in urine and Cranial ultrasonography examination.



Management

1. Monitoring: a bed side respiratory and heart rate monitor with alarm if respiration ceases for more than 20 seconds or if the heart rate drops below 100 bpm

All infants <35 weeks' gestational age should be monitored for apneic spells for at least the first week after birth.

2. Treatment of acute apneic episodes:

stimulation:

(a) Tactile stimulation. Provides excitatory activity in the brainstem to stimulate respiratory activity. This is the most common intervention. Provide tactile stimulation (eg, rubbing the skin, stroking the back, patting the infant, tapping or tickling the feet).
(b) Olfactory stimulation. Introducing a pleasant odor (vanillin) into the incubator decreased apnea (study only 24 hours) in infants who were unresponsive to caffeine or doxapram


Nasal CPAP

If no response → bag and mask ventilation, suctioning and neck positioning may be needed

3. Treatment of chronic or recurrent apneic episodes of prematurity

1. Correction of any causes

2. Drugs

Caffeine citrate: less toxic and well tolerated than **theophylline**
- Loading: 20 mg/kg/dose IV drip over 30 minutes or orally
- Maintenance: 5mg/kg/day once a day
- It is used to prevent apnea of prematurity in all infants less than 1250 grams

3. CPAP: continuous positive airway pressure

. Effective in treating both obstructive and mixed apnea but not central apnea
. Start with CPAP level of 5 cm, H_2O, and then adjust according to clinical response.
. CPAP is delivered by nasal prongs

4. IMV: Intermittent mandatory ventilation

. If medical therapy and CPAP failed to control the apneic attacks.

Hypoglycemia

Definition Blood glucose < 40 mg/dl in the first 72 hours of life (regardless of the gestational age) or glucose levels at which intervention should be considered based on clinical experience and analysis of the available evidence.
Or: glucose level at which brain function begins to be impaired

The Pediatric Endocrine Society states that by 48 to 72 hours of life, plasma glucose levels should be similar to that of older children and adults (>60 mg/dL).

Note: Aggressive screening and treatment is recommended because hypoglycemia is linked to poor neurodevelopmental outcomeas it affect parietooccipital cortex and subcortical white matter.

Incidence: The reported incidence of hypoglycemia varies with its definition, but it has been estimated to occur in up to **16%** of large-for-gestational-age (LGA) infants and **15%** of small-for-gestational-age (SGA) infants.

Key points

Hypoglycemia is one of the most common metabolic problems seen in neonatal intensive care unit (NICU).
The blood glucose level can often be maintained in the appropriate range by initiating feeding soon after birth.
Most cases of neonatal hypoglycemia are transient, respond readily to treatment, and are associated with an good prognosis. It is very common in infants whose feeding is delayed.
Persistent hypoglycemia is more likely to be associated with abnormal endocrine conditions, including hyperinsulinemia.
Glucose provides the fetus with approximately 60% to 70%of its energy needs
During this normal transition, newborn glucose levels fall to a low point in the first 1 to 2 hours of life, and then increase and stabilize at mean levels of 65 to 70 mg/dL by the age of 3 to 4 hours.
Conditions limiting availability of ketones/lactate increase risk of CNS damage and require maintenance of higher plasma glucose levels.

Types of hypoglycemia

A. Transient hypoglycemia. The majority of hypoglycemia in the newborn period is transient and lasts only a few days. It is very common in infants whose feeding is delayed.

B. Persistent hypoglycemia. Usually defined as hypoglycemia lasting for more than 7 days or in infants who require higher amounts of glucose (>10–12 mg/kg/min) to maintain a normal glucose level for over a week. Some define hypoglycemia as persistent if it continues into infancy (>1 month).

Why hypoglycemia is a problem?

Compared with adults, infants have a higher brain to body weight ratio, resulting in higher glucose demand in relation to glucose production capacity.

Etiology

1. Inadequate Glycogen

a -**Prematurity** (Glycogen stores increase rapidly in the last month of the 3rd trimester. Preterm infants are born before this occurs)

b -**Intrauterine growth retardation**

c -Inadequate calories and delayed onset of feeding

2. Increased Utilization of Glucose (transient): **Sick/Stressed infants-RDS – polycythemia – hypothermia- IDM and /or maternal or infant therapy**

3. Excessive Insulin**:**

1. Islet cell hyperplasia and Infants of Diabetic Mothers (Single most important factor in determining the outcome for the infant is maternal glucose control)

2. Congenital hyperinsulinism (HI). HI is an inappropriate or excessive amount of insulin secreted by the pancreatic islet β cells caused by a group of genetic disorders. It is the most common cause of persistent hypoglycemia.

3. Syndromes associated with hyperinsulinemia (syndromic hyperinsulinemia). Most common is Beckwith-Wiedemann syndrome (hypoglycemia, macroglossia, visceromegaly, omphalocele, ear creases/pits, renal abnormalities, macrosomia). Others include hyperinsulinism/ hyperammonemia syndrome, Perlman, Ondine, and Sotos syndromes.

4. Inborn errors of metabolism- Galactosemia - Maple syrup urine disease- Glycogen storage disease

Infants at High Risk

Infant of diabetic mothers - IUGR and SGA -Preterm (<37 weeks) –Hypothermia - Unwell baby - Maternal or infant therapy with B- blockers - Suspected endocrinal condition (e.g. CAH) - Suspected error of metabolism - Polycythemia.

Infants at Highest Risk

Hemolytic disease of the newborn - Severe fluid restriction- Obvious syndromes (e.g. midline defects and Weidman syndrome) - Neonate on IV fluids or PN

Signs & Symptoms of Hypoglycemia

Asymptomatic, jitteriness, tremors, irritability, hypotonia, lethargy, high-pitched cry, seizures, exaggerated Moro reflex, floppiness, poor suck, tachypnea, cyanosis, hypothermia, and apnea.

Symptoms cannot be attributed to hypoglycaemia if they persist with normoglycaemia within 30 min. Jitteriness is rarely associated with hypoglycaemia in term babies.

Diagnosis

1- Non specific clinical manifestation
2 - Screening. Serial blood glucose levels should be routinely measured in infants who have risk factors for hypoglycemia, and in infants who have symptoms. Screening babies with risk factors at 30 to 60 minutes of life. Infants of diabetic mothers Preterm and SGA usually develop hypoglycemia in the first hours of life.The interval between measurements of glucose levels requires clinical judgment.

Differential Diagnosis

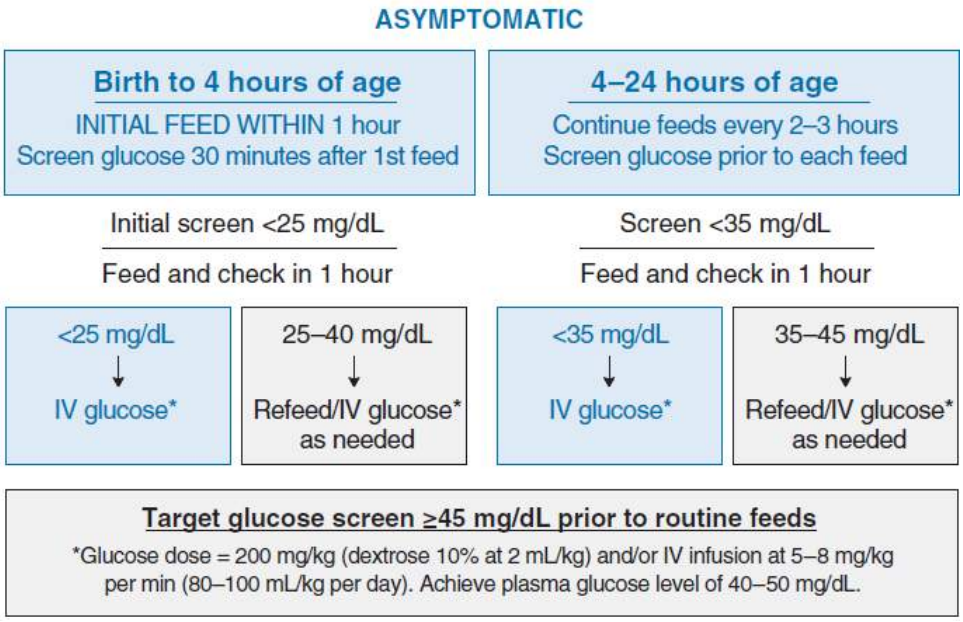
1. Sepsis 2. CNS disease 3. Hypocalcemia 4. Hyponatremia or hypernatremia 5.Hypomagnesemia 6. Adrenal insufficiency 7. organ failure.

Management

Treatment decisions depend on the clinical situation and infant characteristics.
- Anticipation and prevention by continuous monitoring of blood glucose for infants at risk for hypoglycemia
- As soon after birth as their condition allows, they should be nursed or given formula per the mother's preference. This feeding should be repeated every 2 to 3 hours and if not possible or still low after feeding, 10% dextrose (2 ml /kg). Early breast feeding enhances gluconeogenesis and increases the production of gluconeogenic precursors.
Babies who are breast-fed have lower glucose levels but higher ketone body levels than those who are formula-fed.

Diagnosis of hyperinsulinemia:

-Evaluation requires drawing blood for insulin, cortisol, and amino acids at a time when the glucose level is less than 40 mg/dL.
-Measurement of plasma beta-hydroxybutyrate and free fatty acid levels can be useful, because decreased levels of these substances can indicate excessive insulin action even if insulin levels are not significantly elevated.



AAP guidelines recommend treatment for low blood sugar in the following settings:

1. Symptomatic infants at any age with a plasma glucose <40 mg/dL.
2. Asymptomatic infants (birth to 4 hours) with a plasma glucose <40 mg/dL.
3. Asymptomatic infants (4‑24 hours) with a plasma glucose <45 mg/dL.

Never diagnose or treat hypoglycemia based on screening reagent strips alone as test strips can vary 10–20 mg/dL from the actual level

Oral dextrose gel: use of 40% dextrose gel to treat mild hypoglycemia ??

IV therapy

a. Indications:

1- Inability to tolerate oral feeding

2-Symptoms

3- Oral feedings do not maintain normal glucose levels

4- Glucose levels less than 25 mg/dL

b. Urgent treatment:

200 mg/kg of glucose over 1 minute, to be followed by continuing therapy discussed subsequently This initial treatment is equivalent to 2 mL/kg of dextrose 10% in water (10% D/W) infused intravenously

c. Continuing therapy:

- Infusion of glucose at a rate of 6 to 8 mg of glucose/kg per minute
- 10% D/W at a rate of 86.4 mL/kg per day or 3.6 mL/kg per hour gives

Historically, providers have administered hydrocortisone, 10 mg/kg/day intravenously in two divided doses, if it is difficult to maintain glucose values in the normal range despite 12 to 15 mg of glucose per kilogram per minute. Hydrocortisone reduces peripheral glucose utilization, increases gluconeogenesis, and increases the effects of glucagon.

Diazoxide (8 to 15 mg/kg/day in divided doses every 8 to 12 hours) may be given orally for infants who are persistently hyperinsulinemic.
Octreotide (5 to 20 µg/kg/day subcutaneously or intravenously divided every 6 to 8 hours). A long-acting somatostatin analog that inhibits insulin secretion.
Glucagon (0.2 mg/kg intramuscularly, subcutaneous (SC), or IV, maximum 1.0 mg) is rarely used.
If medical treatment does not control the blood glucose level consider surgical treatment by **subtotal pancreatectomy**.

Monitoring of blood glucose:

1. Screening babies with risk factors at 30 to 60 minutes of life and according to result reassess according to guidelines.
2. Check blood glucose at least 6-8 hrly in:
unstable or acutely ill babies [respiratory distress syndrome (RDS), septicemia, necrotising enterocolitis (NEC)].
3. **Check blood glucose at least once a day in stable babies:**
a. <32 weeks gestation for first week
b. Baby receiving TPN
c. with severe unexpected dehydration or metabolic acidosis
d. with poor weight gain while receiving >120 kcal/kg/day

Bedside glucose meters (use only FDA cleared for testing in neonates) are sufficiently accurate and precise for in-hospital use: it is attached to the patients' existing IV lines and catheters, from which the device automatically draws a 0.12 mL sample every fifteen minutes.

Hyperglycemia

Definition: is usually defined as a whole blood glucose level higher than 125 mg/dL or plasma glucose values higher than 145 mg/dL.

Clinical features

There are usually not any specific symptoms associated with neonatal hyperglycemia, but the major clinical problems associated with hyperglycemia are hyperosmolarity, osmotic dieresis and poor weight gain

Risk factors

a. Immaturity of pancreatic function (e.g. extremely premature infants and smallfor-gestational-age)
b. Insulin resistance
c. Glucose overload (e.g. equipment failure, administrator error)
d. Stress (e.g. infection, pain)
e. Side effects of a medication (e.g. glucocorticoid treatment)
f. Lipid infusion. Free fatty acids are associated with increased glucose levels.
g. Neonatal diabetes mellitus (rare disorder)

Treatment

If possible, discontinue or decrease medications that worsen hyperglycaemia
If glucose delivery rate >10 mg/kg/min, decrease glucose in increments to 6‑10 mg/kg/min. If on TPN, 8‑10 mg/kg/min is acceptable
If glycosuria and hyperglycaemia >12 mmol/L persists despite an appropriate glucose infusion rate, consider treating with insulin at 0.05 units/kg/hr (bolus or infusion) and titrate according to response. Target blood glucose while on insulin is 6‑8 mmol/L

Hypocalcemia

Definition: Neonatal hypocalcemia is defined as a total serum calcium concentration of **<7 mg/dL** or an ionized calcium concentration of **< 4 mg**/dL.

Pathophysiology

Hormonal regulation of calcium homeostasis: The principal calcitropic or calcium-regulating hormones are parathyroid hormone (PTH) and 1, 25-dihydroxyvitamin D (1, 25[OH] 2D), also referred to as calcitriol. When the ECF-ionized calcium level declines, parathyroid cells secrete PTH. PTH mobilizes calcium from bone, increases calcium resorption in the renal tubule, and stimulates renal production of 1,25(OH)2D. PTH secretion causes the serum calcium level to rise and the serum phosphorus level either to be maintained or to fall. Vitamin D is synthesized from provitamin D in the skin after exposure to sunlight and is also ingested in the diet. Vitamin D is transported to the liver, where it is converted to 25(OH) D (the major storage form of the hormone). This is transported to the kidney, where it is converted to the biologically active hormone 1, 25(OH) 2D (calcitriol). Calcitriol increases intestinal calcium and phosphate absorption and mobilizes calcium and phosphate from bone.

Etiology

1. Prematurity. Preterm infants are capable of mounting a PTH response to hypocalcemia, but target organ responsiveness to PTH may be diminished.
2. Infants of diabetic mothers (IDMs)
3. Asphyxia
4. Congenital. Parathyroids may be absent in DiGeorge.
5. Pseudohypoparathyroidism. Maternal hyperparathyroidism.
6. Magnesium deficiency (including inborn error of intestinal magnesium transport) impairs PTH secretion.
7. Vitamin D deficiency (rarely a cause in the first weeks of life).
8. Alkalosis and bicarbonate therapy.
9. Rapid infusion of citrate-buffered blood (exchange transfusion) chelates ionized calcium.
10. Shock or sepsis.
11. Phototherapy may be associated with hypocalcemia by decreasing melatonin secretion and increasing uptake of calcium into the bone.
12. High phosphate intakes
13. Inadequate intake of calcium(malabsorption, limitations of TPN)

Most common causes of early (first 3 days)

1. Prematurity - Preterm infants are capable of mounting a PTH response to hypocalcemia, but target organ responsiveness to PTH may be diminished - 2. Infants of diabetic mothers (IDMs) - 3. Asphyxia - 4. Congenital. Parathyroids may be absent in DiGeorge

Most common causes of late (after 3 days) hypocalcemia

1- High phosphate intakes 2. Hypoparathyroidism

Diagnosis

a. Hypocalcemia increases both cellular permeability to sodium ions and cell membrane excitability. The **signs are usually nonspecific**: apnea, seizures, jitteriness, increased extensor tone, clonus, hyperreflexia, and strider (laryngospasm).
b. Early-onset hypocalcemia in preterm newborns is often **asymptomatic** but may show apnea, seizures, or abnormalities of cardiac function.
c. Late-onset syndromes, in contrast, may present as **hypocalcemic seizures.**

Laboratory studies

a. There are three definable fractions of calcium in serum:
(I) Ionized calcium (50% of serum total calcium).
(ii) Calcium bound to serum proteins, principally albumin (40%).
(iii) Calcium complexed to serum anions, mostly phosphates, citrate, and sulfates (10%).
Ionized calcium is the only biologically available form of calcium.
b. Assessment of calcium status using ionized calcium is preferred, especially in the first week of life.
c. Calcium concentration reported as milligrams per deciliter can be converted to molar units by dividing by 4 (e.g., 10 mg/dL converts to 2.5 mmol/L).
d. Postnatal changes in serum calcium concentrations**: At birth, the umbilical serum calcium level is elevated (10–11 mg/dL). In healthy term babies, calcium concentrations decline for the first 24 to 48 hours; the nadir is usually 7.5 to 8.5 mg/dL.** Thereafter, calcium concentrations progressively rise to the mean values observed in older children and adults

Monitoring

Suggested schedule for monitoring calcium levels in infants, such as VLBW, IDM, and birth depression, who are at risk for developing hypocalcemia are as follows:

i. Ionized calcium at 12, 24, and 48 hours of life.
ii. Total serum phosphorus and total serum magnesium for infants with hypocalcemia.
iii. Other lab tests, including serum concentrations of PTH, 25(OH) D, and 1, 25(OH) 2D are not usually needed unless neonatal hypocalcemia does not readily resolve with calcium therapy. It is extremely rare that 1, 25(OH) 2D is ever measured in neonates.
iv. A prolonged electrocardiographic QTc interval is a traditional indicator that is typically not clinically useful in the newborn period.

Imaging

Absence of a thymic shadow on a chest radiograph and the presence of conotrunchal cardiac abnormalities may suggest a diagnosis of 22q11.2 deletion syndrome, also known as CATCH22 or DiGeorge sequence.

Treatment

a. Therapy with calcium is usually adequate for most cases. In some cases Concurrent therapy with magnesium is indicated.
b. Rapid intravenous infusion of calcium can cause a sudden elevation of serum calcium level, leading to bradycardia or other dysrhythmias.**Intravenous calcium should only be "pushed" for treatment of hypocalcemic crisis (e.g., seizures)** and done with careful cardiovascular monitoring.

c. Infusion by means of the umbilical vein may result in **hepatic necrosis** if the catheter is lodged in a branch of the portal vein.
d. Rapid infusion by means of the umbilical artery can cause **arterial spasms** and, at least experimentally, intestinal necrosis and thus, is generally not indicated.
e. Intravenous calcium solutions are incompatible with sodium bicarbonate since calcium carbonate will precipitate.
f. Extravasation of calcium solutions into subcutaneous tissues can cause severe necrosis and subcutaneous calcifications.

Calcium preparations:

Calcium gluconate 10% solution is preferred for intravenous use. Calcium glubionate syrup (Neo-Calglucon) is a convenient oral preparation. However, the high sugar content and osmolality may cause gastrointestinal irritation or diarrhea.

i. If the ionized calcium level drops to 1 mmol/L or less a continuous **intravenous calcium infusion may be commenced**. For use without other TPN components, a **dose of 40 to 50 mg/kg/day** of elemental calcium are typical.

ii. It may be desirable to prevent the onset of hypocalcemia for newborns who exhibit cardiovascular compromise (e.g., severe respiratory distress syndrome, asphyxia, septic shock, and persistent pulmonary hypertension of the newborn). Use a continuous calcium infusion, preferably by means of a central catheter, to maintain ionized calcium of 1 to 1.4 mmol/L

iii. Emergency calcium therapy (for active seizures or profound cardiac failure thought to be associated with severe hypocalcemia) consists of
100 to 200 mg/kg of 10% calcium gluconate (9–18 mg of elemental calcium/kg) by intravenous infusion over 10 to 15 minutes.

Repeat the dose in 10 minutes if there is no clinical response.
The use of vitamin D or active vitamin D (1, 25[OH]2D) in this circumstance is controversial and not usually necessary. If a serum 25(OH)D level was obtained and is <10 to 12 ng/mL, then 1,000 IU of vitamin D should be given daily and the value rechecked in 14 to 21 days. Rarely should higher doses of vitamin D be given to neonates.

Hypercalcemia

Definition

Neonatal hypercalcemia (serum total calcium level **>11 mg**/dL, serum ionized calcium level >1.45 mmol/L) may be asymptomatic and discovered incidentally during routine screening. Alternatively, the presentation of severe hypercalcemia **(>16 mg**/dL or ionized calcium >1.8 mmol/L) can require immediate medical intervention. Very mild hypercalcemia (serum calcium**11–12 mg/dL**) is common and does not require any intervention at all.

Etiology

a. Imbalance in intake or use of calcium.
b. Clinical adjustment of TPN by removing the phosphorus can rapidly lead to hypercalcemia **c**. Extreme prematurity
d. Hyperparathyroidism
e. Hyperthyroidism. Thyroid hormone stimulates bone resorption and bone turnover.
f. Hypophosphatasia, an autosomal recessive bone dysplasia
g. Increased intestinal absorption of calcium.
h. Hypervitaminosis D
k. Idiopathic neonatal/infantile hypercalcemia
l. subcutaneous fat necrosis is a sequela of trauma or asphyxia.
m. Acute renal failure.

Diagnosis

1. Clinical presentation

Hypotonia, encephalopathy, poor feeding, vomiting, constipation, polyuria, hepatosplenomegaly, anemia, and extra skeletal calcifications, including nephrocalcinosis.
b. Milder hypercalcemia may present as feeding difficulties or poor linear growth

History

a. Maternal/family history of hypercalcemia or hypocalcemia, parathyroid disorders, and nephrocalcinosis
b. Family history of hypercalcemia or familial hypocalciuric hypercalcemia
c. Manipulations of TPN

Physical examination

a. Small for dates (hyperparathyroidism, Williams syndrome).
b. Craniotabes, fractures (hyperparathyroidism), or characteristic bone dysplasia (hypophosphatasia).
c. “Elfin” facies (Williams syndrome).

d. Cardiac murmur (supravalvular aortic stenosis and peripheral pulmonic stenosis associated with Williams syndrome).
e. Indurated, bluish-red lesions (subcutaneous fat necrosis).
f. Evidence of hyperthyroidism.

Laboratory evaluation

a. The clinical history, serum and urine mineral levels of phosphorus, and the urinary calcium: creatinine ratio (UCa/UCr) should suggest a likely diagnosis.
i. A very elevated serum calcium level (>16 mg/dL) usually indicates primary hyperparathyroidism or, in VLBW infants, phosphate depletion or the inability to utilize calcium for bone formation.
ii. Low serum phosphorus level indicates phosphate depletion, hyperparathyroidism, or familial hypocalciuric hypercalcemia.
iii. Very low UCa/UCr suggests familial hypocalciuric hypercalcemia.
b. Specific serum hormone levels (PTH, 25[OH]D) may confi rm the diagnostic impression in cases where obvious manipulations of diet/TPN are not apparent. Measurement of 1,25(OH)2D is rarely indicated unless hypercalcemia persists in infants _1,000 g with no other apparent etiology.
c. A very low level of serum alkaline phosphatase activity suggests hypophosphatasia (confi rmed by increased urinary phosphoethanolamine level).
d. Radiography of hand/wrist may suggest hyperparathyroidism (demineralization, subperiosteal resorption) or hypervitaminosis D (submetaphyseal rarefaction).

Treatment

1. Emergency medical treatment (symptomatic or calcium >16 mg/dL, ionized Ca >1.8 mmol/L).
a. Volume expansion with isotonic saline solution. Hydration and sodium promote urinary calcium excretion. If cardiac function is normal, infuse normal saline solution (10–20 mL/kg) over 15 to 30 minutes.
b. Furosemide (1 mg/kg intravenously) induces calciuria.
2. Inorganic phosphate may lower serum calcium levels in hypophosphatemic patients by inhibiting bone resorption and promoting bone mineral accretion.
a. Glucocorticoids are effective in hypervitaminosis A and D and subcutaneous fat necrosis by inhibiting both bone resorption and intestinal calcium absorption; they are ineffective in hyperparathyroidism.
b. Low-calcium, low-vitamin D diets are an effective adjunctive therapy for subcutaneous fat necrosis and Williams syndrome.
c. Calcitonin is a potent inhibitor of bone resorption. The antihypercalcemic effect is transient but may be prolonged if glucocorticoids are used concomitantly.
There is little reported experience in neonates.
d. Parathyroidectomy with autologous reimplantation may be indicated for severe persistent neonatal hyperparathyroidism.

Hypomagnesemia

Definition: serum magnesium level of <1.6 mg/dL

Etiology: 1. Insufficient stores 2. Iatrogenic(exchange transfusion) 3. Infant of diabetic mother 4. Idiopathic with hypocalcemia 5. May be with therapeutic cooling of the newborn 6.Decrease renal reabsorption(Renal tubulopathies such as Bartter syndrome) 7. Chronic diarrhea

Clinical picture: Similar to hypocalcemia can also include apnea and poor motor tone.

Treatment: Magnesium sulfate. The 50% solution contains 500 mg or 4 mEq/mL. Correct severe hypomagnesemia (<1.6 mg/dL) with 50 to 100 mg/kg of magnesium sulfate intravenously given over 1 to 2 hours.The dose may be repeated after 12 hours. Obtain serum magnesium levels before each dose**.**

Hypermagnesemia

Definition
Elevated serum magnesium level (>3 mg/dL)

Etiology
Hypermagnesemia is usually due to an exogenous magnesium load exceeding renal excretion capacity.
a. Magnesium sulfate therapy for maternal preeclampsia or preterm labor.
b. Administration of magnesium-containing antacids to the newborn.
c. Excessive magnesium in parenteral nutrition.

Diagnosis
- Severe hypermagnesemic symptoms are unusual in neonates with serum magnesiumlevel >6 mg/dL.
- The common curariform effects include apnea, respiratory depression, lethargy, hypotonia, hyporeflexia, poor suck, decreased intestinal motility, and delayed passage of meconium.

Treatment
1. Often, the only intervention necessary for hypermagnesemia is removal of the source of exogenous magnesium.
2. Exchange transfusion, peritoneal dialysis, and hemodialysis are not used in the newborn period.
3. For hypermagnesemic babies, begin feedings only after suck and intestinal motility are established. Rarely, respiratory support may be needed.

Neonatal Cold Injury (Hypothermia)

Definition

Lowering of body temperature below 35.5 C0 or core temperature below normal range (<36.5°C)

Etiology

1. More common in premature infant due to
.Immaturity of heat regulating center
. Diminished intake
. Small muscle bulk
.Associated illness
2 .Cold environment sometimes dot to negligence, abuse or ignorance with inadequate drying, clothing
3. Sepsis

Preterm "golden hour

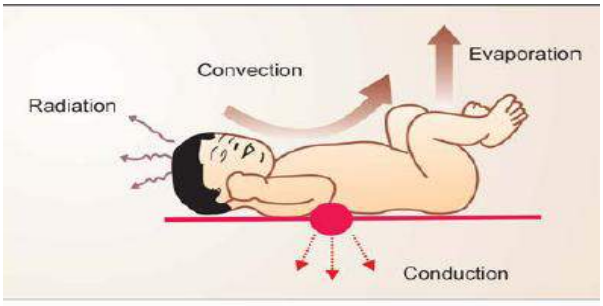
delivery room temperature, 25°C–26°C; radiant warmer turned on prior to delivery; prewarmed blankets and hat; <29 weeks' gestation, use polyethylene bag and chemical mattress; transport in prewarmed incubator

Heat sources Mother (skin-to-skin contact): optimal in stable term or near-term newborn,Radiant warmer: temporary for infants needing resuscitation, Incubator: for premature or other at-risk newborns requiring ongoing management, Autonomous incubators that provide a controlled,heat, humidity, and oxygen environment to support,at-risk infants

, Automatic (servo) and manual control

Clinical picture

1. Peripheral vasoconstriction (cold extremities, edema and sclerema, pallor or a bright red color due to failure of oxyhemoglobin to dissociate at low temperature)
2. CNS depression (lethargy, poor feeding)
3. GIT: vomiting and abdominal distension
4. Renal: oliguria, hyperkalemia and AKI
5. CVS: bradycardia and hypotension
6. Increased metabolism: hypoglycemia, hypoxia and metabolic acidosis
7. Increased pulmonary artery pressure: shallow irregular breathing, distress and tachypnea



Modes of heat loss

8. Sometimes there is generalized bleeding, including pulmonary hemorrhage.

Treatment

1. Warming: uncertain whether warming should be rapid or slow.
2. Correction of hypoglycemia, acidosis and hypotension
3. Stop oral feeding
4. Supplementary oxygen and normal saline bolus
5. Sepsis and bleeding should be evaluated and treated


Keeping the baby warm

Hyperthermia

Definition

Elevation of body temperature to 38 -39 C0 in the second or third day of life

Persistent hyperthermia following correction of the thermal environment may be a sign of underlying infection or other metabolic derangement and should prompt a clinical evaluation.

Etiology

1. Dehydration fever
2 .Environmental:high incubator temperature
3. Sepsis
4. CNS malformation
5. Medications

Clinical picture

1. Skin: warm, flushed or pink initially, then pale later
2. Loss of weight, low urine output and depressed fontanel

Treatment

1. Lower the environmental temperature and give oral or parenteral fluids
2. Treatment of underlying environmental or infectious causes.

Neonatal Bleeding

It is a commonly potential serious condition. Initial clinical assessment should include evaluation of the general condition, onset and site of bleeding and other associated manifestations

The haemostatic mechanism in the neonate differs from that in the older child. In neonates, there is decreased activity of several clotting factors, diminished platelet function, and suboptimal defense against clot formation.

Etiology

1. Deficient of the procoagulant vitamin K–dependent clotting factors and anticoagulant proteins C and S

A. Transient deficiency of vitamin K dependent factors

- Hemorrhagic disease of the newborn
- Drug induced: The mother might have received certain drugs during pregnancy that can cause bleeding in the first 24 hours of the infant's life(Phenytoin (Dilantin, phenobarbital, salicylates and Warfarin)
- Total parenteral nutrition

B. Acquired e.g. disseminated intravascular coagulation (DIC), necrotizing enterocolitis (NEC), renal vein thrombosis (RVT), Extracorporeal membrane oxygenation (ECMO)and

liver disease

C. Inherited abnormalities e.g., hemophilia

2. Platelet problems

A. Qualitative disorders include hereditary conditions e.g., storage pool defects, Glanzmann thrombasthenia, Bernard-Soulier syndrome (large platelets normal in number), platelet-type VWD (6) and transient disorders that result from the mother's use of antiplatelet agents.

B. Quantitative disorders (Thrombocytopenia)

Platelet count <150 x 109/L

1. increases destruction in the peripheral blood

- Immune: isoimmune thrombocytopenia. Maternal ITP, lupus or drugs

- Non immune: infection, DIC and NEC

2. Decreased production by bone marrow e.g. sepsis and fanconi anemia, congenital amegakaryocytic thrombocytopenia and Congenital leukemia.

3. Other causes of bleeding

. Birth trauma: cephalhematoma, rupture liver and spleen

. Prematurity and hypoxia may lead to intracranial or pulmonary hemorrhage

Main causes of neonatal bleeding according to newborn conditions

Bleeding in doing well baby

1.Swallowed maternal blood (bloody vomiting during the first 2 days without bleeding fro other sites)

2. Hemorrhagic disease of the newborn

3. Inherited or immune thrombocytopenia or coagulation defects

Bleeding in sick baby

1.Stress gastric ulceration

2.Consumptive thrombocytopenia

3.DIC or NEC

4.Surgical emergencies

Investigation of neonatal bleeding

1. Complete blood picture
2. Bleeding profile: PT, PTT and INR
3. Liver function tests
4. Fibrinogen and fibrin degradation product in suspected DIC
5. The Apt test is used to rule out maternal blood
6. Specifi c factor assays as von Willebrand panels

Treatment of bleeding

A. Vitamin K1 (Aquamephyton). An intravenous or intramuscular dose of 1 mg is administered in case the infant was not given vitamin K at birth

B. FFP) (10 mL/kg) is given intravenously for active bleeding and is repeated every 8 to 12

hours as needed C. Platelets If there is no increased platelet destruction (as a result of DIC, immune platelet problem, or sepsis)

D. Fresh whole blood The baby is given 10 mL/kg; more is given as needed.
E. Clotting factor concentrates. When there is a known deficiency of factor VIII or IX,
F. Treatment of specific disorders as DIC,NEC

Hemorrhagic Disease of The Newborn (HDN)

Definition

Bleeding in otherwise healthy newborn due **to moderate transient deficiency of vitamin K dependent coagulation factors**

Incidence

The most common cause of neonatal bleeding: **1 out of 200 to 400** newborn if not given vitamin K at birth

Etiology

1. Transient deficiency of vitamin K dependent factors 2, 7, 9 and 10 due to deficiency of vitamin K 2. Reduced vitamin K stores
3. Liver immaturity or disease
4. If vitamin K is not given after birth
5. Disturbance of bacterial flora in the intestine due to use of broad spectrum antibiotics
6. Maternal drugs as phenytoin, Phenobarbital lead to vitamin K deficiency during first 24 hours after delivery
7. Late hemorrhagic disease may occur with malabsorption
8. Breast milk is a poor source of vitamin k

Clinical picture

1. Onset: 2-3 days (early hemorrhagic disease), 4-12 weeks (late hemorrhagic disease)
2. Common sites: gastrointestinal, umbilical and adrenal hemorrhage
3. Occult bleeding: intracranial or intra-abdominal

Investigations

1. PT, PTT and clotting time are prolonged
2. Decrease levels of factors 2, 7, 9and 10
3. Anemia if there is excessive bleeding
4. Normal platelet count

Prevention

1.10 mg vitamin **K to mother** before birth and 1 mg vitamin K to all newborn shortly after birth
2.Vitamin K1, 1 mg/week **orally for the first 3 months** of life, may prevent late hemorrhagic disease

Treatment

1. Vitamin K 1-5 mg IM and repeated in 24 hours
2. Fresh frozen plasma and blood transfusion if needed

Disseminated Intravascular Coagulation (DIC)

Definition

It is a serious condition characterized by **consumption of platelet and several coagulation factors in process of formation of intravascular clots**, The baby usually

appears sick and may have petechiae, GI hemorrhage,oozing from venipunctures, infection, asphyxia, or hypoxia.

Etiology

It associated with severe illness, The main precipitating factors are: Hypoxia, acidosis, hypothermia and septicemia

Diagnosis

Thrombocytopenia - Prolonged thrombin, Prothrombin and partial thromboplastin times Demonstration of fibrin degradation products (FDPS) and Fibrinogen is decreased

Prognosis is poor

Treatment

a. Treatment of the underlying
b. Confirm that vitamin K1 has been given
c. Platelets and FFP
d. If the bleeding persists
- Exchange transfusion with fresh citrated whole blood or reconstituted whole blood
- Continued transfusion with platelets, packed RBCs, and FFP as needed.
- Administration of cryoprecipitate (10 mL/kg) for hypofibrinogenemia.
– Heparinization If consumption coagulopathy is associated with thrombosis of large vessels and not with concurrent bleeding,

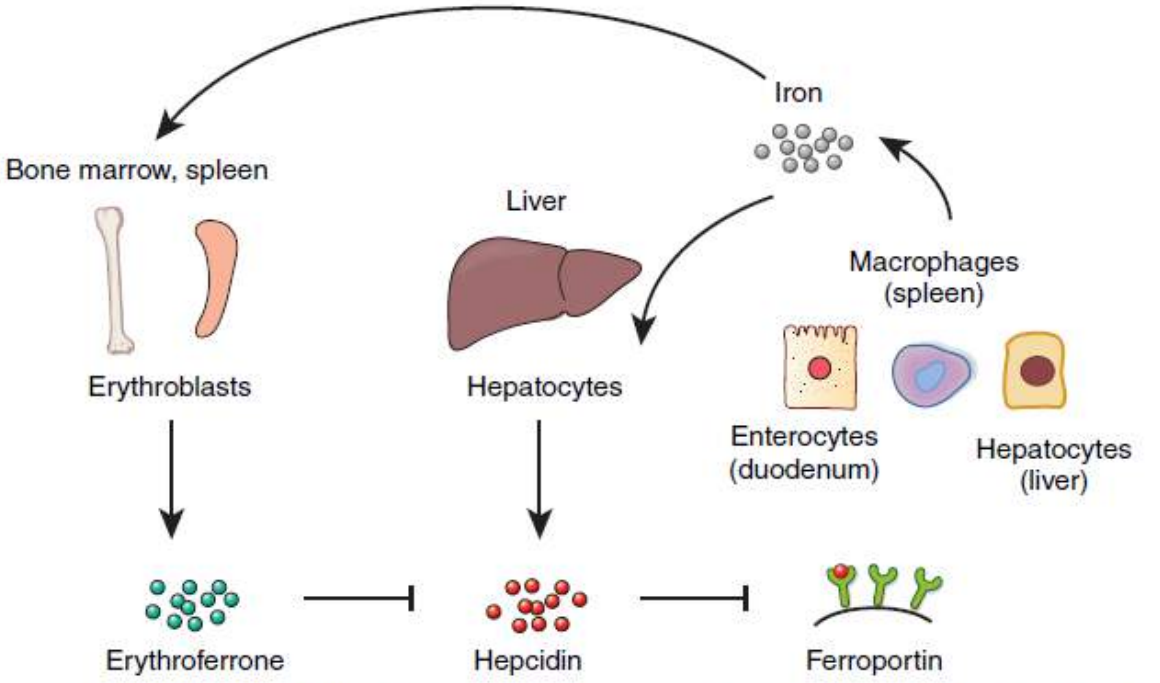
Neonatal Anemia

Anemia is a term typically used to describe either a low hemoglobin (Hb) or hematocrit (Hct). Although the word anemia is **loosely used in clinical medicine**, the exact meaningis is difficult to define. There are a number of approaches to the definition of anemia in the newborn. Statistically, anemia can be defined as the red cell number, Hct or Hb less than 2 SD below the mean value.

Hemoglobin vs. Hematocrit: Hemoglobin is typically expressed as a concentration per unit volume, that is, the amount in grams per liter or deciliter of whole blood. Hematocrit is the volume of red blood cells as a proportion of total blood volume.

Hemoglobin (Hb) = hemoatocrit (Hct)/ 3

Erythrocyte maturation is regulated by **growth factors** produced by the fetus. Erythropoietin (Epo) glycoprotein that binds to specific cell surface receptors on erythroid precursors, **is the primary regulator** of fetal erythropoiesis. Epo does not cross the placenta and is produced by the fetus in the liver. the primary stimulus for Epo production is hypoxia with or without anemia. Fetal Epo increases until birth.



Schematic diagram of the interaction between iron metabolism and erythropoiesis

The Physiologic Anemia of Infancy

Etiology

1. **In utero**, the fetal aortic oxygen saturation is 45%, the erythropoietin levels are high, and the RBC production is rapid. The fetal liver is the major site of erythropoietin production.
2. After birth, the oxygen saturation is 95%, and the erythropoietin is undetectable. RBC production by day 7 is <1/10th the level in utero**. Reticulocyte counts are low, and the hemoglobin level falls.**
3. Despite dropping hemoglobin levels, the ratio of hemoglobin A to hemoglobin F increases and the **levels of 2, 3-diphosphoglycerate (2, 3-DPG)** (which interacts with hemoglobin A to decrease its affinity for oxygen, thereby enhancing oxygen release to the tissues) are high. As a result, oxygen delivery to the tissues actually increases. **This physiologic "anemia" is not a functional anemia in that oxygen delivery to the tissues is adequate**.
4. At 8 to 12 weeks, hemoglobin levels reach their nadir, oxygen delivery to the tissues is impaired, renal erythropoietin production is stimulated, and RBC production increases.
5. Infants who have received transfusions in the neonatal period have lower nadirs than normal because of their higher percentage of hemoglobin A.
6. During this period of active erythropoiesis, iron stores are rapidly utilized. The reticuloendothelial system has adequate iron for 15 to 20 weeks in term infants. After this time, the hemoglobin level decreases if iron is not supplied.

Anemia of Prematurity

Definition: Anemia of prematurity is characteristically **normocytic and normochromic with reticulocytopenia** and is most commonly seen in preterm newborns beyond 4 weeks of postnatal age. This is an exaggerated state, analogous to the "physiologic" anemia seen in term newborns at 8 to 12 weeks postnatal age.

Etiology

a. RBC survival is decreased.
b. There is a relatively more rapid rate of growth in premature babies than in term infants. For example, a premature infant gaining 150 g/week requires approximately a 12 mL/week increase in total blood volume.
c. Many preterm infants have reduced red cell mass and iron stores because of iatrogenic phlebotomy for laboratory tests. This has been somewhat ameliorated with the use of micro techniques.
d. Vitamin E deficiency is common in small premature infants, unless the vitamin is supplied exogenously e. comparison to mature newborns, preterms have a poorer bone marrow response, which is one of the important factors resulting in anemia of prematurity

Treatment

1.Asymptomatic; no treatment required (HB level is 9 mg/dl or more
2. Asymptomatic infants with hematocrit value ≤ 18% **(HB ≤ 6g/dl)**: transfusion of packed RBCs
3. Symptomatic infants (hematocrit value < 25-30) **on mechanical ventilation**: transfusion of packed RBCs
4.Iron administration before the age of 10 to 14 weeks does not increase the nadir of the hemoglobin level or diminish its rate of reduction. However, this iron is stored for later use.
5. Once the nadir is reached, RBC production is stimulated, and iron stores are rapidly depleted because less iron is stored in the premature infant than in the term infant.

Etiology of pathological Anemia in the Neonate

A. Blood loss

1. Obstetric causes of blood loss, including the following malformations of placenta and cord

2. Occult blood loss

3. Bleeding in the neonatal period may be due to the following causes:

a. Intracranial bleeding
b. Massive cephalhematoma, subgaleal hemorrhage, or hemorrhagic caput succedaneum
c. Retroperitoneal bleeding
d. Ruptured liver or spleen
e. Adrenal or renal hemorrhage
f. Gastrointestinal
i. Peptic ulcer
ii. Necrotizing enterocolitis
iii. Nasogastric catheter
g. Bleeding from umbilicus

4. Iatrogenic causes.

B. Hemolysis

Neonatal hemolytic anemia

Is manifested by a decreased Hct, increased reticulocyte count, and an Increased bilirubin level

1. Immune hemolysis:

a. Rh incompatibility
b. ABO incompatibility
c. Minor blood group incompatibility (e.g., c, E, Kell, Duffy)
d. Maternal disease (e.g., lupus) or drugs

2. Hereditary RBC disorders:

a. RBC membrane defects such as spherocytosis, elliptocytosis
b. Metabolic defects. Glucose-6-phosphate dehydrogenase (G6PD) deficiency
c. Hemoglobinopathies

3. Acquired hemolysis

a. Infection: bacterial or viral
b. Disseminated intravascular coagulation
c. Vitamin E deficiency and other nutritional anemias
d. Microangiopathic hemolytic anemia

C. Diminished RBC production: is manifested by a decreased Hct, decreased Reticulocyte count, and normal bilirubin level.

1. Diamond-Blackfan syndrome.
2. Congenital leukemia or other tumor.
3. Infections, especially rubella and parvovirus
4. Osteopetrosis, leading to inadequate erythropoiesis
5. Drug-induced suppression of RBC production
6. Physiologic anemia or anemia of prematurity.

Diagnostic Approach to Neonatal Anemia

A. The **family history** should include questions about anemia, jaundice, gallstones, and splenectomy.

B. The **obstetric history** should be evaluated.

C. The **physical examination** may reveal an associated abnormality and provide clues to the origin of the anemia. **D. Complete blood cell count.** Capillary blood Hct is 2.7% to 3.9% higher than venous Hct. Warming the foot reduced the difference from 3.9% to 1.9% .

E. Reticulocyte count (elevated with chronic blood loss and hemolysis, depressed with infection and production defect). **F. Blood smear**.

G. Coombs test and bilirubin level.

H. Apt test on gastrointestinal blood of uncertain origin.

I. Kleihauer-Betke preparation of the mother's blood. A 50-mL loss of fetal blood into the maternal circulation will show up as 1% fetal cells in the maternal circulation.
J. Ultrasound of abdomen and head.
K. Parental testing. Complete blood cell count, smear, and RBC indices are useful screening studies. Osmotic fragility testing and RBC enzyme levels (e.g., G6PD, pyruvate kinase) may be helpful in selected cases.
L. Studies for infection. Toxoplasmosis, rubella, cytomegalovirus (CMV), and herpes simplex.
M. Bone marrow (rarely used, except in cases of bone marrow failure from hypoplasia or tumor).

Clinical picture of neonatal anemia
1. Acute blood loss leads to pallor,anemic heart failure, shock, with cyanosis, poor perfusion, and acidosis. 2. Chronic blood loss produces pallor, poor weight gain, poor feeding and apnea. 3. Chronic hemolysis is associated with pallor, jaundice, and hepatosplenomegaly.

Treatment of neonatal anemia

Healthy, asymptomatic newborns will self-correct a mild anemia, provided that iron intake is adequate

A. Transfusion

1. Indications for transfusion:
a. Infants with significant respiratory disease or congenital heart disease
b. Infants with ABO incompatibility.
c. Premature babies may be quite comfortable with hemoglobin levels of 6.5 to 7 mg/dL.

B. Prophylaxis

1. Term infants should be sent home from the hospital on iron-fortified formula (2 mg/kg/day) if they are not breastfeeding.
2. Premature infants: a. Iron supplementation in the preterm infant prevents late iron deficiency. Routinely supplement iron in premature infants at a dose of 2 to 4 mg of elemental iron/kg/day once full enteral feeding is achieved. **b.** Mother's milk or formulas similar to mother's milk, in that they are low in linoleic acid, are used to maintain a low content of polyunsaturated fatty acids in the RBCs.**c.** Vitamin E (15 to 25 IU of water-soluble form) is given daily until the baby is 38 to 40 weeks' postconceptional age (this is usually stopped at discharge from the hospital).**d.** These infants should be followed up carefully, and additional iron supplementation may be required.**e**. Recombinant human erythropoietin (rh-EPO) has been evaluated as a promising measure in ameliorating anemia of prematurity.

Polycythemia

Introduction: As the central venous hematocrit rises, there is increased viscosity and decreased blood flow. When the hematocrit increases to >60%, there is decreased oxygen delivery leading to increased risk of microthrombus formation. If these events occur in the cerebral cortex, kidneys, or adrenal glands, significant damage may result

Definitions: Polycythemia is defined as venous hematocrit of at **least 65%.** Hematocrit measurements vary greatly with site of sample, and capillary hematocrit may be up to 20% higher than venous.

Incidence: The incidence of polycythemia is **1% to 5%** in term newborns. Polycythemia is increased in babies that have intrauterine growth restriction (IUGR), are small for gestational age (SGA), and are born postterm.

Causes of polycythemia

A. Placental red cell transfusion

1. Delayed cord clamping may occur either intentionally or in unattended deliveries. When the cord is clamped within 1 minute after birth, the blood volume of the infant is approximately 80 mL/kg and when the cord is clamped 2 minutes after delivery, the blood volume of the infant is 90 mL/kg.
2. Cord stripping (thereby pushing more blood into the infant).
3. Holding the baby below the mother at delivery
4. Maternal-to-fetal transfusion
5. Twin-to-twin transfusion
6. Forceful uterine contractions before cord clamping

B. Placental insufficiency

1. SGA and IUGR infants.
2. Maternal hypertension syndromes (preeclampsia, renal disease, etc.).
3. Postterm infants.
4. Infants born to mothers with chronic hypoxia (heart disease, pulmonary disease).

C. Other conditions

1. Infants of diabetic mothers (increased erythropoiesis)
2. Some large-for-gestational-age (LGA) babies
3. Infants with congenital adrenal hyperplasia, Beckwith-Wiedemann syndrome, neonatal thyrotoxicosis, congenital hypothyroidism, trisomy 21, trisomy 13, trisomy 18.
4. Drugs (maternal use of propranolol)
5. Dehydration of infant
6. **Sepsis (increase in fibrinogen, lower RBC deformability)**

Clinical findings

Most infants with polycythemia are asymptomatic mostly symptomatic if peripheral venous hematocrit is >70%.

A. Central nervous system (CNS). Poor feeding, lethargy, hypotonia, apnea, tremors, jitteriness, seizures, cerebral venous thrombosis.

B. Cardiorespiratory. Cyanosis, tachypnea, heart murmur, congestive heart failure, cardiomegaly and elevated pulmonary vascular resistance

C. Renal. Decreased glomerular filtration, decreased sodium excretion, renal vein thrombosis, hematuria, proteinuria.
D. Other. Other thrombosis, thrombocytopenia, poor feeding, increased jaundice, persistent hypoglycemia, hypocalcemia, testicular infarcts, necrotizing enterocolitis (NEC), priapism, disseminated intravascular coagulation.

Diagnosis

The capillary blood or peripheral venous hematocrit level should be determined in any baby who appears plethoric, who has any predisposing cause of polycythemia, who has any of the symptoms mentioned in IV, or who is not well for any reason.
Warming the heel before drawing blood for a capillary hematocrit and if the capillary blood hematocrit is above 65%, the peripheral venous hematocrit should be determined.

Management

A. Once other causes of illness have been considered and excluded (e.g., sepsis, pneumonia, hypoglycemia), any child with **symptoms** that could be due to hyperviscosity should be considered for **partial exchange transfusion** if the peripheral venous hematocrit is >65%.
B. Asymptomatic infants with a peripheral venous hematocrit between 60% and 70% can usually be managed by **increasing fluid intak**e and repeating the hematocrit in 4 to 6 hours.
C. Many neonatologists perform an exchange transfusion when the peripheral venous hematocrit is >70% in the absence of symptoms.
D. The following formula can be used to calculate the exchange with normal saline that will bring the hematocrit to 50% to 60%. In infants with polycythemia, the blood volume varies inversely with the birth weight. the blood is taken from the umbilical vein and replace it with normal saline in a peripheral vein. Because randomized trials show no advantage with albumin and there is less chance of infection, nonhuman products, such as saline, are preferred

$$\text{Volume of exchange in mL} = \frac{(\text{blood volume/kg} \times \text{weight in kg}) \times (\text{observed hematocrit} - \text{desired hematocrit})}{\text{observed hematocrit}}$$

Neonatal Infections

Key point

1.The fetus and newborn infant are less capable of responding to infection because of immunologic immaturity → clinical symptoms may be quite severe or even fatal.
2. Maternal infection, the source of transplacental fetal infection, is often undiagnosed during pregnancy

3. The most common microbial causes of EOS include GBS, Escherichia coli, viridans streptococci, Enterococcus, and a variety of Enterobacteriaceae such as Klebsiella and Haemophilus spp. A wide variety of etiologic agents infect the newborn, including bacteria, viruses, fungi, protozoa, and mycoplasmas.

Classification

1. Congenital infections: (transmitted to the fetus in utero Transplacently) congenital infections have gone by the acronym TORCH (T -toxoplasmosis, O -other, R -rubella, C -cytomegalovirus, H -herpes simplex virus)

2. Acquired infections: Perinatal infections

a. Serious infections e.g. septicemia, meningitis and pneumonia

b. Superficial infections e.g. conjunctivitis, oral moniliasis and umbilical infection

Congenital Infections

Transplacental infection may occur at **any time** during gestation, and signs and symptoms may be **present at birth or may be delayed for months or years**

Etiology: 1 – Toxoplasmosis.2 – Chlamydia. 3 – Congenital Rubella. 4 – Cytomegalovirus.5 – Herpes simplex virus type2 6 – Others - Syphilis, AIDS - Parvovirus B19, Hepatitis B - Varicella zoster and Tuberculosis (TB).

Clinical presentation of congenital infection

Red flag signs suggestive of neonatal infection:

1.Systemic antibiotics given to mother for suspected bacterial infection within 24 hr of birth
2.Seizures
3.Signs of shock
4. Need for mechanical ventilation in a term baby
5.Suspected or confirmed infection in a co-twin

May result in early spontaneous abortion, congenital malformation, intrauterine growth restriction, premature birth, stillbirth, acute or delayed disease in the neonatal period, or asymptomatic persistent infection with sequelae later in life.

General features: 1 – Suggestive maternal history: fever during pregnancy.2 –Small for gestational age.3 – Thrombocytopenia or unusual rash. 4 – Hepatosplenomegaly

Specific features that may suggest the cause:

Seizures: toxoplasmosis, CMV, Herpes simplex

Chorioretinitis: toxoplasmosis, CMV

Calcification intracranial: Toxoplasmosis and CMV

Congenital cataract: Congenital Rubella and Herpes simplex

Congenital heart disease: Rubella

Microcephaly(Rubella and CMV) or **Macrocephaly** and hydrocephalus (Toxoplasmosis)

Mucous membrane, eye and skin lesions and CNS abnormalities, fever, shock, DIC, hepatitis: Herpes simplex

Investigations of congenital infection

Toxoplasmosis: High serum IGM antibodies

Rubella : Virus detection as early as possible by PCR, Serological tests: high IGM antibodies

Cytomegalovirus: Virus detection within 2 – 3 weeks after birth by viral cultures or PCR

Herpes simplex: virus detection by PCR or viral cultures from scraping of the skin lesions, serum, urine, stool, oropharynx, nasopharynx and conjunctivae.

Treatment of congenital infection

1. Intensive supportive care when needed: Fluid balance, oxygen, thermoregulation, nutrition

2. Specific antiviral and antimicrobial agents: Gancyclovir for CMV, Acyclovir for Herpes simplex

Neonatal Sepsis

Definition: Clinical syndrome of systemic illness accompanied by bacteremia or (less commonly) fungal infection. occurring in the first month of life and is the commonest cause of death in neonates

Incidence: 1-8/1000 live births **and** 13-27/1000 live births for infants < 1500g

Mortality rate: is 13-25%, higher rates in premature infants and those with early fulminant disease

Risk factors for neonatal sepsis

1- Neonatal risk factors: Prematurity, Low birth weight, Delayed enteral feeding and prolonged parenteral nutrition Perinatal asphyxia and Male gender. Risk for neonatal late-onset sepsis (LOS) increases with lower gestational age and birth weight and with longer duration of central venous access, mechanical ventilation, and use of total parenteral nutrition.

2 – Maternal risk factors: Maternal fever, Maternal Leukocytosis, Maternal urinary tract infection, Prolonged rupture of membranes, Intrapartum maternal infection, Purulent foul smelling amniotic fluid. Any microorganism inhabiting the genitourinary or lower gastrointestinal tract may cause intrapartum and postpartum infection. The most common bacteria are GBS and E. coli. The more common viruses are CMV, HSV, enteroviruses, and HIV.

3 – Personal and equipment: Inadequate infection control, too crowded units, and improper nurse to patient ratio

Clinical manifestation of neonatal sepsis : Early-onset disease can manifest as asymptomatic bacteremia, generalized sepsis, pneumonia, and/or meningitis. The clinical signs of EOS are usually apparent in the first hours of life; >90% of infants are symptomatic by 24 hours of age.

1- Early signs (lethargy, drowsiness , not doing well, poor feeding, vomiting and abdominal distention)

2- Vital signs (fever or hypothermia,tachprnia, apnea, or respiratory distress, tachycardia or bradycardia)

3- Other signs (DIC, purpura, bleeding, jaundice, septic shock, acute renal failure, sclerema and septic localization)

Initial Signs and Symptoms of Infection in Newborn Infants

GENERAL Fever, temperature instability "Not doing well" Poor feeding Edema	**CARDIOVASCULAR SYSTEM** Pallor; mottling; cold, clammy skin Tachycardia Hypotension Bradycardia
GASTROINTESTINAL SYSTEM Abdominal distention Vomiting Diarrhea Hepatomegaly	**CENTRAL NERVOUS SYSTEM** Irritability, lethargy Tremors, seizures Hyporeflexia, hypotonia Abnormal Moro reflex Irregular respirations Full fontanel High-pitched cry
RESPIRATORY SYSTEM Apnea, dyspnea Tachypnea, retractions Flaring, grunting Cyanosis	**HEMATOLOGIC SYSTEM** Jaundice Splenomegaly Pallor Petechiae, purpura Bleeding
RENAL SYSTEM Oliguria	

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SIRS: The systemic inflammatory response to a variety of clinical insults, manifested by 2 or more of the following conditions:

Temperature instability <35°C (95°F) or >38.5°C (101.3°F)

Respiratory dysfunction: Tachypnea >2 SD above the mean for age, Hypoxemia (PaO2 <70 mm Hg on room air)

Cardiac dysfunction: Tachycardia >2 SD above the mean for age, Delayed capillary refill >3 sec, Hypotension >2 SD below the mean for age

Perfusion abnormalities: Oliguria (urine output <0.5 mL/kg/hr), Lactic acidosis (elevated plasma lactate and/or arterial pH <7.25)

Altered mental status

Sepsis: The systemic inflammatory response to an infectious process

Classifications of neonatal sepsis

1- Early onset sepsis 2- Late onset sepsis

Early Onset Neonatal Sepsis Vs, Late Onset Neonatal Sepsis		
	Early Onset	**Late Onset**
onset	Before or at 72 hours	After 72 hours
source	Maternal	environmental
organisms	Gram negative dominent	Gram positive dominent
Presentation	Fulminant, multisystem involvement, pneumonia frequent	Slowly progressive, focal meningitis frequent
mortality	15- 50%	10-20 %

Differential diagnoses: Include transient tachypnea of the newborn, meconium aspiration syndrome, intracranial hemorrhage, congenital viral disease, and congenital cyanotic heart disease. In infants presenting at more than 24 hours of age, closure of the ductus arteriosus in the setting of a ductal-dependent cardiac anomaly can mimic sepsis. Other diagnoses that should be considered in the infant presenting beyond the first few hours of life with a sepsis-like picture include bowel obstruction, necrotizing enterocolitis (NEC), and inborn errors of metabolism.

Management of neonatal sepsis

1. Investigations: sepsis screen

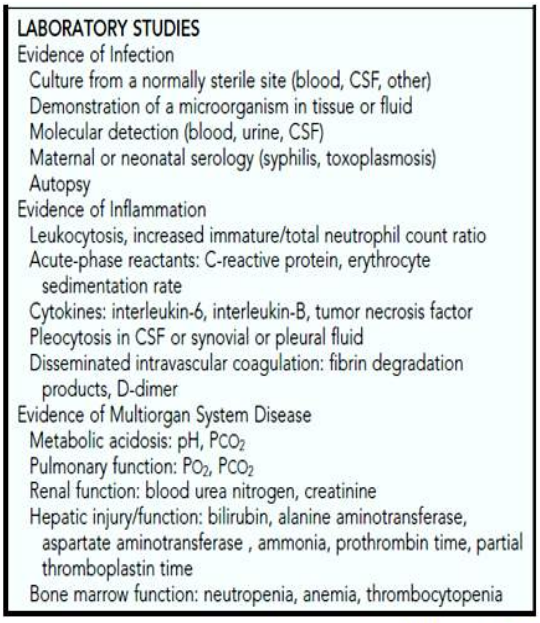
1. Complete blood picture

- leukocytosis above 20000 cell/mm3 or less than 5000 cell/mm^3
- Neutropenia < less 2000. I/T ratio: immature neutrophil to total neutrophil (I/T) > 2

2. Acute phase reactants:

CRP is positive (negative CRP is < 6mg/dl)

3. Blood cultures: (positive in 50% of cases) and urine culture, Swabs from: Eyes, ear, umbilical catheters Tips of removed endotracheal tubes, or central lines


LABORATORY STUDIES
Evidence of Infection
- Culture from a normally sterile site (blood, CSF, other)
- Demonstration of a microorganism in tissue or fluid
- Molecular detection (blood, urine, CSF)
- Maternal or neonatal serology (syphilis, toxoplasmosis)
- Autopsy

Evidence of Inflammation
- Leukocytosis, increased immature/total neutrophil count ratio
- Acute-phase reactants: C-reactive protein, erythrocyte sedimentation rate
- Cytokines: interleukin-6, interleukin-B, tumor necrosis factor
- Pleocytosis in CSF or synovial or pleural fluid
- Disseminated intravascular coagulation: fibrin degradation products, D-dimer

Evidence of Multiorgan System Disease
- Metabolic acidosis: pH, P_{CO_2}
- Pulmonary function: P_{O_2}, P_{CO_2}
- Renal function: blood urea nitrogen, creatinine
- Hepatic injury/function: bilirubin, alanine aminotransferase, aspartate aminotransferase , ammonia, prothrombin time, partial thromboplastin time
- Bone marrow function: neutropenia, anemia, thrombocytopenia

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4. CSF examination and culture

5. Blood sugar: Hypoglycemia or hyperglycemia

2. Antibiotics

1. Route: IV (avoid oral and IM due to poor absorption)

2. When to start

- Asymptomatic full term + risk factor → do CBC, CRP observation
- symptomatic full term + risk factor → do sepsis screen (including blood culture) + start antibiotics

- Asymptomatic preterm + risk factors → do sepsis screen (including blood culture) + start antibiotics

3. Protocol

First line : penicillin eg ampicillin+ Aminoglycosides eg Gentamycin
Second line: depending on the isolated organism

4. Duration

Probable sepsis : 5-7 days
Clinically definite sepsis but culture –ve : 10-14 days
Proven culture +ve sepsis : 14 days
Meningitis: 3 weeks
Septic arthritis 4-6 weeks

Adjunctive immunotherapies for sepsis: Double-volume exchange transfusions, granulocyte infusions, the administration of intravenous immunoglobulin (IVIG), and treatment with granulocyte-colony stimulating factor (G-CSF) and granulocyte macrophage-colony stimulating factor (GM-CSF) have all been investigated with variable results.

Pentoxifylline. Is active in preventing the microvascular complications of sepsis, and decrease the production of tumor necrosis factor (TNF. Pentoxifylline has been studied in a small number of preterm infants with LOS with potential improvement in mortality.

3. Basic life support and monitoring

4. Measures to prevent / minimize infections

Caregiver

Hand washing and proper hygiene of caregiver

Baby

Exclusive breast feeding, keep cord dry uncovered, proper management of IV lines and no unnecessary intervention

Unit

Cot and incubators should be well spaced, proper nurse to patient ratio and proper disinfection of equipment

Prognosis: Bacterial sepsis and meningitis continue to be major causes of morbidity and mortality in newborns, particularly in premature infants. Survivors of sepsis can have severe neurologic sequelae due to central nervous system (CNS) infection as well as from secondary hypoxemia resulting from septic shock, persistent pulmonary hypertension, and severe parenchymal lung disease.

Fungal Infections

A. Mucocutaneous candidiasis. Fungal infections in the well-term infant are generally limited to mucocutaneous disease involving C. albicans.
Immaturity of host defenses and colonization with Candida before complete establishment of normal intestinal flora probably contribute to the pathogenicity of Candida in the neonate. Oral and gastrointestinal colonization with Candida occurs before the development of oral candidiasis (thrush) or diaper dermatitis. Candida can be acquired through the birth canal or through the hands or breast of the mother.
Oral candidiasis in the young infant is treated with a non absorbable oral antifungal medication, which has the advantages of little systemic toxicity and concomitant treatment of the intestinal tract.
Nystatin oral suspension (100,000 U/mL) is standard treatment (1 mL is applied to each side of the mouth every 6 hours for a minimum of 10 to 14 days). Ideally, treatment is continued for several days after lesions resolve.
Fluconazole (6 mg/kg IV or orally (PO) once followed by 3 mg/kg IV/PO each day) can be used for severe oral candidiasis if nystatin oral therapy is not effective.
Systemic fluconazole is also highly effective in treating chronic mucocutaneous candidiasis in the immunocompromised host. Infants with chronic, severe thrush refractory to treatment should be evaluated for an underlying congenital or acquired immunodeficiency. Oral candidiasis in the breastfed infant is often associated with superficial or ductal candidiasis in the mother's breast. Concurrent treatment of both the mother and infant is necessary to eliminate continual crossinfection. Breastfeeding of term infants can continue during treatment.
Candidal diaper dermatitis is effectively treated with topical agents such as 2% nystatin ointment, 2% miconazole ointment, or 1% clotrimazole cream. Concomitant treatment with oral nystatin to eliminate intestinal colonization is often recommended but not well studied. **It is reasonable to use simultaneous oral and topical therapy for refractory candidal diaper dermatitis.**
B. Systemic candidiasis. Systemic candidiasis is a serious form of nosocomial infection in VLBW infants. Invasive candidiasis is associated with overall poorer neurodevelopmental outcomes and higher rates of threshold retinopathy of prematurity, compared to matched VLBW control infants. Gastrointestinal tract colonization of the low BW infants often precedes invasive infection, and risk factors for colonization and invasive disease are similar. The use of H2 blockers or systemic steroids have also been identified as independent risk factor for the development of invasive fungal infection.
Clinical manifestations: Candidiasis due to in utero infection can occur. Congenital cutaneous candidiasis can present with severe, widespread, and desquamating skin involvement. Pulmonary candidiasis can occur in isolation or with disseminated infection and presents as a severe pneumonia. Most cases of systemic candidiasis, however, present as LOS in VLBW infants, most often after the second or third week of life. The initial

clinical features of late-onset invasive candidiasis are often nonspecific and can include lethargy, increased apnea or need for increased ventilatory support, poor perfusion, feeding intolerance, and **hyperglycemia**. **Both the total WBC and the differential can be normal early in the course of infection, and although thrombocytopenia is a consistent feature**,

Diagnosis: Candida can be cultured from standard pediatric blood culture systems; the time to identification of a positive culture is usually by 48 hours

Treatment. Systemic candidiasis is treated with amphotericin B, 0.5 to 1.0 mg/kg/day for durations of 7 to

14 days after a documented negative blood culture if the infection is considered to be catheter associated and

the catheter has been promptly removed. Otherwise, recommended length of treatment for neonatal candidemia is 3 weeks and for longer periods if specific end-organ infection is present. CNS disease can be treated with nonliposomal amphotericin alone; an additional second agent, commonly 5-fluorocytosine (flucytosine 5-FC) (50 to 150 mg/kg/day) or fluconazole (6 mg/kg/day) should be added only if initial therapy with amphotericin is not effective. Flucytosine achieves good CNS penetration, and appears to be safe in infants, but is only available for enteral administration, limiting its utility in sick VLBW infants.

Removal of central catheters in place when candidemia is identified is essential to the eradication of the infection. Delayed catheter removal is associated with persistent candidemia and increased mortality.

Further evaluation of the infant with invasive candidiasis should include renal and brain ultrasonography to rule out fungal abscess formation and ophthalmologic examination to rule out endophthalmitis. In infants who are persistently fungemic despite catheter removal and appropriate therapy, an echocardiogram to rule out endocarditis or vegetation formation is warranted.

5. Prevention. Minimizing use of broad-spectrum antibiotics (particularly cephalosporins and carbapenems) and H2 blockers may be helpful in preventing disseminated candidiasis. Several randomized, placebo-controlled trials of prophylactic fluconazole administration toprevent invasive fungal infection in VLBW infants have been published since 2001. All the trials demonstrated decreased rates of colonization with fungal species, and most also demonstrated decreased rates of invasive fungal infection.

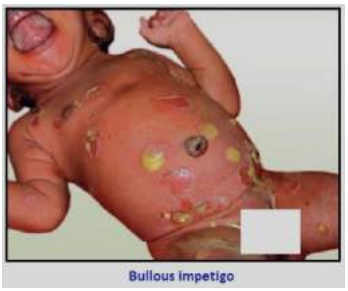
Superficial Neonatal Infection

Conjunctivitis

The most serious from the birth canal.Gonococcal infection: purulent discharge with swelling in the 1st - 3rd days. Chlamydia trachomatis eye infection usually presents with watery to purulent discharge, together with swelling of the eyelid at 1-2 weeks of age. **Treatment:** Local erythromycin drops at birth are prophylactic


Ophthalmia neonatorum

Chlamydia: oral erythromycin
More purulent discharge may occur in staphylococcal or streptococcal infection → topical antibiotics
Gonorrhea: systemic 3rd generation cephalosporin
Mild sticky eyes: cleaning with saline or water

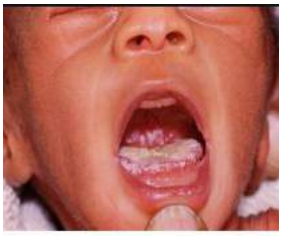

Bullous impetigo

Skin infection: pustules, abscess and impetigo

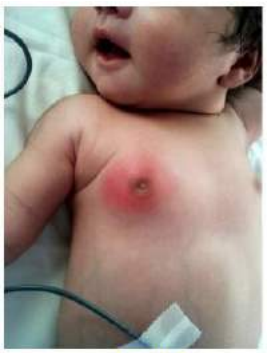
Umbilical sepsis (omphalitis): the skin surrounding the umbilicus becomes red inflamed with offensive discharge and may complicate with sepsis. **Treatment:** systemic antibiotics

Umbilical granuloma: **Etiology**: unknown but more with wetting and poor care of the stump. **Clinical picture**: pink red polyp not covered by skin, serosanguinous discharge. **Treatment**: nitrate and if large one need ligature around the base of the exposed stump

Thrush (oral moniliasis or candidates): infection acquired during delivery or from infected nipple. Clinical picture: appear as white adherent plaques on buccal mucosa and if removed will leave a raw painful area. **Treatment**: Nystatin oral suspension or miconazole oral gel**.**


Thrush

Mastitis: may be 2ry to squeezing the breast. Clinical picture: red hot swollen breast bud (staph.Infection). **Treatment:** systemic antibiotics


Mastitis

Birth Injuries

Definition

Birth injuries are caused by mechanical forces during passage of the baby through the birth canal either naturally or by traction or instrumental intervention.

Risk factors for birth injuries

.Prematurity .Small maternal stature or .primigravida .Maternal pelvic abnormalities

.Prolonged or unusual rapid labor .Oligohydramnios .Malpresentations of the fetus

.Use of midforceps or vacuum extraction .Very low birth weight. .Fetal macrosomia or large fetal head. .Fetal anomalies

Incidence: Morbidity due to birth trauma is 2.8 /1000 and mortality 0.5 /100,000

Types of birth injuries

1 - Cranial injuries: A – Sugaleal hemorrhage and cephalhematoma B – Intracranial hemorrhage

2 - Nerve injuries: A – Erb,s palsy and klumk,s paralysis B - Phrenic nerve paralysis C – Facial palsy

3 - Muscle injuries: stern mastoid hematoma is the commonest

4 - Bone injuries: fracture clavicle is the commonest

5 - Abdominal injuries: liver hematoma is the commonest followed by spleen ,adrenal and Scrotal hematoma.

6 - Skin and soft tissue injury: Erythema, Abrasions, Eccchymosis, Subcutaneous fat necrosis, Scalp lesions and Lacerations.

7- Bony and musculoskeletal injuries: Fracture of clavicle, Fracture of long bones, Dislocations of joints, Sternomastoid tumor. Skull fracture may either linear, or depressed

Caput Succedaneum

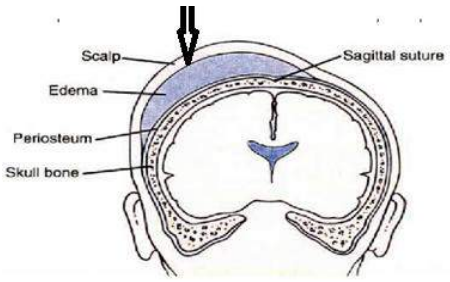
It is a diffuse edematous swelling of subcutaneous soft tissue of the scalp over the presenting part of the head presenting at birth

May extend over the middle line and may be associated with ecchymotic patches.The edema subsides spontaneously within the first few days

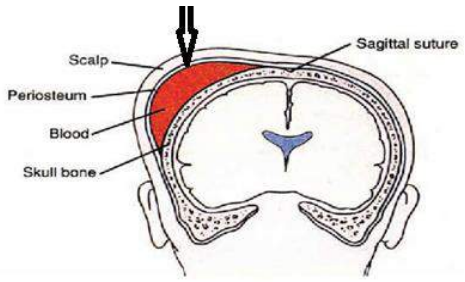
Cephalhematoma

It is a subperiosteal hemorrhage that presents as a firm swelling limited to the surface of one cranial bone usually the parietal presenting hours after birth.

.Anemia and jaundice are the main complications
.Associated skull fractures or even intracranial hemorrhage should be excluded
.Subsided spontaneously over 2 -8 weeks
.May be complicated with anemia, jaundice and skull fracture
.Blood transfusion may needed if significant anemia is present



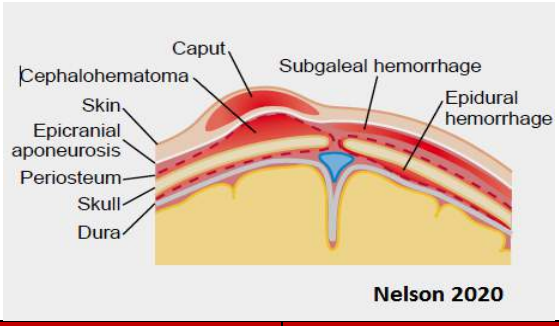
Caput Succedeneum



Cephalhematoma

Subgaleal (Subaponeurotic) hemorrhage

is a hemorrhage between the scalp aponeurosis and subperiosteam
.Spontaneous or follow vacuum extraction
.Presents at birth and may increase in size rapidly
.Hypovolemic shock, anemia and jaundice may occurs
.Fresh frozen plasma or whole blood may be needed



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	Caput succedaneum	cephalhematoma	Subgaleal hemorrhage
Composition	Edema of SC tissue	Blood collection	Blood collection
Site	SC tissue Over the presenting part	Subperiosteal Parietal bone	Under aponeurosis Entire length of the scalp
Onset	At birth	Few hours after birth	At birth
Extent	Cross suture lines	Localized by suture lines	Cross suture lines
Consistency	Soft (edema)	Firm	Fluctuant
Resolution	Few days	Weeks to months	2-3 weeks
Associated complication	Skin eccymosis	Fracture Anemia, jaundice	
Investigation	No	Hb, Bilirubin, X ray, CT	
` treatment	No	According to complication	

Intracranial injuries

A. subdural hemorrhage and epidural hemorrhage
B. Subarachnoid hemorrhage
C. Intraparenchymal hemorrhage
D. Germinal matrix hemorrhage

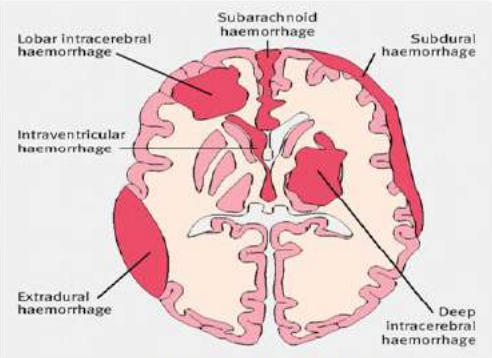
Incidence: mainly in preterm, it occurs in 40%of preterm babies below 34 weeks

Etiology: predisposing factors: Birth hypoxia – birth trauma – coagulation defects – congenital vascular anomalies – convulsions – prematurity

Clinical picture and complications

The majority of intracranial hemorrhage occurs within first 72 hours

It may asymptomatic in 50% of cases



Intracranial hemorrhage

Manifestations:Convulsions, disturbed conscious level and may be coma, Bulging fontanel, suture separation,Poor feeding, apnea, anemia and hyperbilirubinemia

Complications: Hydrocephalus, epilepsy, cerebral palsy and deafness

Investigations

Imaging:cranial ultrasound and CT or MRI if cranial ultrasound is not available

Laboratory:CBC, coagulation profile and serum bilirubin

Prevention:Vitamin K 20 mg for mother once 2 days before delivery and 1 mh to the baby after birth

Treatment: Incubation and care (blood or plasma if needed and vitamin K to treat coagulopathy Control of convulsions by phenobarbitone and phenytoin

Treatment of complications: Neurosurgical consultations

Spinal cord injuries

Spinal cord injury present in 4 ways

High cervical or brain stem injury present as stillbirth

Med cervical injury present with central respiratory depression

Sevens cervical vertebra or lower may be revisable

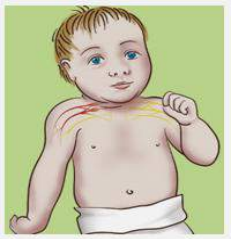
Partial spinal injury or spinal artery occlusion may result in subtle neurological signs and spasticity

Peripheral nerve injuries

Injuries to brachial plexus following traction on the head and neck is common and leads to paralysis of one upper limb

Erb's palsy (C5, 6)

It occur in breech presentation or shoulder dystocia from traction on the brachial plexus nerve roots. Affecting arm and forearm with adducted arm pronated forearm taking policeman position. Absent Moro reflex and intact rasp in affected side. Nerve conduction velocity is recommended.


Erb's palsy

Diaphragmatic paralysis is more common with Erbs than Klumpke's

Klompke's palsy (C7, 8, T1)

occur in breech presentation or shoulder dystocia from traction on the brachial plexus nerve roots.affecting muscles of the hand making the hand midway between flexion and extension. Intact Moro and absent grasp reflex in affected side **.** Nerve conduction velocity is recommended

Phrenic palsy (C4, 5, 6)

It result in paralysis of the diaphragm. Paralysis of one upper limb similar to Erb's palsy occur in addition to unilateral diaphragmatic paralysis.Cyanosis and irregular breathing may occurs.

Facial nerve injury (cranial nerve 7)

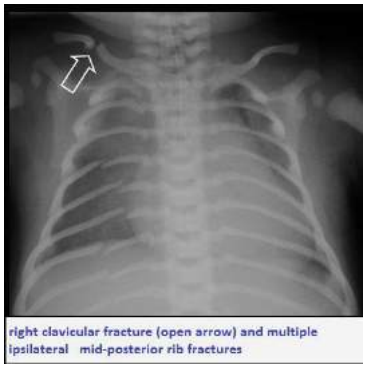
Injury to the facial nerve is the most common peripheral nerve injury in neonates (1%) it usually results from forceps pressure and result in absent facial or forehead movement .
A. central facial nerve injury less frequent than peripheral nerve injury
B. peripheral nerve injury
C. peripheral nerve branch injury results in paralysis that is limited to only one group of facial muscles
DD includes Mobius syndrome, intracranial hemorrhage, congenital hypoplasia of the depressor anguli oris muscle
The prognosis of acquired facial nerve injury is excellent
Recovery usually complete by 3 weeks
Initial management is directed at prevention of corneal injuries by using artificial tears

Recurrent laryngeal nerve injury

Unilateral abductor paralysis may be caused by recurrent laryngeal nerve injury.
Unilateral abductor paralysis is often asymptomatic at rest, but has hoarseness and Inspiratory strider on crying
Unilateral injury usually resolves by 6 weeks of age without intervention and treatment
Bilateral injury has variable prognosis; tracheotomy may needed

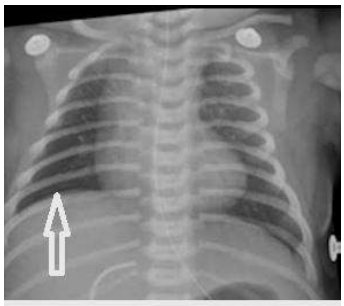
Sternocleidomastoid injury

The most likely cause is a muscle compartment syndrome resulting from intrauterine positioning, torticollis can arise during delivery as the muscle is hyper extended and ruptured.
Head tilt to the side of the lesion
Prompt treatment may lessen or correct torticollis
D.D. Include cervical vertebral anomalies, hemangiomas and teratoma
Treatment include stretching of the involved muscle several times /day
Recovery typically occurs within 3 to 4 months


right clavicular fracture (open arrow) and multiple ipsilateral mid-posterior rib fractures

Fractures
Fracture of clavicle is most common

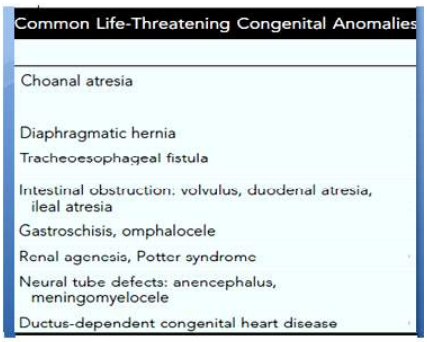
Visceral injuries
liver injury and formation of subcapsular hematoma
Splenic injury may also occur alone or in association with liver injury


Unilateral Diaphragmatic paralysis

Neonatal Surgical Emergencies

Potential surgical condition presenting in the fetus

1.Polyhydramnios
2.Oligohydramnios
3.Meconium peritonitis
4.Fetal ascites
5.Dystocia
6.Fetal surgery



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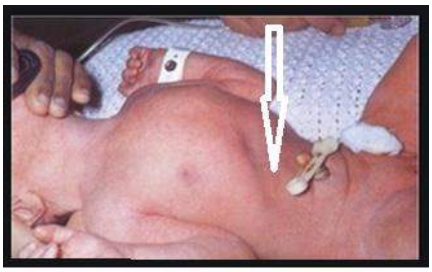
Postnatal surgical disorders (Diagnosis by presenting symptoms)

a. **Respiratory distress:**
   1. Choanal atresia
   2. Laryngotracheal clefts
   3. Tracheal agenesis

4. EA with or without tracheoesophageal fistula
5. Congenital lobar emphysema
6. Cystic adenomatoid malformation
7. DH (Diaphragmatic Hernia)
8. Biliary tracheobroncheal communication


Scaphoid abdomen

Scaphoid abdomen

1. DH (Diaphragmatic Hernia)
2.EA without tracheoesophageal fistula

Excessive mucus and salivation

EA with or without tracheoesophageal fistula

Abdominal distension

1. Pneumoperitoneum
2.Intestinal obstruction

Vomiting

The causes of vomiting can be differentiated by the presence of or absence of bile
Bilious vomiting. The presence of bile- stained vomit in the newborn should be treated as a life-threatening emergency. Surgical consultation should be obtained immediately. **Bilious emesis is malrotation until proven otherwise**.bile stained emesis is occasionally seen in infant without intestinal obstruction who have decreased motility
Non bilious emesis Feeding excessive volume

b. Milk (human or formula) intolerance
c. Decreased motility
   Prematurity
   Antenatal exposure to MgSO4 or exposure to narcotics
   Sepsis with ileus
   CNS lesion
d. Lesion above ampulla of Vater
   .Pyloric stenosis
   .Upper duodenal stenosis
   .Annular pancreases

Failure to pass meconium

1.Imperforate anus
2. Microcolon
3. Mucus plug
4. Other causes of intestinal obstruction

Failure to develop transitional stools after the passage of meconium

1. Volvulus
2. Malrotation

Hematemesis and hematochezia

- NEC
- Gastric or duodenal ulcers(stress, steroid)
- GIT obstruction

Nan surgical condition causing Hematemesis and hematochezia (more common)
- Milk intolerance/allergy
- Instrumentation (nasogastric tube, Endotracheal tube)
- Swallowed maternal blood
- Coagulation disorders

- Volvulus
- Intussusceptions
- Polyps, hemangiomas
- Meckel divertculum
- Cirsoid aneurysm
- Duplication of small intestine

Abdominal masses

- Genitourinary anomalies
- Hepatosplenomegaly
- Tumors

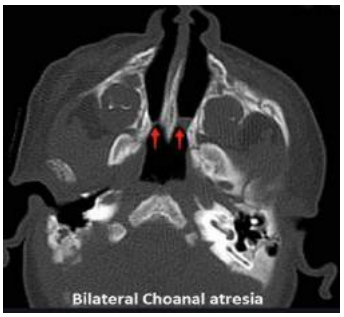
Choanal Atresia

Pathology

.

Obstruction of the posterior nares by bony or membranous septum.

It may be bilateral or unilateral



Diagnosis

. Cyanosis on closure of the mouth or feeding

. Cyanosis improves when the baby cries, as the oral airway passage is used at this time

. Inability to pass a suction catheter through the nares

Treatment

Keep the mouth opened using airway followed by surgical treatment

Congenital Diaphragmatic Hernia (Bochdalek)

Incidence: is between 1/2,000 and 1/5,000 live births.The overall survival from the CDH Study Group is 67%.

A diaphragmatic hernia is defined as a communication between the abdominal and thoracic cavities with or without abdominal contents in the thorax

.The etiology is usually congenital but may be traumatic.

The symptoms and prognosis depend on the location of the defect and associated anomalies.

The term congenital diaphragmatic hernia typically refers to the Bochdalek form.

Pathology

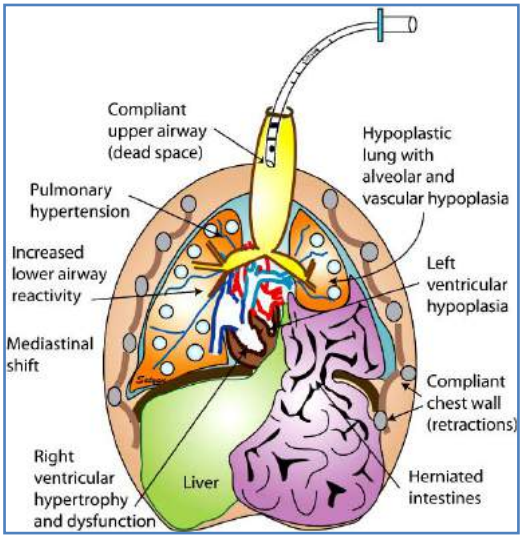
Part of the intestine with or without the liver herniates through an opening in the diaphragm during intrauterine life. It is usually associated with malrotation of the intestine andhypoplasia of the lungs. Defects are more common on the left (85%) and are occasionally (<5%) bilateral.

Clinical picture

1.Respiratory distress is a cardinal sign in babies with CDH It may occur immediately after birth or there may be a “honeymoon” period of up to 48 hr during which the baby is relatively stable.

2. Difficult resuscitation, all infants with diaphragmatic hernia should be intubated

immediately after delivery nor at the time of postnatal diagnosis, bag and mask ventilation is contraindicated
3. The apex beat is displaced to the right side
4. Scaphoid abdomen
5. Bowel sounds may also be heard in the chest
6. A small group of infants with CDH present beyond the neonatal period.



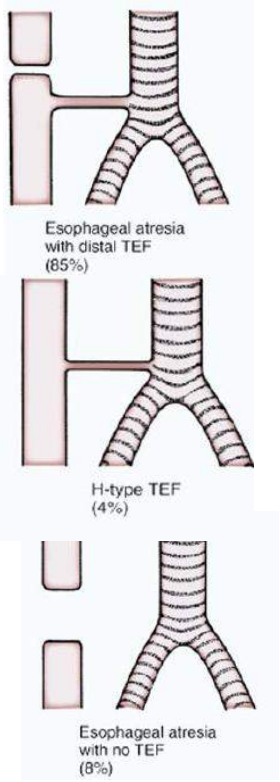
Complication
. Pulmonary hypoplasia
. Respiratory failure

Investigations
. Prenatal ultrasound (between 16 and 24 wk of gestation)
. High-speed fetal MRI
. X ray is diagnostic

Treatment
. Nasogastric suction to prevent distention of the intra thoracic bowel
. Aggressive respiratory support and surgical treatment

Tracheoesophageal fistula

There are five common anatomic variants with Type C (esophageal atresia/distal TEF) accounting for 85% of cases



Incidence: 1/3000–4000 live births. Most commonly seen in association with VACTERL association (Vertebral, Anorectal, Cardiac, Tracheal, Esophageal,Renal/Genitourinary, Limb)

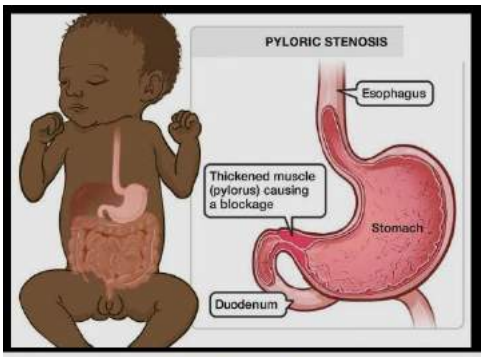
Clinical picture
Prenatal history of polyhydramnios in one-third of cases, due to esophageal atresia At birth :
.Failure to pass Nasogastric tube
.Choking, dribbing of saliva and respiratory distress
.Cyanosis with feeding due to airway obstruction by excess secretions and aspiration of saliva and .milk
.Gasless abdomen is suggestive of isolated esophageal atresia
.Distal fistula may present with significant abdominaldistention
.Associated anomalies 50% of cases

Investigation:
X ray with Nasogastric tube in the esophagus

Management:
Make infant NPO and initiate acid suppression and IV fluids
Mechanical ventilation (TEF needs HFV) and surgical management

Hypertrophic Pyloric Stenosis

- Incidence is 1/1000–3/1000 live births
- Idiopathic hypertrophy of py loric muscle resulting in narrowing and elongation of pyloric channel
- Results in gastric outlet obstruction
-Typically presents between 3–6 weeks of age with progressive projectile vomiting
-Hallmark of physical exam is palpation of "olive" in the epigastric area
- Diagnosis is confirmed with ultrasound
- Treatment includes correction of metabolic derangement and surgical pyloromyotomy



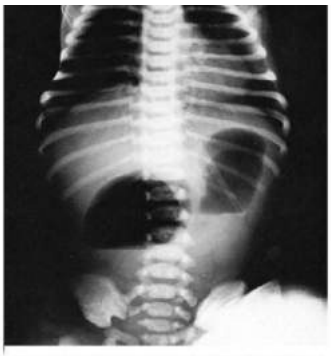
Pyloric stenosis

Intestinal Obstruction

Small intestinal obstruction

Causes :duodenal atresia, jeujenal atresia and ileal atresia. intestinal malrotation or volvolus. meconium ileus

Diagnosis: bilious vomiting early with high lesions and abdominal distension later on
X ray: multiple air fluid level or **double bubble sign** in duodenal atresia


Double buble sign seen with duodenal atresia (Avery's 2019)

Treatment: surgical

Large intestinal obstruction

Hirschsprung disease

Pathology: absent myenteric nerve plexus in the rectum and distal colon

Clinical picture: delayed passage of meconium and abdominal distension

Treatment: Surgical intervention.Colostomy is indicated when there is enterocolitis or when adequate decompression cannt be achieved

Imperforate anus

. Should be excluded in routine examination of any neonate
. Detailed examination as anomalies are found in 60% of cases
. Most cases need colostomy performed in the neonatal period
. Surgical repair is performed later on

Gestational Age Assessment

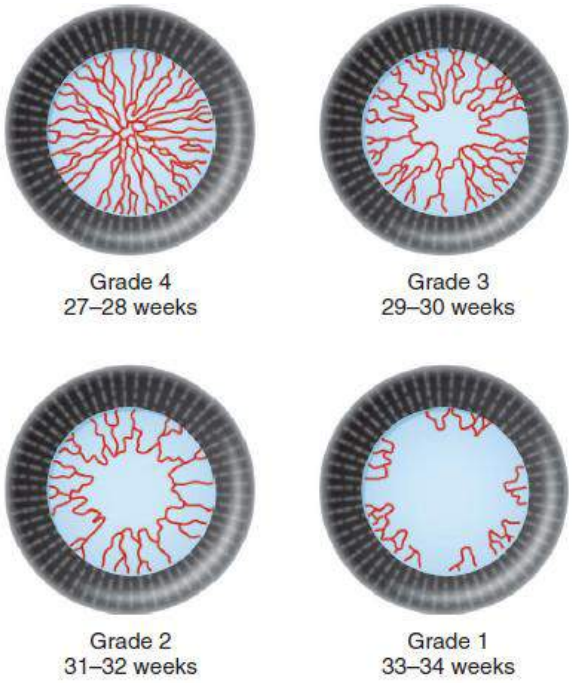
Gestational age is routinely estimated by calculation from **date of last menstrual period (LMP), antenatal ultrasound scanning or by clinical examination** of the infant after birth.

Postnatal gestational age assessment

1. Rapid assessment of gestational age in the delivery room. There are multiple methods for rapid assessment of gestational age. Most include some of the following physical characteristics: skin texture, skin color, skin opacity, edema, lanugo hair, skull hardness, ear form, ear firmness, genitalia, breast size, nipple formation, and plantar skin creases. One method for rapid gestational age assessment includes the most useful clinical signs in differentiating among premature, borderline mature, and full-term infants, which are as follows (in order of utility): creases in the sole of the foot, size of the breast nodule, nature of the scalp hair, cartilaginous development of the earlobe, scrotal rugae, and testicular descent in males.

Criteria For Rapid Gestational Assessment At Delivery			
Feature	36 Weeks and Earlier	37–38 Weeks	39 Weeks and Beyond
Creases in soles of feet	1 or 2 transverse creases; posterior three-fourths of sole smooth	Multiple creases; anterior two-thirds of heel smooth	Entire sole, including heel, covered with creases
Breast nodule	2 mm	4 mm	7 mm
Scalp hair	Fine and woolly; fuzzy	Fine and woolly; fuzzy	Coarse and silky; each hair single stranded
Earlobe	No cartilage	Moderate amount of cartilage	Stiff earlobe with thick cartilage
Testes and scrotum	Testes partially descended; scrotum small, with few rugae	?	Testes fully descended; scrotum normal size with prominent rugae
Clinical significance of gestational age and an objective method for its assessment, Pediatr Clin North Am. 1966 Aug;13(3):835-862.			

2. Direct ophthalmoscopy of the lens is another method for determination of gestational age at 27 to 34 weeks only. It is based on the normal embryologic process of the gradual disappearance of the anterior lens capsule vascularity between 27 and 34 weeks of gestation. Before 27 weeks, the cornea is too opaque to allow visualization; after 34 weeks, atrophy of the vessels of the lens occurs. This method is reliable to ±2 weeks.



Grading system for assessment of gestational age by examination of the anterior vascular capsule of the lens. (Reproduced with permission from Hittner HM, Hirsch NJ, Rudolph AJ: Assessment of gestational age by examination of the anterior vascular capsule ofthe lens, J Pediatr. 1977 Sep;91(3):455-458.)

3. Examinations based on physical and neuromuscular maturity

Clinical assessment is based on changes in physical and neurologic characters with gestational age based on these changes many scoring systems have been described. One such system which is most widely used is the modified Dubowitz (Ballard) '**New Ballard Scoring System**'. This system is reliable for the entire infant population **(from extremely premature to post mature)** and there are some limitations to this method, especially with use of the neuromuscular component in sick newborns. There are 6 neurologic and 6 physical parameters. **If the infant is >26 weeks' gestation, there is no optimal age of examination up to 96 hours and may extend to 2 weeks of gestational age**

New Ballard Scoring System

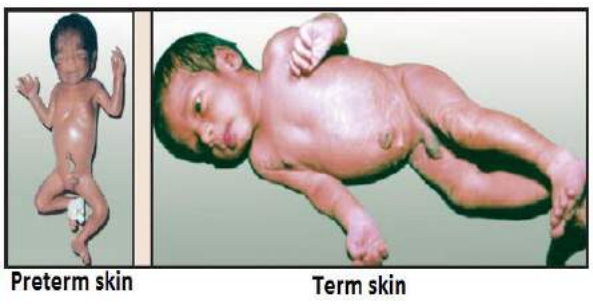
A. Physical parameters (6)

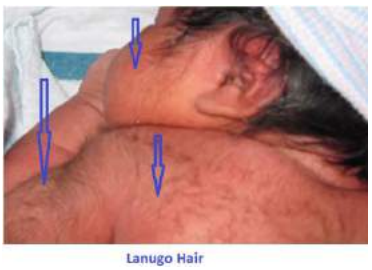
1. Skin

Look for translucency over the abdominal wall and score according to the following table

2. Lanugo hair

Look for lanugo over the back and score





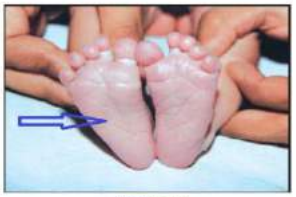
3. Plantar Surface

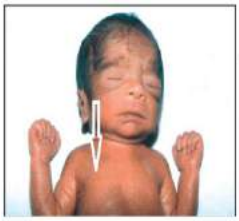
Measure foot length from tip of great toe to back of heal Look for deep cracks and score

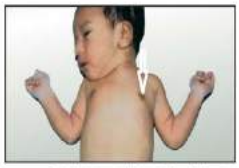
4. Breast

Pickup between finger and thumb, and assess the development does not depend on the nutrition or sex


Preterm sole


Term sole


Preterm baby-breast. Note barely visible nipple


Term baby-breast. Note well-formed breast

5. Eye/Ear

Test for lid fusion by trying to separate the lids by gentle traction; they are inseparable if tightly fused.

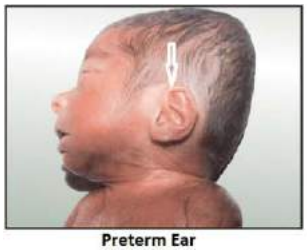
a. Inspect upper pinna above meatus

b. For firmness, palpate and fold upper pinna and observe recoil

6a. Genitals—Male

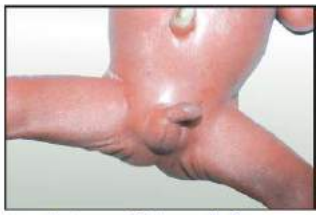
Examine the level of testis

Examine rugosity of scrotal skin


Preterm Ear


Term Ear


Term - Male genitalia


Preterm - Male genitalia

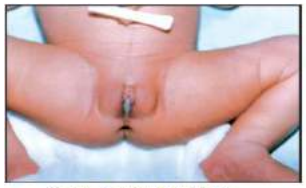
6b. Genitals—Females

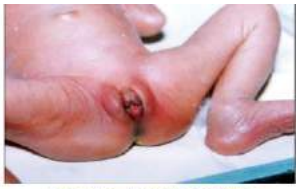
Labia minora and clitoris look prominent in preterms, gradually labia majora grow and completely cover minora in term infants.

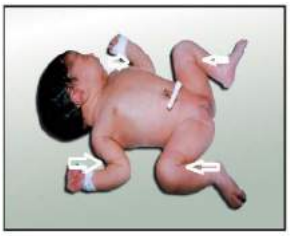
B. Neuromuscular parameters (6)

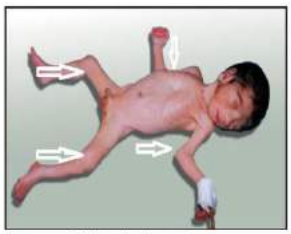
1. Posture

Infant should be quiet and lie supine.


Term - Female genitalia


Preterm - Female genitalia


Term baby - posture


Preterm baby - posture

2. The square window

is assessed by flexing the wrist and measuring the minimal angle between the palm and flexor surface of the forearm. This angle decreases with advancing gestational age.

3. The scarf sign

is assessed by pulling the hand across the chest to encircle the neck as scarf and observing the position of the elbow in relation to the midline.


Term square window

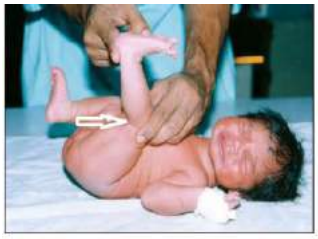

Preterm square window


Term baby - Scarf sign

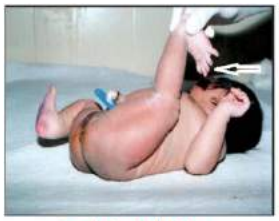

Preterm baby - Scarf sign

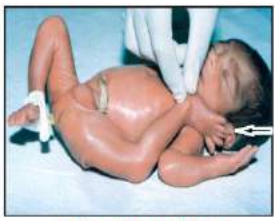
4. The popliteal angle, one should first flex the hips with the thighs alongside the abdomen rather than over the front. With the hips held in flexion, the knee is then extended as far as possible to estimate the popliteal angle

5. the heel to ear maneuver, the legs are held together and pressed as far as possible toward the ears without lifting the pelvis from the examination


Term baby Popliteal angle


Preterm baby Popliteal angle

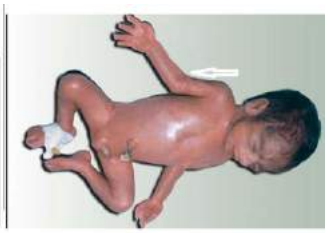

Term baby - Heal to Ear


Preterm baby - Heal to Ear

6. Arm recoil

is assessed by first flexing the elbow and holding the arm against the forearm for 2 to 5 seconds. The elbow is then fully extended and released with observation of how quickly and fully the infant resumes a flexed posture.


Term - Arm recoil


Preterm - Arm recoil

	−1	0	1	2	3	4	5
Skin	Sticky, friable, transparent	Gelatinous, red, translucent	Smooth, pink, visible veins	Superficial peeling and/or rash, few veins	Cracking, pale areas, rare veins	Parchment, deep cracking, no vessels	Leathery, cracked, wrinkled
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald	
Plantar surface	Heel-toe 40-50 mm: −1 <40 mm: −2	>50 mm, no crease	Faint red marks	Anterior transverse crease only	Creases on ant 2/3	Creases over entire sole	
Breast	Imperceptible	Barely perceptible	Flat areola, no bud	Stripped areola, 1-2 mm bud	Raised areola, 3-4 mm bud	Full areola, 5-10 mm bud	
Eye/ear	Lids fused loosely (−1) tightly (−2)	Lids open, pinna flat, stays folded	Slightly curved pinna; soft; slow recoil	Well-curved pinna, soft but ready recoil	Formed and firm, instant recoil	Thick cartilage, ear stiff	
Genitals, male	Scrotum flat, smooth	Scrotum empty, faint rugae	Testes in upper canal, rare rugae	Testes descending, few rugae	Testes down, good rugae	Testes pendulous, deep rugae	
Genitals, female	Clitoris prominent, labia flat	Prominent clitoris, small labia minora	Prominent clitoris, enlarging minora	Majora and minora equally prominent	Majora large, minora small	Majora cover clitoris and minora	

Physical criteria for maturity(Nelson 2020)

	−1	0	1	2	3	4	5
Posture							
Square window (wrist)	>90°	90°	60°	45°	30°	0°	
Arm recoil		180°	140-180°	110-140°	90-110°	<90°	
Popliteal angle	180°	160°	140°	120°	100°	90°	<90°
Scarf sign							
Heel to ear							

Neuromuscular criteria for maturity (Nelson2020)

Score	Weeks
– 10	20
– 5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

Maturity rating (Nelson 2020)

Interpretation of New Ballard Scoring System depend on maturity rating: Maturity rating: The physical and neurologic scores are added to calculate gestational age

4. Metabolic gestational age dating. Prediction models have been developed using
newborn metabolic profile, hemoglobin levels, and analyte data from the newborn metabolic screening profiles. The results were very favorable, and one study predicted gestational age within 1 week of the actual gestational age in two-thirds of the infants. This method is accurate and may be useful in resource-poor countries where ultrasound is not readily available. DNA methylation on cord blood and blood spot samples has also been studied and accurately estimates gestational age.

Routine Care of the Newborn

A proper care during early neonatal period prevents many serious consequences. It involves the basic principles of providing warmth feed, keeping the baby clean and early picking up of danger signs. Participation of the whole family in the care should be encouraged. Healthy newborns should remain in the delivery room with their mother as long as possible to promote immediate initiation of breastfeeding and early bonding.

Transitional Care

A. The transitional period is usually defined as the first 4 to 6 hours after birth. During this period, the infant's pulmonary vascular resistance decreases, blood flow to the lungs is greatly increased, overall oxygenation and perfusion improve, and the ductus arteriosus begins to constrict or close.

B. Common signs of disordered transitioning are (i) respiratory distress, (ii) poor perfusion with cyanosis or pallor, or (iii) need for supplemental oxygen.

C. Infants are evaluated for problems that may require a higher level of care, such as gross malformations and disorders of transition.

D. The infant should be evaluated every 30 to 60 minutes during this period, including assessment of heart rate, respiratory rate, and axillary temperature; assessment of color and tone; and observation for signs of withdrawal from maternal medications. . Infants with signs of disordered transitioning require transfer to a higher level of care.

Suctioning of the mouth after delivery

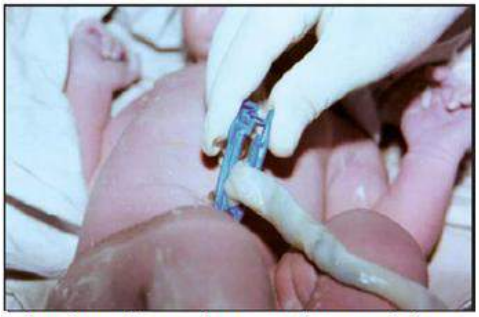
The routine care includes the following:

Clearing the airway

Proceed through the following steps

1.As the head is delivered, begin gentle suction of the baby's mouth

2.Suspend the baby with the head down for few seconds to drain away the fluid.
3. Lay the baby on his back and suck out the back of the mouth and nostrils with catheter. Deep suctioning of the airway with a suction catheter should be avoided. **Deep suctioning can result in reflex bradycardia due to vagal nerve stimulation**.
4. If after that the baby has not cried an immediate resuscitation is required


Clambing the cord 2-3 cm from umbilicus

Cutting the umbilical cord

1.Whilst the cord is attached, the baby should be below the level of the placenta
2.Wait until pulsation has ceased then milk the cord towards the baby so to move blood into the baby's circulation 3.The cord is then clamped and cut with a sterile sharp instrument.
4.Two ligatures are tied on the cord, the first 4 -5 cm away from the umbilicus and the second a little further. Then cut the cord between the two ligatures
5.Ethyl alcohol70% is applied daily on the umbilical stump
6.The cord normally dried with exposure to air, shrink and fall off in one to two weeks
7. Clamping of the umbilical cord should be done after at least 30 to 60 seconds. Delayed clamping for 1 minute leads to a transfer of approximately 80 mL of extra blood to the term neonate

Prevention of Hypothermia

Prevention of hypothermia is perhaps the most essential need of any infant. The thermoregulatory mechanism in infants is less efficient making them prone for hypothermia and its ill effects.


Kangaroo mother care

1.Ensure that room is warm (ideal temperature 24-25.5°C, humidity 40-50%).
2.Keep the baby completely covered including head.
3.Use radiant room heaters if necessary.
4.Keep the baby close to mother, allow skin-to-skin contact and kangaroo mother care.
5.Avoid giving bath, if insisted; use proper precautions
6.Record temperature regularly and when in doubt,

Care of the eyes

1.Wipe of any fluid on the eyes with clean swab
2. All newborns should receive prophylaxis against gonococcal ophthalmia neonatorum within 1 to 2 hours of birth, regardless of the mode of delivery. Prophylaxis is administered as a single ribbon of 0.5% erythromycin ointment or 1% tetracycline ointment bilaterally in the conjunctival sac
3.Kohl should be avoided as it cause lead poisoning

Bathing

The precautions to be taken are:

1.Give bath only to stable babies.

2.Water should be sterilized before hand by boiling.

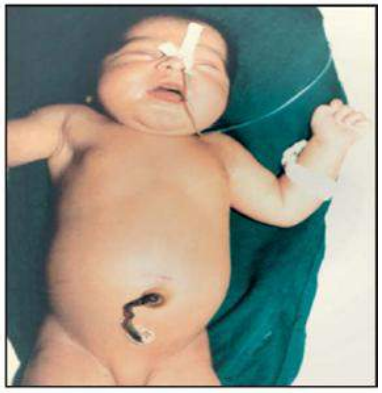
3.Avoid immersion baths for preterms.
4.Temperature of bath water should not exceed 37°C.
5.Use soaps with neutral pH.
6.Soaping should be followed by thorough rinsing: remember all soaps are potential irritants including "baby soaps".
7.The whole process should not last for more than 5 minutes.
8.Completely dry the infant after bath.
9.Take special precaution to dry up skin folds.
10. Wrap the baby completely after drying.

Recording Daily Weight

The baby should be weighed in the labor room immediately after initial stabilization and this should be taken as birth weight. Thereafter it is recommended to weigh at least once a day in case of normal infants. Babies should be weighed naked using electronic scales.

Watching for Danger Signs

Apparently healthy infants should be carefully watched for following dangerous signs and early intervention should be done. lethargy or excessive crying, no stool in first 24 hours, no urine in first 72 hours, choking after feeding, jaundice before 24 hours or persisting beyond one week, hurried breathing and apnea, refusal of feeds, central cyanosis, distention of abdomen, convulsions, vomiting/diarrhea, bleeding , hypotonia and sudden fall or rise of temperature


Danger sign (abdominal distension)

Gestational age assessment (see later)

Screening for Congenital Disorders

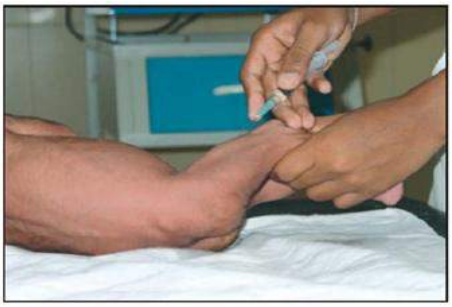
Screening in the newborn period plays an important role in disorders which are difficult to detect clinically, but early intervention yields dramatic benefits

Breast-Feeding

All mothers should be emotionally and physically prepared during pregnancy for successful breastfeeding. The first feed is usually offered within 1-2 hours after birth.

Vitamin K

A single intramuscular dose of 0.5 to 1 mg of vitamin K1 oxide (phytonadione) should be given to all newborns before 6 hours of age to prevent vitamin K deficiency bleeding (VKDB). Oral vitamin K


Administration of vitamin K i.m

preparations are not recommended

Immunization

1. Administration of the first dose of hepatitis B vaccine for all infants, even if the mother is hepatitis B surface antigen (HBsAg) negative and should be within 12 hours of age when the maternal HBsAg is positive or unknown. Infants of HBsAg positive mothers also require hepatitis B immune globulin (HBIG) 2. Immunization is carried out as per the schedule. BCG- Oral Polio vaccine

Cord blood

Cord blood is saved up to 14 to 21 days, depending on blood bank policy.

Bilirubin screening

Before discharge, all newborns should be screened for the risk of subsequent development of significant hyperbilirubinemia.

Routine assessment

A. The infant's physician should perform a complete physical examination within 24 hours of birth.

B. Vital signs, including respiratory rate, heart rate, and axillary temperature, are recorded every 8 to 12 hours.

C. Each urine and stool output is recorded in the baby's chart. The first urination should occur by **30 hours** of age. The first passage of meconium is expected by **48 hours** of age. Delayed urination or stooling is cause for concern and must be investigated.

D. Daily weights are recorded in the infant's chart.

Feedings

The frequency, duration, and volume of each feed will depend on whether the infant is breastfeeding or bottle-feeding.

A. The breast-fed infant should feed as soon as possible after delivery, and feed 8 to 12 times per day. B. **Infant formula** is offered to infants for whom breastfeeding is contraindicated or at the request of a mother who desires to bottle-feed. Infants are fed at least every 3 to 4 hours.

Newborn circumcision

A. Adequate analgesia must be provided for neonatal circumcision.

E. Circumcision in the newborn can be performed using one of three different methods:1. Gomco clamp 2. Mogen clamp 3. Plastibell device

Care of the Extremely Low Birth Weight Infant

Protocol for Standardizing Care of the Extremely Low Birth Weight (ELBW) Infant

1. Prenatal consultation

a. Parental education

b. Determining parental wishes when viability is questionable

c. Defining limits of parental choice; need for caregiver–parent teamwork

2. Delivery room care

a. Define limits of resuscitative efforts

b. Respiratory support
c. Low tidal volume ventilation strategy
d. Prevention of heat and water loss: immediately wrapping the undried baby's body and extremities in plastic wrap or placing them in a plastic bag

e. Early surfactant therapy

3. Ventilation strategy

a. Low tidal volume, short inspiratory time
b. Avoid hyperoxia and hypocapnia
c. Early surfactant therapy as indicated
d. Define indications for high-frequency ventilation

4. Fluids

a. Early use of humidified incubators to limit fluid and heat losses
b. Judicious use of fluid bolus therapy for hypotension
c. Careful monitoring of fluid and electrolyte status
d. Use of double-lumen umbilical venous catheters for fluid support

5. Nutrition

a. Initiation of parenteral nutrition shortly after birth
b. Early initiation of trophic feeding with maternal milk
c. Advancement of feeding density to provide adequate calories for healing and growth

6. Cardiovascular support

a. Maintenance of blood pressure within standard range
b. Use of dopamine for support as indicated
c. Corticosteroids for unresponsive hypotension

7. PDA

a. Avoidance of excess fluid administration
b. Early medical therapy when hemodynamically significant PDA is present
c. Surgical ligation after failed medical therapy

8. Infection control

a. Scrupulous hand washing, use of bedside alcohol gels
b. Limiting blood drawing, skin punctures
c. Protocol for CVL care, acceptable dwell time
d. Minimal entry into CVLs, no use of fl uids prepared in NICU

Neonatal Vomiting

Introduction

Vomiting or, more often, regurgitation is a relatively frequent symptom during the neonatal period. **It is a common manifestation of overfeeding, inexperienced feeding technique, or normal reflux.** When vomiting occurs **shortly after birth and is persistent**, the possibilities of intestinal obstruction, metabolic disorders, and increased intracranial pressure must be considered.

Clinical assessment of vomiting

1. A history of maternal polyhydramnios suggests upper gastrointestinal (esophageal, duodenal, ileal) atresia.
2. Bile-stained emesis suggests intestinal obstruction beyond the duodenum but may also be idiopathic.
3. The diagnosis of esophageal atresia can be suspected if **unusual drooling** from the mouth is observed and if **resistance** is encountered during an attempt to pass a catheter into the stomach.
4. Vomiting caused by obstruction of the **small intestine** usually begins on the 1st day of life and is frequent, persistent, usually nonprojectile, copious.
5. Persistent vomiting may occur with congenital diaphragmatic hernia.
6. The vomiting associated with pyloric stenosis may begin any time after birth but may not assume its characteristic pattern before the 2nd-3rd wk. **Prostaglandins and erythromycin may cause pyloric stenosis if administered to a premature infant**.
7. Vomiting with obstipation is a common early sign of Hirschsprung disease.
8. Vomiting may occur with many other disturbances that do not obstruct the digestive tract, such as milk allergy, adrenal hyperplasia of the salt-losing variety, galactosemia, hyperammonemias, organic acidemias, increased intracranial pressure, septicemia, meningitis, and urinary tract infection.

Differentiation of causes of vomiting as Bilious or Non bilious

1. Bilious vomiting

Bilious emesis is malrotation until proven otherwise

1. The presence of bile-stained vomit in the newborn should be treated as a life-threatening emergency.

2. Surgical consultation should be obtained immediately.

3. Unless the infant is clinically unstable, a contrast study of the upper gastrointestinal tract should be obtained as quickly as possible.

4.Intestinal obstruction may result from **malrotation** with or without midgut volvulus; **duodenal, jejunal, ileal, or colonic atresias; annular pancreas; Hirschsprung disease; aberrant superior mesenteric artery; preduodenal portal vein; peritoneal bands; persistent omphalomesenteric duct; or duodenal duplication**.

2. Nonbilious vomiting

a. Feeding excessive volume

b. Milk (human or formula) intolerance

c. Decreased motility

i. Prematurity
ii. Antenatal exposure to MgSO4 or antenatal, prenatal, or postnatal exposure to narcotics
iii. Sepsis with ileus
iv. Central nervous system (CNS) lesion

d. Lesion above ampulla of Vater

i. Pyloric stenosis
ii. Upper duodenal stenosis
iii. Annular pancreas (rare)

Differentiation of causes of vomiting as abdominal or extraabdominal

1.Abdominal

Irritation of stomach by swallowed amniotic fluid
. Vomiting after food—faulty feeding techniques
. Meconium ileus
. Congenital adhesion bands
. Hypertrophic pyloric stenosis
. Duodenal atresia, pyloric atresia
. Intussusception
. Intestinal obstruction, strangulated hernia

2. Extra-abdominal

. Sepsis—Meningitis, systemic infection
. Cardiac failure
. Birth asphyxia, foreign body
. Brain injury
. Intracranial hemorrhage
. Drugs