Ministry of Education and Science of Ukraine
Ministry of Health of Ukraine
Sumy State University
Medical Institute

Redko O. K.,
Petrashenko V. O.,
Loboda A. M.

NEONATOLOGY

Lecture notes

Sumy
Sumy State University
2021

Ministry of Education and Science of Ukraine
Ministry of Health of Ukraine
Sumy State University

NEONATOLOGY

Lecture notes
for students of specialty *222 "Medicine"*
of full-time course of studies

Approved at the meeting
of the department of Pediatrics
as lecture notes on the discipline
"Pediatrics".
Minutes № 1 of 27.08.2021.

Sumy
Sumy State University
2021

Neonatology : lecture notes / compilers: O. K. Redko, V. O. Petrashenko, A. M. Loboda. – Sumy : Sumy State University, 2021. – 189 p.

Department of Pediatrics MI

CONTENS

1. BIRTH ASPHYXIA. HYPOXIC-ISCHEMIC ENCEPHALOPATHY (HIE)

Asphyxia (from Greek *a-*, *"without" and* sphygmos – "heartbeat") is a condition of severely deficient supply of oxygen to the body that arises from being unable to breathe normally. An example of asphyxia is choking. Asphyxia causes generalized hypoxia, which primarily affects the tissues and organs.

Birth asphyxia, is characterized by clinical and laboratory evidence of acute or subacute brain injury due to asphyxia. The primary causes of this condition are systemic hypoxemia and/or reduced cerebral blood flow (CBF).

Statistical data. In the United States and in most technologically advanced countries, the incidence of **birth asphyxia**is 1–4 cases per 1 000 births.

International. Birth asphyxia is the cause of 23 % of all neonatal deaths worldwide. More than a million children who survive birth asphyxia develop problems such as cerebral palsy, mental retardation, learning difficulties, and other disabilities.

Age. The symptoms of moderate-to-severe birth asphyxia are almost always manifested at birth or within a few hours after.

The term **"Asphyxia"** as the diagnosis may be used directly after birth.

History: no single aspect of history diagnostic of asphyxia.

■ Fetal distress: decreased fetal heart rate variability; late decelerations; prolonged fetal bradycardia; abnormal biophysical profile; fetal scalp pH < 7.2.

■ Meconium-stained amniotic fluid.

■ Resuscitation at birth.

■ Umbilical cord pH < 7.0 & base excess > -12.

■ Apgar score < 3 at 5 min of life; ACOG defines asphyxia by constellation of findings (cord pH < 7.0, Apgar score < 3 at age 5 min, neurological findings c/w asphyxia & multiorgan system dysfunction).

Pathophysiology

The initial compensatory adjustment to an asphyxial event is an increase in CBF due to hypoxia and hypercapnia. This is accompanied by a redistribution of cardiac output to essential organs, including the brain, heart, and adrenal glands. A blood pressure (BP) increase due to increased release of epinephrine further enhances this compensatory response. See the image below.

Fetal response to asphyxia illustrating the initial redistribution of blood flow to vital organs. With prolonged asphyxial insult and failure of compensatory mechanisms, cerebral blood flow falls, leading to ischemic brain injury.

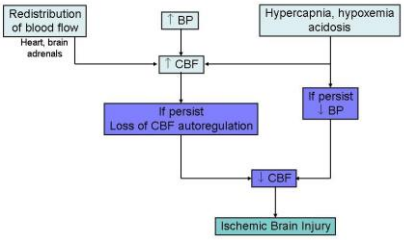


Figure 1 – Patogenesis of ischemic brain injury

In the fetus and newborn suffering from acute asphyxia, after the early compensatory adjustments fail, the CBF can become pressure-passive, at which time brain perfusion depends on systemic BP. As BP falls, CBF falls below critical levels, and the brain injury secondary to diminished blood supply and a lack of sufficient oxygen occurs. This leads to intracellular energy failure. During the early phases of brain injury, brain temperature drops, and local release of neurotransmitters, such as gamma-aminobutyric acid transaminase (GABA), increase. These changes reduce cerebral oxygen demand, transiently minimizing the impact of asphyxia.

At the cellular level, neuronal injury in asphyxia is an evolving process. The magnitude of the final neuronal damage depends on duration and severity of the initial insult combined to the effects of reperfusion injury, and apoptosis. At the biochemical level, a large cascade of events follow hypoxic-ischemic encephalopathy injury.

Excitatory amino acid (EAA) receptor over activation plays a critical role in the pathogenesis of neonatal hypoxia-ischemia. During cerebral hypoxia-ischemia, the uptake of glutamate the major excitatory neurotransmitter of the mammalian brain is impaired. This results in high synaptic levels of glutamate and EAA receptor over activation, including N-methyl-D-aspartate (NMDA), amino-3-hydroxy-5-methyl-4 isoxazole propionate (AMPA), and kainate receptors. NMDA receptors are permeable to Ca^{++} and Na^{+}, whereas AMPA and kainate receptors are permeable to Na^{+}. Accumulation of Na^{+} coupled with the failure of energy dependent enzymes such as $Na^{+/}$ K^{+} -ATPase leads to rapid cytotoxic edema and necrotic cell death. Activation of NMDA receptor leads to intracellular Ca^{++} accumulation and further pathologic cascades activation.

EAAs accumulation also contributes to increasing the pace and extent of programmed cell death through secondary Ca^{++} intake into the nucleus. The pattern of injury seen after hypoxia-ischemia demonstrate regional susceptibility that can be largely explained by the excitatory circuity at this age (putamen, thalamus, perirolandic cerebral cortex). Finally, developing oligodendroglia is uniquely susceptible to hypoxia-ischemia, specifically excitotoxicity and free radical damage. This white matter injury may be the basis for the disruption of long-term learning and memory faculties in infants with hypoxic-ischemic encephalopathy.

Intracellular Ca^{++} concentration increases following hypoxia-ischemia as a result of (1) NMDA receptor activation, (2) release of Ca^{++} from intracellular stores (mitochondria and endoplasmic reticulum [ER]), and (3) failure of Ca^{++} efflux mechanisms. Consequences of increases intracellular Ca^{++} concentration include activation of phospholipases, endonucleases, proteases, and, in select

neurons, nitric oxide synthase (NOS). Activation of phospholipase A2 leads to release of Ca^{++} from the ER via activation of phospholipase C. Activation of proteases and endonucleases results in cytoskeletal and DNA damage.

During the reperfusion period, free radical production increases due to activation of enzymes such as cyclooxygenase, xanthine oxidase, and lipoxygenase. Free radical damage is further exacerbated in the neonate because of immature antioxidant defenses. Free radicals can lead to lipid peroxidation as well as DNA and protein damage and can trigger apoptosis. Finally, free radicals can combine with nitric oxide (NO) to form peroxynitrite a highly toxic oxidant.

NMDA receptor activation results in activation of neuronal NOS vi as PSD-95 and results in the early and transient rise in NO concentration observed in the initial phase of hypoxia. Inducible NOS is expressed in response to the marked inflammation secondary to cerebral ischemia and results in a second wave of NO overproduction that can be prolonged for up to 4–7 days after the insult.

This excessive NO production plays an important role in the pathophysiology of perinatal hypoxic-ischemic brain injury. NO neurotoxicity depends in large part on rapid reaction with superoxide to form peroxynitrite. This, in turn, leads to peroxynitrite-induced neurotoxicity, including lipid peroxidation, protein nitration and oxidation, mitochondrial damage and remodeling, depletion of antioxidant reserve, and DNA damage.

Inflammatory mediators (cytokines and chemokines) have been implicated in the pathogenesis of hypoxic-ischemic encephalopathy and may represent a final common pathway of brain injury. Animal studies suggest that cytokines, particularly interleukin (IL)-1b contributes to hypoxic-ischemic damage. Exact mechanisms and which inflammatory mediators are involved in this process remain unclear.

Following the initial phase of energy failure from the asphyxial injury, cerebral metabolism may recover following

reperfusion, only to deteriorate in a secondary energy failure phase. This new phase of neuronal damage, starting at about 6–24 hours after the initial injury, is characterized by mitochondrial dysfunction, and initiation of the apoptotic cascade. This phase has been called the "delayed phase of neuronal injury."

The duration of the delayed phase is not precisely known in the human fetus and newborn but appears to increase over the first 24–48 hours and then start to resolve thereafter. In the human infant, the duration of this phase is correlated with adverse neurodevelopmental outcomes at 1 year and 4 years after insult.

Pathophysiology of hypoxic-ischemic brain injury in the developing brain. During the initial phase of energy failure, glutamate mediated excitotoxicity and Na+/K+ ATPase failure lead to necrotic cell death. After transient recovery of cerebral energy metabolism, a secondary phase of apoptotic neuronal death occurs. ROS = Reactive oxygen species.

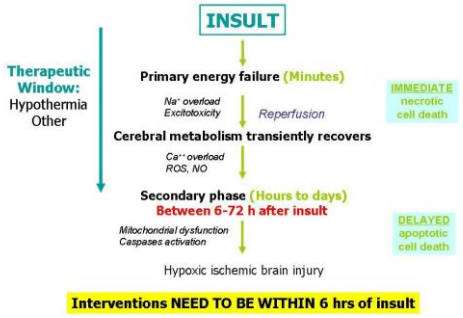


Figure 2 – Hypothermia

Additional factors that influence outcome include the nutritional status of the brain, severe intrauterine growth restriction, preexisting brain pathology or developmental defects of the brain, and the frequency and severity of seizure disorder that manifests at an early postnatal age (within hours of birth).

The scheme of the pathogenesis of asphyxia:

Lack of oxygen → Compensatory mechanisms activation → Anaerobe glycolysis → Catecholamine output → Circulation centralization → Methabolic acidosis → Concentration of the blood → Microthrombosis of the microcirculatory channel → Damage of all organs and systems with predominant damage of the brain → Decompensation →Suprarenal insufficiency Arterial hypotension → Shock.

Signs & symptoms:

■ Neurol:

➢ Birth-12 hrs: impaired consciousness (coma), hypotonia, seizures;

➢ 12–24 hrs: variable changes in level of alertness, seizures, apnea, jitteriness, weakness; preterm, lower extremity weakness; full-term, upper extremity weakness; some exhibit hemiparesis;

➢ 24–72 hrs: persistent (but lessening) stupor; disturbed sucking, swallowing, gag; weakness.

■ Renal (oliguria/anuria, proteinuria, hematuria, electrolyte, acid base disturbances: metabolic acidosis, hyponatremia, hyperkalemia, hypocalcemia).

■ Hepatic (transaminase elevation, direct hyperbilirubinemia, hypoglycemia).

■ Cardiopulm (pulmonary hypertension, hypotension, meconium aspiration syndrome).

■ Gastrointestinal (ischemic bowel injury).

■ Hematologic (thrombocytopenia, increase in nucleated RBCs, coagulopathy).

Tests

■ Neurol dysfunction:

➢ EEG; US at age 24 hours; CT scan or MRI on day 4–7 (a diffusion MRI can be abnormal < 24 hours), NMR spectroscopy (high lactate peak & decreased n-acetyl aspartate);

➢ Lumbar puncture in infants w/ seizures, lethargy or coma (to r/o other etiologies);

➢ Serum ammonia in infants w/ coma or seizures.

■ Venous or arterial blood gas for acid-base status.
■ Serum Na, K, Ca, K, BUN, creatinine.
■ Serum ALT/AST/total & direct bilirubin (liver function).
■ Bedside monitoring of serum glucose (btwn 0.5 & 2 hrs after birth, q4 h for 1st 24 hrs).
■ Platelet count (at least one determination).
■ Note: frequency of monitoring depends on degree of abnormalities detected.

Differential diagnosis:

■ Multiple organ systems injured w/asphyxia.
■ However, w/ constellation of historical features, neurological abnormalities at birth & multisystem injury, perinatal asphyxia should be strongly suspected.

Management

What to do first:

■ ABCs (airway, breathing, circulation); see "resuscitation".

General measures:

■ Fluid restriction to 60 cc/kg/day (infants w/ adequate urine output) or insensible H_2O loss + urine output (oliguric or anuric infants); avoid overhydration (unproven efficacy).
■ No K until urine output established.
■ I/V glucose (4–6mg/kg/min).
■ NPO for 48–72 hrs w/ Hx of severe acidosis.
■ Monitor fluid intake, urine output.
■ Maintain BP; perfusion (avoid systemic hypotension, hypertension).
■ Avoid marked hypercarbia or hypocarbia (optimal range 35–45 mmHg).
■ Maintain normoxemia: avoid overheating.

Specific therapy:

■ The use of systemic hypothermia has been shown to decrease the risk of neurological morbidity (see hypothermia treatment).

Hypothermia Therapy:

➢ ***Hypothermia started within 6 hrs of insult & continued for 72 hrs.***

Selective head cooling & mild systemic hypothermia (rectal temp 34–35 ^{0}C) with cool-cap.

Whole-body hypothermia (esophageal temperature 33–34 ^{0}C) w/ cooling blanket. Both safe & effective in reducing combined outcome of death or neurologic disability at 18mo

➢ Other neuroprotective strategies not proven to be effective

Extensive experimental data suggest that mild hypothermia (3–4 °C below baseline temperature) applied within a few hours (no later than 6 h) of injury is neuroprotective. The neuroprotective mechanisms are not completely understood. Possible mechanisms include (1) reduced metabolic rate and energy depletion; (2) decreased excitatory transmitter release; (3) reduced alterations in ion flux; (4) reduced apoptosis due to hypoxic-ischemic encephalopathy; and (4) reduced vascular permeability, edema, and disruptions of blood-brain barrier functions.

What is the optimal timing of initiation of hypothermia therapy?

Cooling must begin early, within 6 hours of injury. Experimental evidence strongly suggests that the earlier the better.

What is the optimal duration of hypothermia therapy?

The greater the severity of the initial injury, the longer the duration of hypothermia needed for optimal neuroprotection. The optimal duration of brain cooling in the human newborn has not been established.

What is the best method?

Two methods have been used in clinical trials: selective head cooling and whole body cooling.

In selective head cooling, a cap (CoolCap) with channels for circulating cold water is placed over the infant's head, and a pumping

device facilitates continuous circulation of cold water. Nasopharyngeal or rectal temperature is then maintained at 34–35 °C for 72 hours.

In whole body hypothermia, the infant is placed on a commercially available cooling blanket, through which circulating cold water flows, so that the desired level of hypothermia is reached quickly and maintained for 72 hours.

The relative merits and limitations of these 2 methods have not been established.

What is the optimal rewarming method?

Rewarming is a critical period. In clinical trials, rewarming was carried out gradually, over 6–8 hours.

Can the use of aEEG improve candidates selection?

Predefined subgroup analysis in the CoolCap trial suggested that head cooling had no effect in infants with the most severe aEEG changes.

The findings were beneficial only in infants with less severe aEEG changes.

Hypothermia therapy has been recommended as the standard of care since 2010 by the AHA and ILCOR: "During the postresuscitation period in greater than or equal to 36-week gestation neonates with evolving moderate or severe encephalopathy, hypothermia should be offered in the context of clearly defined protocols similar to published trials."

Hypothermia therapy should be conducted under strict protocols and reserved to regional referral centers offering comprehensive multidisciplinary care and planning to conduct long-term neurodevelopmental follow-up. Implementation requires thorough and ongoing education to avoid complications such as overcooling Ideally, all infants should be registered in national registry whenever possible.

Follow-up:

■ CT or MRI at age 6mo if initial scan indicates injury.

■ Enrollment in high-risk neonatal follow-up clinic complications and prognosis.

■ Neurol outcome in term infants depends on severity of neonatal neurological syndrome; death or sequelae (mental retardation orcerebral palsy) occur in 25–30 % of infants w/ hypoxic-ischemic encephalopathy.
■ Seizures increase risk of neurological sequelae by 2–5.
■ Longer abnormal neurological signs persist, greater the risk of sequelae.
■ EEG, brain imaging provide prognostic information.
■ Permanent dysfunction in other organ systems very unlikely.

HYPOXIC-ISCHEMIC ENCEPHALOPATHY (HIE)

Incidence 1.0–1.5 % (9 % in < 36 wks gestation, 0.5 % > 36 wks gestation).

Infants with moderate-to-severe neonatal encephalopathy, preconceptual and antepartum risk factors identified in 69 % of cases; 24 % of infants have a combination of antepartum and intrapartum risk factors, whereas only 5 % of infants has only intrapartum risk factors, 5 % has no identifiable risk factors.

History:

■ Antepartum: maternal diabetes, pregnancy-induced hyper-tension, placental insufficiency, IUGR, maternal hypotension; prematurity, fetal malformation.
■ Intrapartum: maternal bleeding (placenta previa, abruption placentae); maternal hypotension-shock; cord prolapse; dystocia; traumatic delivery, prolonged expulsive period; infection.
■ Postpartum: severe pulmonary disease; cyanotic congenital heart disease; sepsis; cardiovascular collapse.

Physical:

■ Majority of intrauterine hypoxic-ischemic insults do not exhibit overt signs or subsequent neurological injury.
■ Neurologic signs shortly after birth c/w recent intrapartum insult.
■ Spectrum of clinical manifestations from mild to severe; severity correlates w/ duration & severity of the hypoxic-ischemic insult.

■ Moderately to severely affected infants show: generalized hypotonia, paucity of spontaneous movements, depressed reflexes, cranial nerve palsies, seizures:

– onset w/in 12–24 h of birth c/w intrapartum insult;
– may be secondary to hypoglycemia;
– 5-min Apgar score ≤5, need for intubation in the delivery room & umbilical cord arterial pH ≤ 7.0 significantly associated w/ seizures.

➢Lethargy, obtundation, or coma.

Multiorgan Dysfunction

Hypoxic-ischemic injury of ≥ 1 organs in ≥ 80 % w/ HIE. Multiorgan systems involvement is a hallmark of hypoxic-ischemic encephalopathy. Organ systems involved following a hypoxic-ischemic events include the following:

Heart (73–78 %)

May present as reduced myocardial contractility, severe hypotension, passive cardiac dilatation, tricuspid regurgitation, congestive heart failure, myocardial necrosis.

Lungs (80–86 %)

Patients may have severe pulmonary hypertension requiring assisted ventilation, respiratory distress syndrome.

Renal (65–72 %)

Acute renal failure presents as oliguria and, during recovery, as high-output tubular failure, leading to significant water and electrolyte imbalances; syndrome of inappropriate antidiuretic hormone (SIADH); acute tubular or cortical necrosis.

Liver (80–85 %)

Elevated liver function test results, hyperammonemia, decreased clotting factors; elevated indirect, direct bilirubin.

GI dysfunction(80–85 %)

Poor peristalsis and delayed gastric emptying are common; necrotizing enterocolitis. Intestinal injuries may not be apparent in the first few days of life or until feeds are initiated.

Hematologic (32–54 %)

Disturbances include increased nucleated RBCs, neutropenia or neutrophilia, anemia if HIE due to hemorrhage, thrombocytopenia, disseminated intravascular coagulopathy. Severely depressed respiratory and cardiac functions and signs of brainstem compression suggest a life-threatening rupture of the vein of Galen (i. e., great cerebral vein) with a hematoma in the posterior cranial fossa.

Metabolic: lactic acidosis, hypoglycemia, hypocalcemia, hypomagnesemia, hyponatremia w/ acute renal failure, SIADH.

Neurologic Findings

Cranial nerves

Lack of reflex activity mediated by the cranial nerves can indicate brainstem dysfunction.

Full-term infants should blink and sustain eye closure in response to a sustained light stimulus. Repeated flashes of light should produce habituation (eg, attenuated blinking) after 3–4 stimuli. Virtually all full-term newborns can track a ball of red wool, and the movement of stripes of at least one eighth of an inch or bigger can elicit opticokinetic nystagmus. Objects and pictures with round contours and facial appearances also make good targets for tracking in the newborn. Tracking is possible in infants with complete destruction of the occipital cortex by virtue of a subcortical pulvinar-collicular system. Retinal hemorrhages are commonly observed in the neonate after vaginal delivery and can result in decreased pupil response. Destruction of the occipital cortex will also not affect pupillary response, because the responsible pathways leave the optic nerve and travel to the Edinger-Westphal nucleus, which sends back axons via the bilateral oculomotor nerves (consensual pupillary reflex).

Neurologic examination may be difficult in the small and frail premature infant, but weakness of the lower extremities sometimes reflects the neuropathologic substrate of periventricular leukomalacia. Over time, the patient with periventricular white-matter lesions develops spastic diplegia affecting the lower extremities more than the upper extremities.

Blinking to light starts at 26 weeks' gestational age, sustained eye closure to light is seen around 32 weeks, and 90 % of newborns track a ball of red wool by 34 weeks. Opticokinetic reflexes can be seen at 36 weeks. The pupil starts reacting to light around 30 weeks, but the light reflex is not consistently assessable until the gestational age of 32–35 weeks. Pupillary reflexes are reliably present at term. Extraocular movements can be elicited by performing the doll's-eye maneuver at 25 weeks' gestation and by performing caloric stimulation at 30 weeks' gestation.

In infants aged 32–34 weeks' gestation, suck and swallow are reasonably coordinated with breathing, but the actions are not perfected until after term.

Patients with mild HIE-NE often have mydriasis. Progression of the disease may produce miosis (even in the dark) responsive to light, and in severe cases (stage 3 of Sarnat classification), the pupils are small or midpositioned and poorly reactive to light, reflecting sympathetic or parasympathetic dysfunction.

The lack of pupillary, eye movement, corneal, gag, and cough reflexes may reflect damage to the brainstem, where the cranial-nerve nuclei are located. Decreased respiratory drive or apnea can be from lesions of the respiratory center, which overlap with vagal nuclei (ambiguous and solitaire) or medullary reticular formation. Ventilator disturbances in HIE may manifest as periodic breathing apnea (similar to Cheyne-Stokes respiration) or just decreased respiratory drive.

Differential Diagnoses

Several inborn errors of metabolism can present in the neonatal period with features of hypoxic-ischemic encephalopathy (HIE). Those include the following:

– nonketotic hyperglycinemia;
– disorders of pyruvate metabolism;
– urea cycle defects;
– zellweger syndrome;
– mitochondrial disorders.

Other diagnosis should also be included in the differential diagnosis, including the following:

– neuromuscular disorders including neonatal myopathies;
– brain tumors;
– developmental defects;
– infections;
– sulphite oxidase deficiency.

Laboratory Studies

There are no specific tests to confirm or exclude a diagnosis of HIE because the diagnosis is made based on the history, physical and neurological examinations, and laboratory evidence. Many of the tests are performed to assess the severity of brain injury and to monitor the functional status of systemic organs. As always, the results of the tests should be interpreted in conjunction with the clinical history and the findings from physical examination.

Laboratory studies should include the following:

– arterial blood gas;
– arterial lactate;
– serum electrolytes, creatinine, LFTs;
– aspartate-aminotransferase;
– brain-specific creatine kinase isoenzyme BB (CK-BB);
– hypoxanthine;
– erythropoietin beta-endorphin;
– CSF: lactate, lactate dehydrogenase; hydroxybutyrate dehydrogenase; neuron-specific enolase; fibrinogen degradation products; ascorbic acid.

Imaging Studies

– Head US: useful for intraventricular hemorrhage & peri-ventricular leukomalacia (PVL); poor for differentiating ischemic & hemorrhagic lesions, insensitive for cortical lesions, may be missed.
– CT scan; normal CT predictive of normal outcome or mild disability; generalized, diffuse hypoattenuation predictive of neonatal death & severe long-term disability; focal, multifocal, & generalized ischemic lesions; diffuse cortical injury not be apparent until several wks after insult; intraparenchymal, intraventricular, subarachnoid,

cerebellar hemorrhages; basal ganglia–thalamic lesions & selective neuronal injury more reliably visualized by MRI.

– MRI: imaging modality of choice; sensitive for focal & multifocal ischemic lesions; diffusion-weighted imaging (DWI) is the most sensitive for detecting ischemia; lesions in parasagittal zone w/mild to moderate insult; bilateral abnormalities, primarily in lateral thalami, posterior putamina, hippocampi, & perirolandic cortices, w/ severe insult; diffuse cortical abnormalities w/ even more severe insult.

In premature infants, MRI more sensitive than sonography in demonstrating PVL lesion, esp. noncystic PVL.

– Magnetic resonance spectroscopy (MRS): decreased ratio of N-acetylaspartate (NAA) to choline & elevated lactate peaks & lactate-to-NAA ratio indirect evidence of ischemia; high lactate-to-choline ratios w/ basal ganglial & thalamic
abnormalities predictive of poor neurologic outcome; increased inorganic phosphorus (31P): occurs in 1st 24–72 hrs, returns to normal over subsequent days.

– Timing of MRI & MRS changes – 1st 24 hrs: increased lactate peak; 24–72 hrs: decreased NAA-to-choline ratio & DWI signal intensity 72 hrs: increased T2-weighted signal intensity; 1–3 wks: generalized atrophy, cystic changes.

– EEG: for Dx neonatal seizures – low-voltage (5–15 μV) activity, electrocerebral inactivity (voltage, < 5 μV), & burst-suppression predictive of a poor outcome; early EEG abnormalities helpful in selecting infants for possible neuroprotective therapies.

Sarnat & Sarnat staging: to monitor & assess severity

The staging system proposed by Sarnat and Sarnat in 1976 is often useful in classifying the degree of encephalopathy. Stages I, II, and III correlate with the descriptions of mild, moderate, and severe encephalopathy described above.

Table 1 – Modified Sarnat Clinical Stages of Perinatal Hypoxic Ischemic Brain Injury

	MILD	MODERATE	SEVERE
Level of Consciousness	Alternating (hyperalert, lethargic,irritable)	Lethargic or obtunded	Stuporous
Neuromuscular Control			
Muscle tone	Normal	Hypotonia	Flaccid
Posture	Normal	Decorticate (arms flexed/legs extended)	Intermittent decerebration (arms and legs extended)
Stretch reflexes	Normal or hyperactive	Hyperactive or decreased	Absent
Segmental myoclonus	Present	Present	Absent
Complex Reflexes			
Suck	Weak	Weak or absent	Absent
Moro	Strong; low threshold	Weak; incomplete; high threshold	Absent
Oculovestibular	Normal	Overactive	Weak or absent
Tonic neck	Slight	Strong	Absent
Autonomic Function	Generalized sympathetic	Generalized parasympathetic	Both systems depressed
Pupils	Mydriasis	Miosis	Variable; often unequal; poor light reflex
Heart Rate Bronchial and Salivary Secretions	Tachycardia Sparse	Bradycardia Profuse	Variable Variable

Continuation of the table 1

GI Motility	Normal or decreased	Increased; diarrhea	Variable
Seizures	None	Common; focal or multifocal	Delayed
EEG Findings	Normal (awake)	Early: low-voltage continuous delta and theta Later: periodic pattern (awake) Seizures: focal 1-to 1-Hz spike-and-wave	Early: periodic pattern with Isopotential phases Later: totally isopotential
Duration	1–3 days Typically < 24h	2–14 days	Hours to weeks

Management

Optimal mgt is prevention by identifying & monitoring at-risk fetus.

Supportive treatment

Se "resuscitation":

– maintain normal BP, optimize cardiac output;
– correct metabolic acidosis;
– maintain serum glucose of 75–100 mg/dL;
– avoid hyperviscosity;
– seizures.

Fluid restriction (glucocorticoids & osmotic agents not recommended).

Neuroprotective treatment.

Anticonvulsants

Acute mgt:

– *Phenobarbital,* 20mg/kg, slow I/V push, if seizures continue, give another 10 mg/kg; if seizures continue, give up to 2 more doses of 5 mg/kg for total dose of 40mg/kg;
– *Phenytoin,* only after failure of response to max phenobarbital, 20mg/kg I/V over at least 30 min;
– *Lorazepam,* 0.05–0.1mg/kg slow I/V push or *Midazolam,* 0.05–0.15 mg/kg I/V over at least 5 min.

Maintenance:
– Phenobarbital, 3–5 mg/kg/day, 12–24 h after loading dose,divided q12h, IV, IM, PO, to maintain serum levels 15–40mcg/mL;
– Phenytoin, 4–8 mg/kg/day in 2 or 3 divided doses, I/V or P/O (not I/M), to maintain trough serum levels 6–15mcg/mL in 1st wks., then 10–20 mcg/mL (Note: oral absorption erratic).

Complications and prognosis

■ Most survivors of hypoxic-ischemic insults do not have major sequelae
■ Normalization of neurologic exam in 1–2 wks is a good prognostic sign
■ Overall risk:
– Death 12.5 %;
– Neurologic handicap 14 %;
– Death or neurologic handicap 25 %.
■ Risk for neurologic sequelae increased w/:
– Apgar score 0–3 at 20 min of age
– Multiorgan failure, particularly oliguria >36 h
– Severity & neurologic signs (also see Sarnat & Sarnat staging)

Mild: good prognosis

Moderate: prognosis difficult to predict (poor if >5 days); delayed arithmetic, reading, &/or spelling skills, difficulties w/attention & short-term memory in nondisabled survivors

*Severe:*high mortality (~80 %) or multiple disabilities (profound mental, spastic CP retardation, cortical blindness, or seizure disorder; hearing usually normal)

– Seizures, esp within first 12 h of insult or difficult to treat
– Abnormal MRI in 1st 24–72 h after insult
– MRS findings of:

Elevated lactate levels & elevated ratio of lactate to NAA Elevated 31P

– Severity & duration of EEG abnormalities

Normal or mildly abnormal EEG pattern w/in 1st days after insult: most likely normal outcomes.

Recovery to normal EEG background activity by day 7 assoc. w/ normal outcome.

Moderate to severely abnormal EEG patterns assoc w/abnormal outcome.

Burst-suppression or isoelectric pattern on any day & prolonged EEG depression >12 days after insult associated with poor outcome.

– Persistent abnormalities of brain stem function incompatible w/long-term survival.
– Abnormal SSEPs, VEPs & BAEPs persisting beyond 7 days of life.
– Increased cerebral blood flow on Doppler sonography w/in 1st 3 days of insult.
– Decreased cerebral resistive index on fetal Doppler sonography.
– Microcephaly at age 3 mo predictive of poor neurodevelop-mental outcome.
– Optic atrophy indicates poor visual outcome.

2. Birth Trauma

Introduction

Injuries to the infant that result from mechanical forces (i. e., compression, traction) during the birth process are categorized as birth trauma.Factors responsible for mechanical injury may coexist with hypoxic-ischemic insult; one may predispose the infant to the other.Injury may occur during labor, delivery, or during resuscitation in the delivery room.

• Incidence of birth injuries:

– 2 %: singleton vaginal deliveries in a cephalic position;

– 1.1 %: cesarean delivery.

Traumatic birth injury can result in physical and neurodevelopmental handicap in neonates.

The outcome of traumatic birth injury is related to the severity of the initial injury. All infants at risk for neurodevelopmental sequelae should be monitored closely for attainment of developmental milestones.

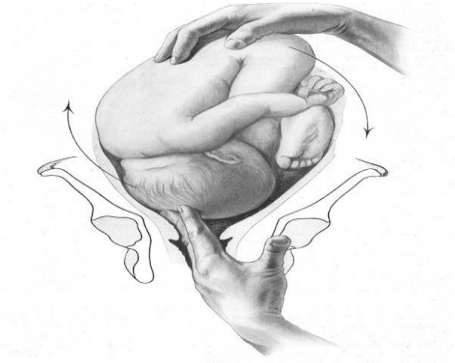


Fig. 529.

Kopflage. Wendung auf den Fuss durch kombinirte Handgriffe (nach Braxton Hicks).

45*

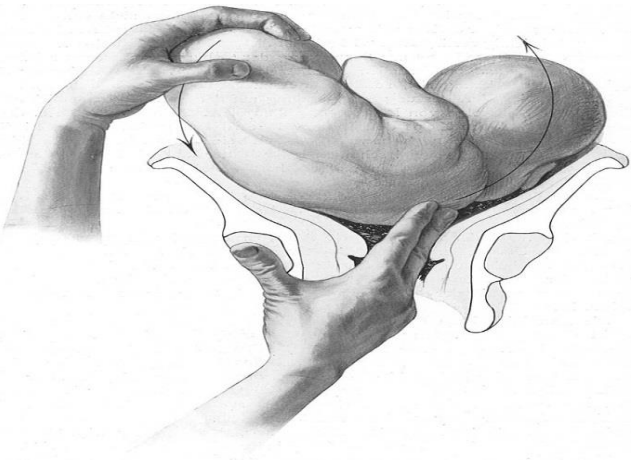


Fig. 528.
Querlage. Wendung auf den Fuss durch kombinirte Handgriffe (nach Braxton Hicks).

Fig. 369.
Dorsoposteriore Querlage mit Armvorfall.
Daumen zeigt bei nach oben gekehrter Volarfläche der Hand nach der linken Seite der Mutter, der vor-

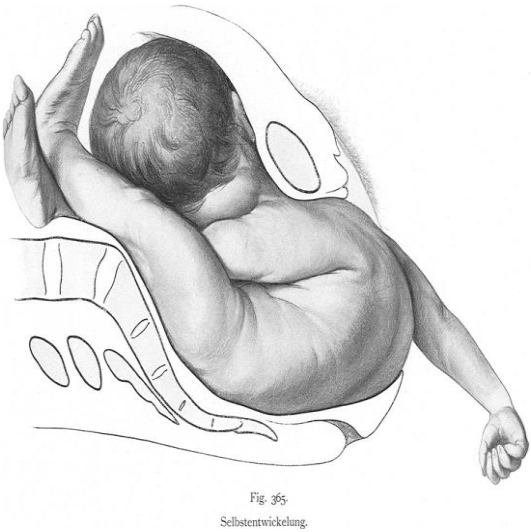


Figure 3 – Kopflage. Wending auf den Fuss durch kombinirte Handgrsffe (nach Braxton Hicka)

Predisposing Factors

1. Macrosomia:

– Fetal weight > 4000 g: increased incidence of birth injuries.

• Two-fold greater in infants weighing 4 000 to 4 900 g

• Three times greater with births weights between 4 500 to 4 999 g

• 4.5 times greater with a birth weight greater than 5 000 g.

- The incidence of birth injury was 7.7 percent in infants with birth weights greater than 4 500 g.

2. Maternal obesity:

– Maternal obesity (defined as a BMI > 40 kg/m2) is associated with an increased risk of birth injuries.

• May be due to the greater use of instrumentation during delivery

• Increase risk of shoulder dystocia (LGA infant)

3. Abnormal fetal presentation:

– Breech presentation with vaginal delivery is associated with an increased risk of birth injury.

• Cesarean delivery reduces the morbidity associated with vaginal delivery of breech infants.

4. Operative Vaginal Delivery - Predisposing Factors

Table 2 – Operative Vaginal Delivery – Predisposing Factors

Outcome	Unassisted	Forceps delivery	Vacuum delivery
Neonatal death	3.7	5.0	4.7
Birth injuries	21.4	109.1	71.6
Neonatal seizures	5.0	8.7	6.5
Assisted ventilation < 30 minutes	147	293	250

5. Other maternal factors:

– Small maternal stature.

– Maternal pelvic anomalies.

Most birth traumas are self-limited and have a favorable outcome. The prevalence of injuries in descending order is: clavicular fracture, facial nerve injury, brachial plexus injury, intracranial injury, bruising and skin lacerations.

Death from birth trauma is most likely when the brain and/or spinal cord are damaged. Such an injury is really infrequent nowadays with wide use of cesarean section.

Birth trauma is closely related to birth asphyxia because many of the conditions which predispose to birth asphyxia also directly increase the risk of trauma during delivery. Trauma also causes shock with anoxic- ischemic damage to the fetal tissues. Separating of effects of birth asphyxia from those of birth trauma is often impossible. Incidence estimated 5–8/1 000 births.

Etiology

Factors predisposing to birth injury:

– asphyxia;
– prolonged or rapid labor;
– precipitous delivery;
– abnormal fetal presentation (e. g., face, breech);
– difficult fetal extraction (e. g., w/ shoulder dystocia);
– instrumental delivery (forceps, vacuum extraction);
– nuchal cord;
– fetal size – very large (macrosomia, LGA infants) or very small;
– fetopelvic disproportion;
– fetal anomalies predisposing to injury (e. g., osteogenesis imperfecta, hepatosplenomegaly).

2.1. Extracranial and cranial lesions

Extracranial injuries occur during delivery and are due to edema or bleeding into various location within the scalp and skull.

Caput Succedaneum (Term Baby)

Figure 4 – Caput succedaneum

Edema or swelling of soft tissue over presenting part of the head. Is soft and superficial, crosses suture lines. Disappears in 48 to 72 hours. Firm, constant pressure in one spot is the easiest way to elicit

the characteristic pitting edema of caput. Related scalp injuries occur in 20 % to 40 % deliveries.

Cephalhematomas

Usually located over the parietal or occipital bone. Cephalohematoma is a subperiosteal collection of blood caused by rupture of vessels beneath the periosteum.

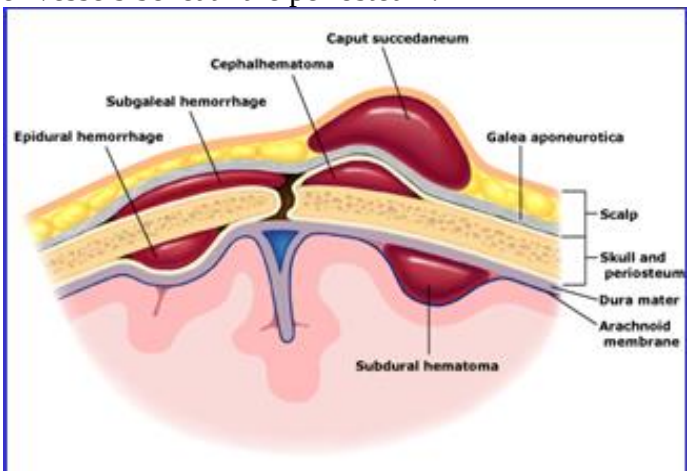


Figure 5 – Scheme of cephalohematoma and caput succedaneum

Non transilluminant, non pulsatile and non compressible swelling.

Incidence:

• 1 % to 2 % of spontaneous vaginal deliveries
• 6 % to 10 % of vacuum extractions (range 1 %–26 %)
• 4 % of forceps deliveries.

Vacuum extraction has a stronger association with cephalhematoma compared with forceps. Metal cups are more likely to cause cephalhematoma than silastic cups or the Omni cup. Vacuum extractions at mid- or low station are associated with a higher incidence (13.11 % and 13.56 %) when compared with vacuum applied at the outlet (6.81 %).

Complications:
– anemia;
– jaundice;
– infection;
– underlying skull fracture (5 % (unilateral) and 18 % (bilateral));
– leptomeningeal cyst.

Outcome:
– disappear in 2 weeks to 3 months;
– no therapy is necessary;

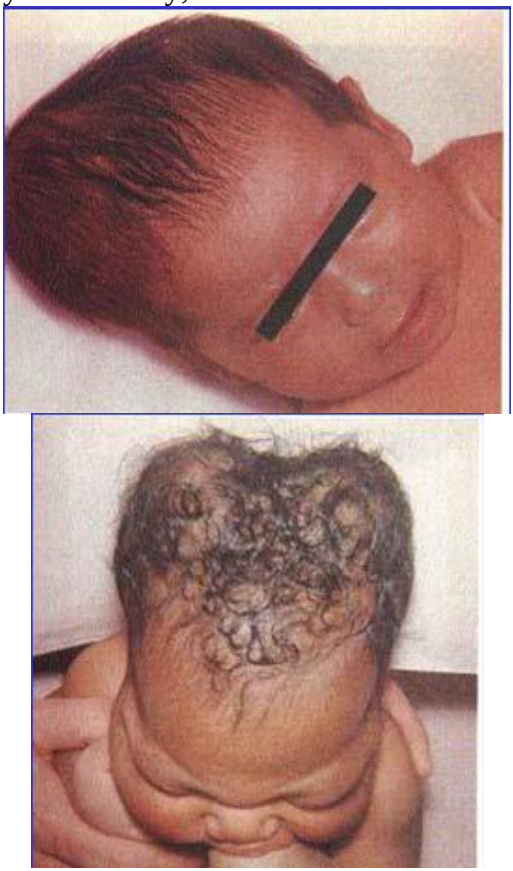


Figure 6 – Right-sided and bilateral cephalohematoma of the parietal bone

The majority of cephalohematomas will resolve spontaneously over the course of a few weeks without any intervention. Calcification of the hematoma can occur with a subsequent bony swelling that may persist for months. Significant deformities of the skull may occur when calcification or ossification of the cephalohematoma occurs.

2.2. Linear Skull Fracture

Parietal bones most commonly involved. Associated with extracranial and intracranial complications. Dural tears may result in leptomeningeal cyst. Diagnosis is made by radiography.

No therapy is indicated. Follow up skull x-ray at several months of age.

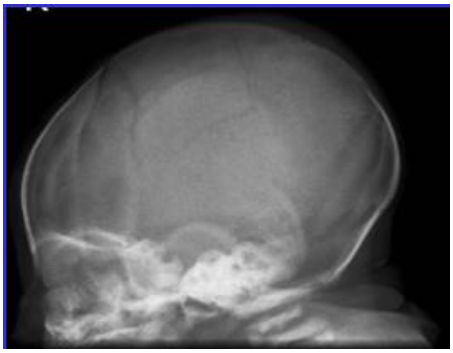
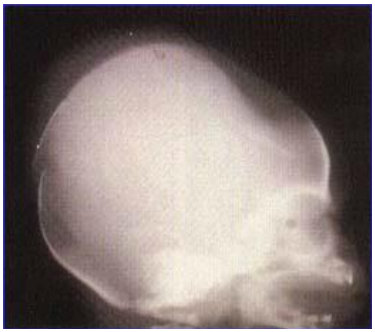


Figure 7 – Parietal bone fracture

Depressed Skull Fracture

"Ping-pong" lesion. Result of localized compression of skull. Parietal bone is the most common site. May be associated with intracranial hemorrhage.



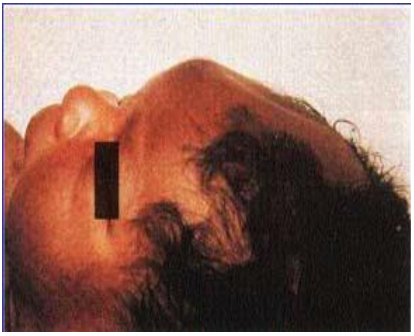


Figure 8 – "Ping-pong" lesion of the frontal bone

Radiologic assessment. Neurosurgical consultation: nonsurgical intervention or neurosurgical intervention.

Multiradiate fractures of skull bones (usually parietal bones bilaterally) – associated with significatal intracranial hemorrahage.

Occipital osteodiastasis: separation of the squamous and lateral parts of the occipital bone (these parts do not fuse until the second year of life). Lower edge of the squamous occipital bone is displaced and rotated inward thus narrowing the foramen magnum. In fatal cases the displacement causes compression of the posterior fossa without massive hemorrhage, or the dura and sinuses are torn resulting in gross subdural hemorrhage in the posterior fossa; laceration of the cerebellum with cereberall emboli within pulmonary and other vessels have been reported.

2.3. Subgaleal Hemorrhage (SGH)

Accumulation of blood beneath the scalp in subaponeurotic space. Subgaleal space extends anteriorly to the orbital margins, posteriorly to nuchal ridge and laterally to temporalis fascia. Overall incidence: 1 in 2 000 births and increases to 1 in 200 in vacuum assisted deliveries. Subgaleal hemorrhage with loss of 20 to 40 % of a neonate's blood volume (= loss of 50 to 100 mL) will result in

hypovolemic shock, DIC, multiorgan failure and neonatal death in up to 25 % of cases.

SGH Diagnosis:

• boggy swelling with ballotable fluid wave over the scalp soon after delivery;

• may cause pitting edema, discoloration of scalp and eye lids

• cardiovascular collapse in severe cases;

• every cm increase in HC = 40 ml of blood in the subaponeurotic space;

• subaponeurotic space can accommodate up to 260 ml of blood (= total blood volume).

SGH: Clinical Presentation:

Pallor, tachycardia, tachypnea, mottling, hypotonia, Delayed capillary refill, hypotension, multiorgan damage due to hypoperfusion, shock, and asphyxia.

SGH Management:

Volume resuscitation with PRBCs, FFP, and normal saline as appropriate for ongoing bleeding. Correction of coagulopathy.

Rarely surgical evacuation of the hematoma to relieve brain compression.

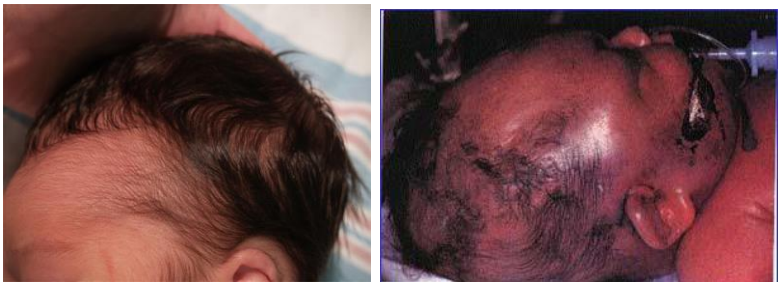


Figure 9 – Accumulation of blood beneath the scalp in subaponeurotic space

Facial Injuries

Ocular Injuries

Minor ocular trauma, such as retinal and subconjunctival hemorrhages, and lid edema, are common and resolve spontaneously without affecting the infant. Resolution of a retinal hemorrhage occurs within one to five days and a subconjunctival hemorrhage within one to two weeks.

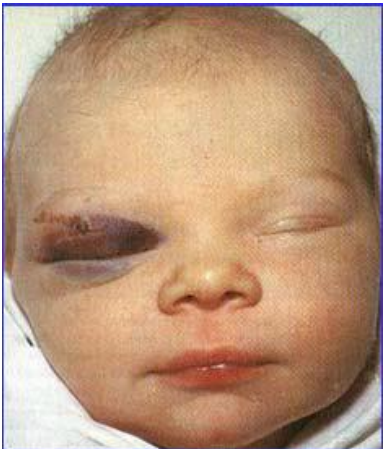


Figure 10 – Ocular injuries

Incidence: about 0.2 % of deliveries with a higher incidenceassociated with forceps-assisted delivery.

Significant ocular injuries include:

– hyphema (blood in the anterior chamber);
– vitreous hemorrhage;
– orbital fracture;
– lacrimal duct or gland injury;
– disruption of Descemet's membrane of the cornea (which can result in astigmatism and amblyopia).

Prompt ophthalmologic consultation should be obtained for patients with, or suspected to have ocular injuries.

2.4. Soft Tissue Injuries

Abrasions. Bruising. Lacerations. Petechiae. Fat Necrosis.

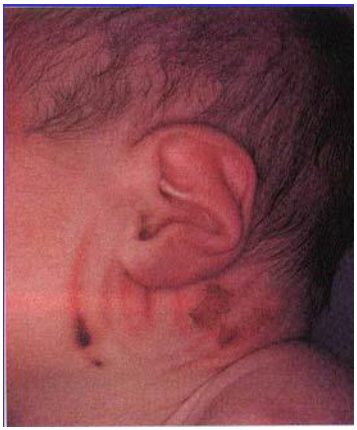


Figure 11 – Soft tissue injuries

Seen over presenting part. Associated with difficult labor and abnormal fetal presentation. Actual bleeding may be present in the soft tissue. Swelling generally disappears in 48 to 72 hrs. Development of severe hyperbilirubinemia. F/U within two days of the hospital discharge is recommended for infants with significant bruising in order to assess them for progressive jaundice.

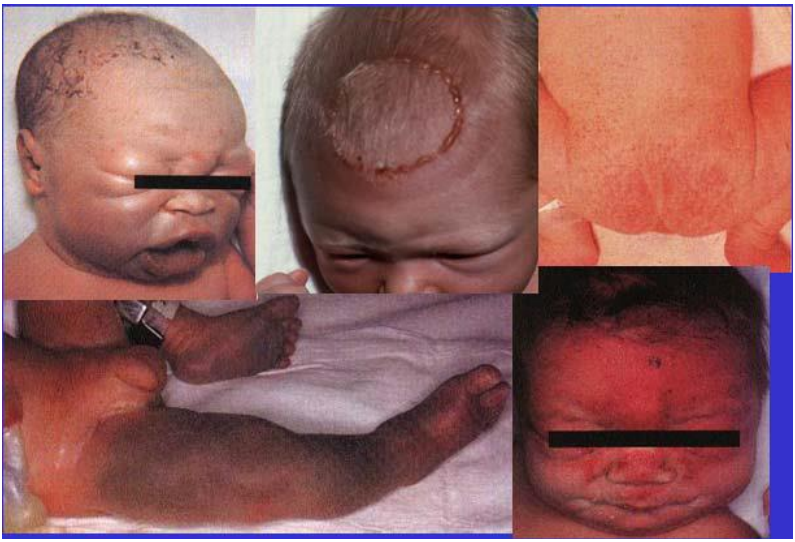


Figure 12 – Soft tissue injuries

Lacerations

Most common birth injury associated with cesarean delivery.The fetal laceration rate ~ 3 %. The lacerations occurred most often on the presenting part of the fetus, typically the scalp and face – 78 % of the lacerations took place when the cesarean delivery was performed emergently. The majority of fetal lacerations are mild, requiring repair with sterile strips only. 3 % are moderate or severe and require plastic surgery.

Caused by scalpel blade during C-section, scissors during an episiotomy, rarely by forceps. Suturing should be done under sterile conditions. Plastic surgeon should be involved in lacerations of the face.

Seen in **breech deliveries**. Resolves spontaneously. Urology opinion for severe scrotal swelling.

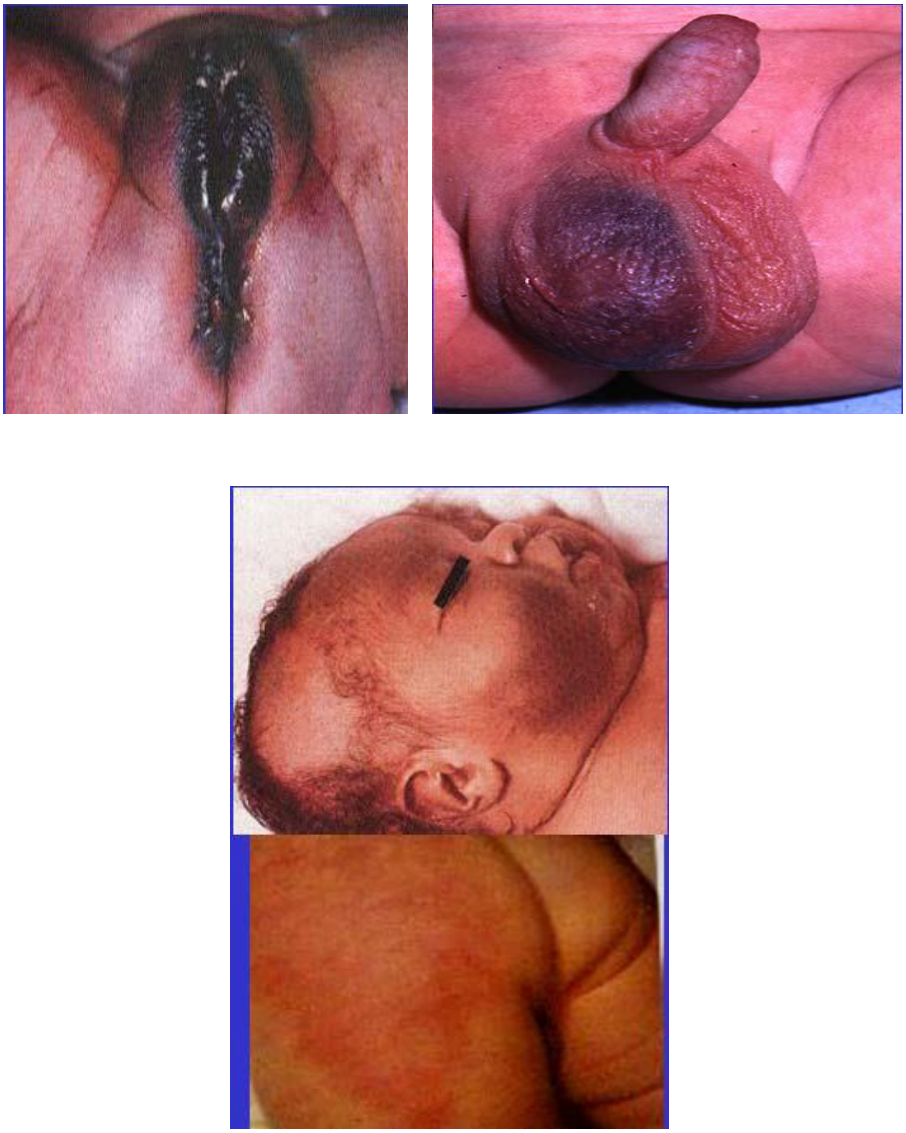


Figure 13 – Soft tissue injuries

Subcutaneous Fat Necrosis. Areas of circumscribed induration with well defined margins, firm on palpation. Commonly seen in the back and buttock, occasionally in the thigh and the cheek. Symptomatic hypercalcemia at 3–4 wks. Monitor serial calcium levels up to 6 months.

2.5. Fractured bone during birth

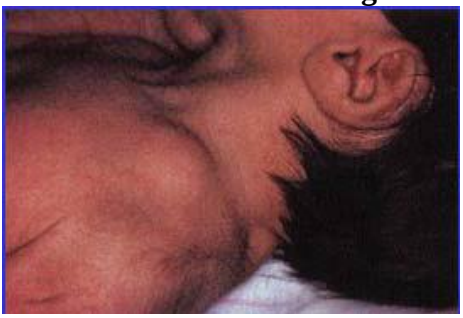


Figure 14 – Left clavicular fracture

Clavicular Fracture

Incidence: 2.7 to 5.7/1 000 live births.

Risk factors: LGA infants, shoulder dystocia, instrumental deliveries, but half w/ normal labor/delivery. Most frequently fractured bone during birth. May be assoc. w/ brachial plexus palsy. More common on right due to LOA fetal position.

Physical Exam Findings: crepitus, edema, asymmetrical bone contour; crying with passive motion, decreased arm movement, palpable bony deformity.

The timing of the presentation and diagnosis of the clavicular fracture is dependent on whether the fracture is displaced or non-displaced.

Displaced (complete) clavicular fractures: accompanied by physical findings in the immediate post delivery period.

Nondisplaced clavicular fracture: asymptomatic; diagnosis is delayed by days or weeks until there is a formation of a visible or palpable.

Diagnosis: radiography.

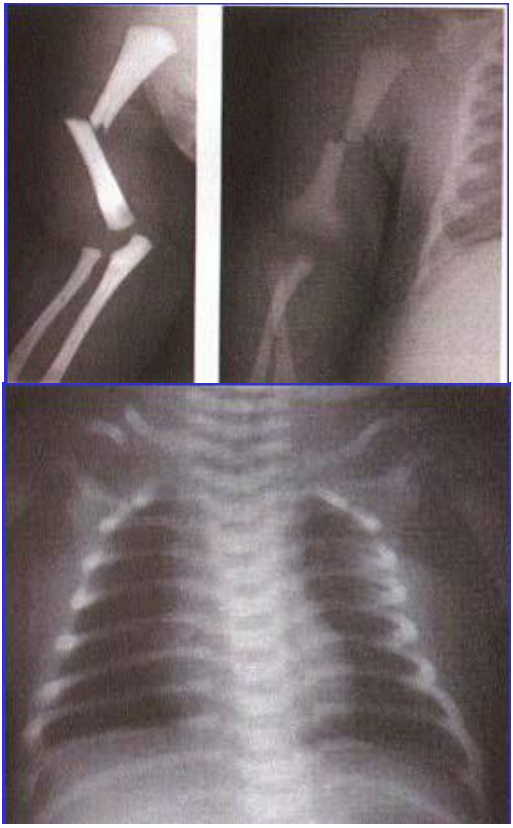


Figure 15 – Fracture of the right humerus (1)
and right clavicle (2)

Treatment: no treatment for asymptomatic incomplete fractures; immobilization of the arm for 7–10 days; parenteral reassurance, gentle handling.

Prognosis: recovery without sequelae.

Long Bone Fractures

Humeral fracture

Most commonly fractured long bone. Incidence: 0.2/1000 deliveries.

Clinical manifestations includes: decreased movement of the affected arm, decreased Moro reflex, localized swelling and crepitation, increased pain response with palpationmovement of the arm.

Evaluation for brachial plexus injury.

The diagnosis is made by a plain radiograph of the arm.

Treatment consists of immobilization of the affected arm with the elbow in 90 degrees flexion to prevent rotational deformities. Outcome is excellent with evidence of callus formation usually seen on radiography by 7 to 10 days.

Radiographs to confirm healingcan be performed at three to fourweeks post injury.

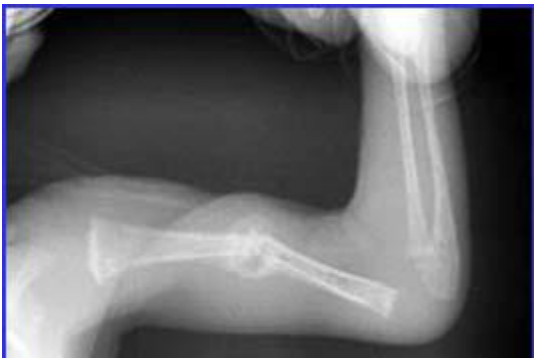


Figure 16 – Fracture of the left humerus

Femur Fracture

The Pavlik harness is used to treat neonatal femoral fractures. Outcome is excellent with evidence of callus formation usually seen on radiography by 7 to 10 days.

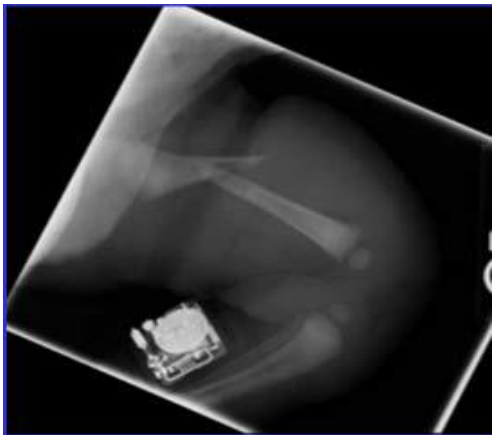


Figure 17 – Left femur fracture

Intraabdominal injuries

Intra-abdominal birth trauma is uncommon and primarily consists of rupture or subcapsular hemorrhage into the liver, spleen, and adrenal gland.

The clinical presentation depends upon the amount of blood loss. Infants with hepatic and splenic rupture may present with sudden pallor, signs of hemorrhagic shock, and abdominal distension and discoloration. Infants with subcapsular hematoma may have a delayed or more insidious onset of symptoms of anemia, which include poor feeding, tachycardia, and tachypnea.Unilateral adrenal hemorrhage may present as an abdominal mass.

US is the best modality to **diagnose** intra-abdominal birth injuries and can be performed at the bedside. CT can also provide useful diagnostic information, buttransport of a critically ill infant to the scanner is more difficult.

The **management** includes fluid resuscitation with blood products and normal saline as appropriate. FFP may be needed to correct any coagulopathy. Laparotomy for infants with hepatic or splenic rupture or if hemodynamically unstable.

2.6. Neurologic Injuries
2.7. Peripheral and cranial nerve injuries

• Facial Nerve Injury.
• Laryngeal nerve injury.
• Brachial Plexus Injury (BPI).
• Phrenic Nerve injury.
• Spinal Cord Injury.

Facial Nerve Injury. Most common neonatal traumatic nerve injury (1 % live births). 33 % of facial nerve injuries occur in spontaneous delivery (caused by pressure on the facial n). Seen after prolonged labor or forceps delivery (2.9 to 5/1 000 forceps delivery). 75 % of cases involve the left side due to higherprevalence of L transverse or L anterior occipital presentation.

Spectrum of signs: absence of nasolabial fold, loss of wrinkling of the forehead, impaired closure of the eye, slight prominence of the cheek.

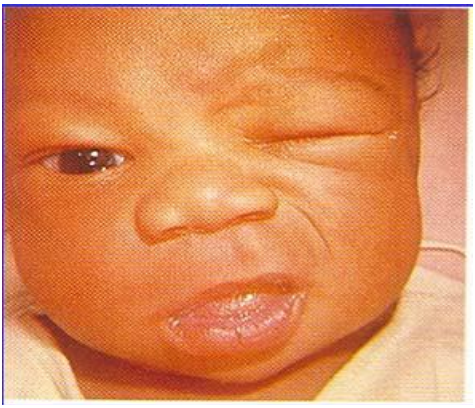


Figure 18 – Facial nerve injury

Management of Facial Nerve Injury:

• no specific therapy is indicated;
• sucking should be observed;
• eye should be protected with methylcellulose drops, eye patch if necessary;
• patient should be re-examined at around 10 days of age;
• electro diagnostic tests may be done
• usually resolves spontaneously and does not require surgery.

Laryngeal nerve injury

Disturbance of laryngeal nerve function may affect swallowing and breathing. Laryngeal nerve injury appears to result from an intrauterine posture in which the head is rotated and flexed laterally. During delivery, similar head movement, when marked, may injure the laryngeal nerve, accounting for approximately 10 % of cases of vocal cord paralysis attributed to birth trauma. The infant presents with a hoarse cry or respiratory stridor, most often caused by unilateral laryngeal nerve paralysis. Swallowing may be affected if the superior branch is involved. Bilateral paralysis may be caused by trauma to both laryngeal nerves or, more commonly, by a CNS injury such as hypoxia or hemorrhage involving the brain stem. Patients with bilateral paralysis often present with severe respiratory distress or asphyxia.

Direct laryngoscopic examination is necessary to make the diagnosis and to distinguish vocal cord paralysis from other causes of respiratory distress and stridor in the newborn. Differentiate from other rare etiologies, such as cardiovascular or CNS malformations or a mediastinal tumor.

Paralysis often resolves in 4–6 weeks, although recovery may take as long as 6–12 months in severe cases. Treatment is symptomatic. Small frequent feeds, once the neonate is stable, minimize the risk of aspiration. Infants with bilateral involvement may require gavage feeding and tracheotomy.

Brachial Plexus Injury (BPI)

Involves traction injury to cervical-thoracic nerve roots C5-T1.

Incidence: ranges globally from 0.2–4 % of live births. Worldwide prevalence is 1–2 %, with the higher numbers being in underdeveloped countries (in the US, the prevalence is approximately 0.2 %). Bilateral in 8 to 23 % of cases.

Breech or abnormal cephalic presentation (56 % of brachial plexus injuries).

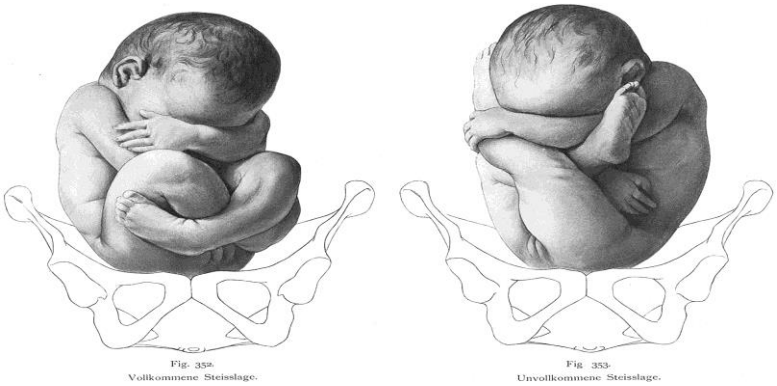


Figure 19 – Breech presentation

Lateral Neck Traction Injury:

BPI in babies may also be a result of abnormal growth through restricted limbs duringgestation. Trauma prior to, or during delivery. Amniotic bands.

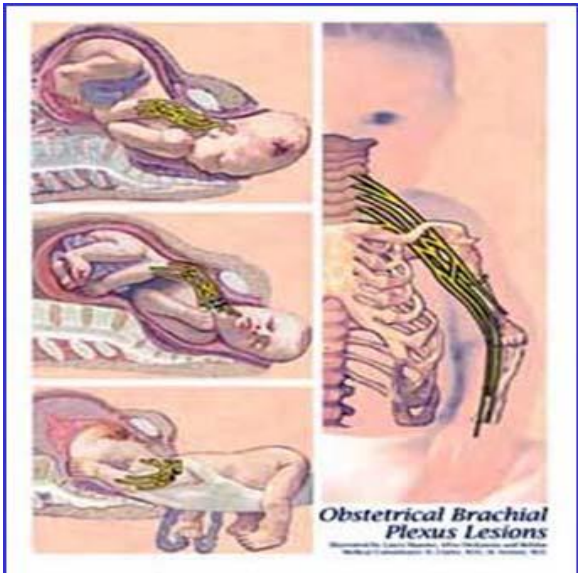


Figure 20 – Mechanism of obstetric brachial plexus injuries
Shoulder dystocia (50 % of brachial plexus injuries)

Oxytocin during labor (50 % of brachial plexus injuries).

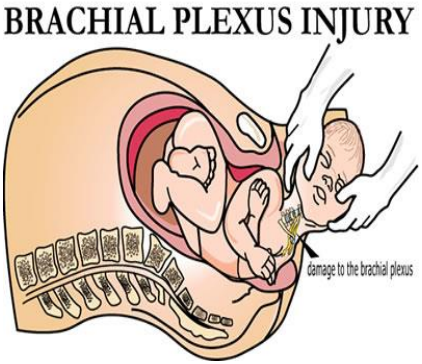


Figure 21 – Mechanism of obstetric brachial plexus injuries

Large fetal size (> 3,500 g in 50–75 % of brachial plexus injuries), low Apgar score (< 4 at 1 min in 39 % of brachial plexus injuries).

Typical pattern: progressive, downward involvement; cephalic to caudal. Weak, hypotonic, hyperextended upper extremity; asymmetric Moro reflex.

Injuries may involve the upper brachial plexus (C5 to C7): affects muscles around the shoulder and elbow; lower plexus (C8 to T1): primarily affects muscles of the forearm and hand; entire brachial plexus: Affects entire upper extremity and often sympathetic fibers of T1. The site and type of nerve root injury determine the prognosis.

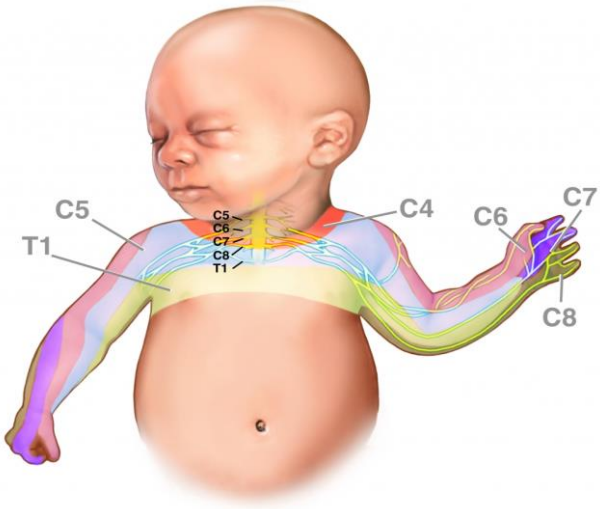


Figure 22 – Topical brachial plexus injuries

Table 3 – Brachial Plexus Injury

	Erb's	Klumpke's	Total
Incidence	90 %	1 %	10 %
Nerve roots	Proximal or Duchenne-Erb's paralysis – injury to C5 and C6 (50 %) Intermediate paralysis – injury to C5–C7 (Erb's plus) (35 %)	Distal or Klumpke's – injury to C8 and T1	C5 to T1
PE finding	Asymmetric Moro Grasp present (C5–C6) Biceps absent	Asymmetric Moro Grasp absent Biceps present Horner's syndrome	Reflexes absent
Arm position	"waiter's tip"	Extended	Flaccid

Erb's palsy: C5, C6, C7; shoulder internally rotated; elbow extended; wrist flexed; hand pronated.

Erb-Klumpke's palsy: C5–T1; Erb's palsy findings + weak hand movement; absent grasp.

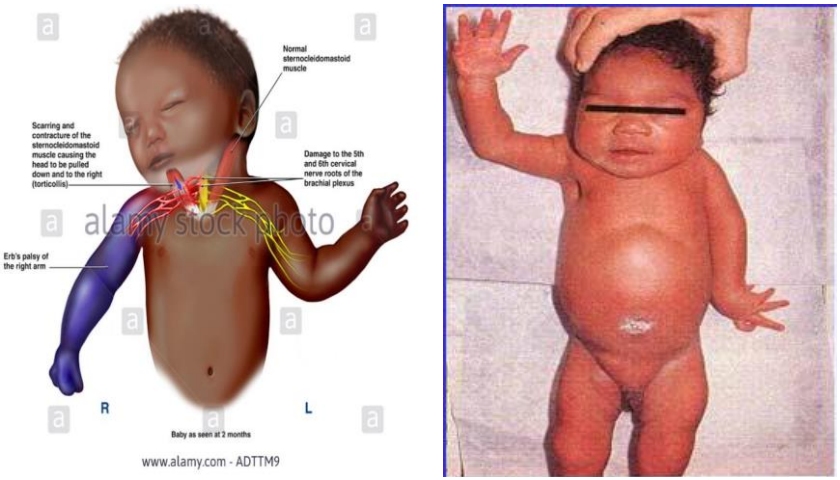


Figure 23 – Erb's palsy and Erb-Klumpke's palsy

Diagnosis:

- meticulous neorologic exam;
- radiographs of cervical spine, clavicles, and humerus;
- fluoroscopy;
- real-time ultrasound scanning;
- electromyographic studies 2 to 3 wks after injury.

Associated lesions:

– fracture of the clavicle, humerus and shoulder dislocation;

– injury to the Phrenic n.: respiratory distress, diaphragmatic palsy (involves C4, C5), asymmetric chest motion, paradoxical breathing pattern;

– injury to the nerve root T1: Horner's syndrome (30 % in Klumpke's palsy) – miosis, ptosis, anhydrosis on affected side.

Figure 24 – Horner's syndrome

Management. Arm should be held in a position of rest; passive exercises after first week; regular F/U until full recovery; if the paralysis persists without improvement for 3–6 months: neuroplasty, neurolysis, end-to-end anastomosis, nerve grafting.

Prognosis. Full recovery: 75–90 % of the cases; permanent impairment: 3–25 % of the cases. Poor prognosis: coexisting Horner's syndrome and diaphragmatic paralysis. Recovery in the first few weeks is a good indicator of final outcome.

Complete recovery is unlikely if no improvement is noted in the first 2 wks of life.

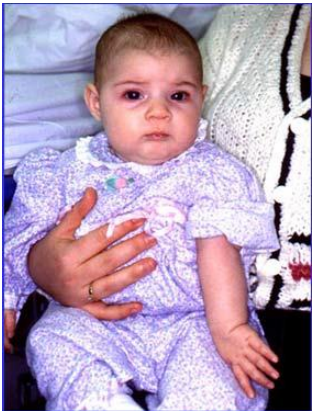


Figure 25 – Erb's paralysis

Phrenic Nerve Paralysis

75 % of cases have associated BPI. Cervical roots involved: C3 to C5. Clinical signs: respiratory distress, diminished breath sounds on affected side.

Symptoms: first day of life.

Diagnosis: chest fluoroscopy, ultrasound.

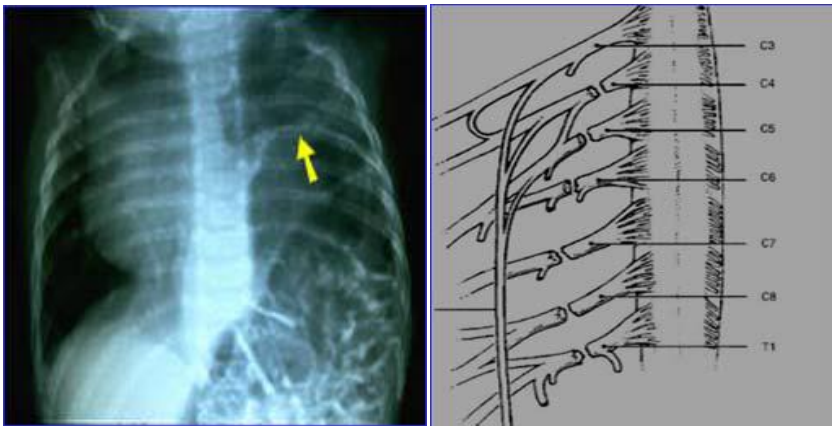


Figure 26 – Phrenic nerve paralysis

Management. Nonsurgical – continuous positive airway pressure, electrical pacing. Surgical plication. Prognosis: 10 to 20 % mortality.

Spinal Cord Injury

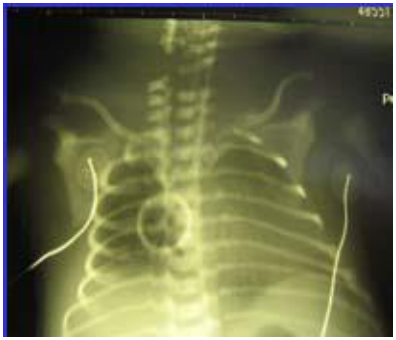


Figure 27 – Spinal cord injury

Incidence: 14 per 10 000 live births. Upper cervical cord injuries are more common and are associated with forceps rotation during vertex delivery.

Lower cervical and thoracic lesions usually occur during vaginal breech delivery, when the head is hyperextended or trapped. Can occur following C-section delivery.

Clinical Findings:

– decreased or absent spontaneous movements;

– absent deep tendon reflexes;

– absent or periodic breathing;

– lack of response to painful stimuli below the lesion;

– abdominal distension, bladder distension, loss of anal sphincter tone.

Diagnosis: X-ray, ultrasonography, MRI.

Management: head, neck, spine immobilization; supportive care, solumedrol; surgical.

Prognosis: in general, poor.

2.8. INTRACRANIAL BIRTH TRAUMA. INTRACRANIAL HEMORRHAGE

The majority of neonates with intracranial hemorrhage have no clinical symptoms, including some with moderate to severe hemorrhages. Neonates, who are clinically symptomatic may present with any of a number of neurologic symptoms, singly or in combination, including decreased level of consciousness, generalized hypotonia, and seizures. However, these manifestations are not specific to intracranial hemorrhage.

An intracranial hemorrhage is the pathologic accumulation of blood within the cranial vault. This condition can be categorized according to the site of origin of the hemorrhage (in some cases, intracranial hemorrhage may involve multiple compartments), as follows:

– subependymal hemorrhage;

– epidural hemorrhage indicates blood between the skull and outside of dura;

– subdural hemorrhage denotes blood between the dura and the arachnoid mater;

– subarachnoid hemorrhage refers to blood between the arachnoid and the pia mater;

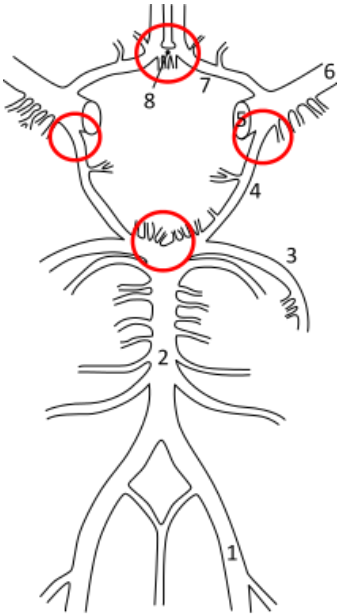
– intraventricular hemorrhage refers to blood within the ventricles;

– intraparenchymal hemorrhage refers to blood within the brain itself.

The true incidence of perinatal intracranial hemorrhage is not known. Clinical series do not identify the group of infants who do not present with clinical events, and autopsy series are biased toward infants with the worst outcomes. The larger autopsy-based studies report small subdural, subarachnoid, and intracerebral hemorrhages in 20–30 % of live births. Larger intraventricular and posterior fossa hemorrhages were less common in these studies, representing 10–15 % of live births. However, these studies represent older cohorts, and incidences have been declining.

More recent imaging-based studies show an inverse relationship between gestational age at birth and the incidence of intraventricular hemorrhage (IVH), ranging from 40–50 % of neonates at less than 26 weeks' gestation to fewer than 5 % of neonates at more than 32 weeks' gestation. A magnetic resonance imaging (MRI) study of full-term neonates found approximately a 25 % incidence of asymptomatic intracranial hemorrhage after vaginal delivery.

Symptomatic intracranial hemorrhage in full-term neonates is much less common, in the range of 4 per 10 000 live births. The incidence is higher, however, in instrumented births.



Legende

1: A. vertebrails
2: A. basilaris
3: A. cerebri posterior
4: A. communicans posterior
5: A. carotis intema
6: A. cerebri media
7: A. cerebri anterior
8: A. communicans anterior

Figure 28 – Artery diagram

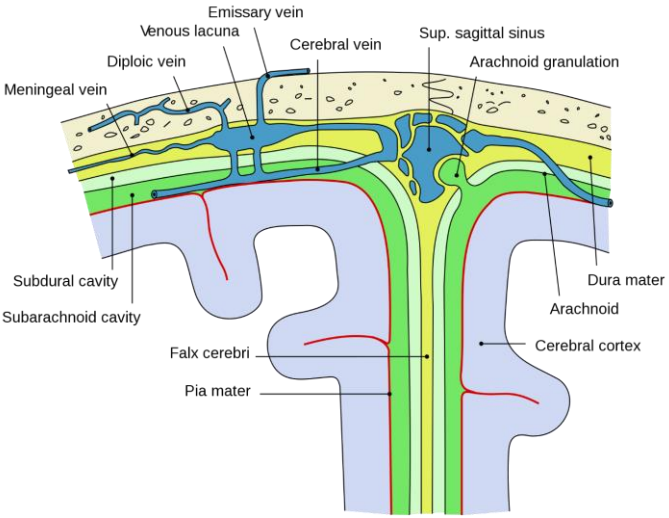


Figure 29 – Venous system diagram

History. Same general risk factors as other birth injuries; in particular: difficult, traumatic cephalic delivery; birth asphyxia; forceps delivery; premature birth, lethargy, hypotonia

Physical exam. Signs of trauma: facial bruising, forceps marks; caput succedaneum, cephalohematoma; extreme molding of skull; facial nerve palsy, asymmetric crying face. Bulging fontanels.

Altered in alertness, responsiveness, muscle tone (often dynamic, not static).

Hyper alertness may progress to coma.Hyperreflexia, clonus may progress to hypotonia.

Abnl pupillary responses, abnl eye movements, depressed suck/swallowing.

Seizures (usually multifocal). Apnea, bradycardia, obtundation, shock. Skull fractures: linear fractures: +/− molding, superficial scalp trauma, or cephalohematoma; depressed skull fracture: palpable “ping-pong ball” depression.

Tests of Brain imaging

Birth Trauma: skull fractures

– head CT or MRI useful for depressed skull fractures, subdural, subarachnoid, infratentorial hemorrhage, edema/infarction, structural malformations.

Note: in the presence of head trauma, altered or deteriorating neurol condition, CT/MR scan is the only reliable way to determine presence, location of bleed that may need immediate neurosurgical attn;

– cranial US useful to detect intraventricular hemorrhage, ventricular dilatation LP to r/o infectious etiology for abnl neurol status (defer w/ cardioresp. instability or signs of increased intracranial pressure). Acid-base status, electrolytes, Ca, Mg, glucose, NH3 to eval for metabolic etiology for abnl neurol status (note: These are screening tests, not diagnostic tests.).

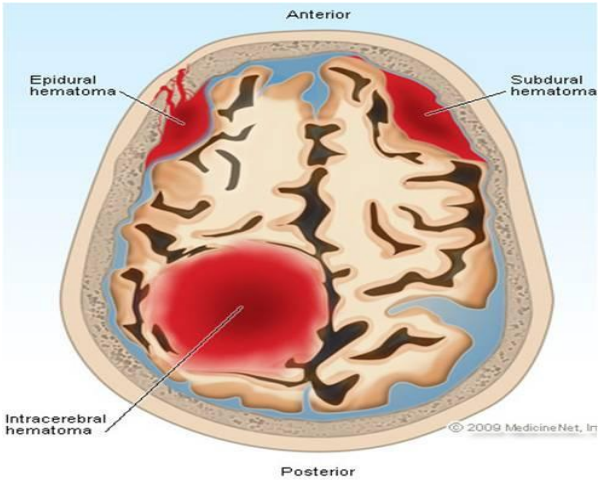


Figure 30 – Birth trauma to the head

Differential diagnosis

DDx of signs. Intracranial hemorrhage, asphyxia may coexist; signs, symptoms may overlap. Metabolic diseases (e. g., urea cycle

defects, branched-chain aminoacidopathies, cytochrome C oxidase deficiency). Sepsis/meningitis. Inherited neuromuscular disorder (e. g., congenital myasthenia or myotonic dystrophy). Drug withdrawal (e. g., from opiates, methadone).

DDx of intracranial hemorrhage.

Epidural hemorrhage:

– usually assoc. w/ linear skull fracture;

– usually silent but may cause neurol deterioration if large.

Subdural hemorrhage:

– severe cranial distortion may lacerate internal dura (tentorium, falx) & rupture adjacent venous structures (eg venous sinuses, vein of Galen, infratentorial vein);

– acute neurol deterioration w/ seizures, coma if hemorrhage large;

– posterior fossa bleeds: danger! Possible brain stem compression, rapid deterioration & death;

– subdural hemorrhage over convexity of brain may have silent or chronic presentation.

Intraventricular, periventricular, subarachnoid hemorrhage:

– VLBW infants: germinal matrix hemorrhage due to hypoxic-ischemic event:

– term infants: choroid plexus hemorrhage due to hypoxic ischemic-traumatic event.

Management. Serial brain imaging. Serial neurologic exams to detect changes in status. Cardiorespir stabilization, supportive care (mechanical ventilation, treatment of shock, electrolyte abnormalities, hypoglycemia, etc.). Anticonvulsants for seizures. Fluid restriction for CNS edema. Antibiotics for possible sepsis/meningitis.

Treat immediately but defer LP in presence of cardiorespir instability or signs of increased intracranial pressure.

Neurosurgical consultation for:

– posterior fossa hemorrhage;

– any significant subdural or epidural hemorrhage assoc w/altered/deteriorating neurologic status;

– depressed skull fracture.

Specific therapy – N/A

Follow-up. Neurodevelopmental.

Complications and prognosis. Epidural hemorrhages: good prognosis for survivors cortical injury. Subdural hemorrhages:

– large hemorrhage due to laceration of tentorium or falx – few survivors;

– smaller subtentorial hemorrhage: hydrocephalus, 15 %; major sequelae, 5–10 %;

– may evolve into chronic subdural effusion (w/ lethargy, vomiting, failure to thrive) when over convexity of brain & require drainage.

Intraventricular, periventricular hemorrhage:

– term infants: most require VP shunt for hydrocephalus; 50 % have major neural deficit; most needing VP shunt;

– preterm infants (see intraventricular hemorrhage).

Table 4 – Grading of Intracranial Hemorrhages in Full-Term Neonates

Grade	Characteristics
Mild	Only 1 compartment or 1 lobe is involved; midline shift is less than 0.5 cm; **or** intraventricular hemorrhage in only 1 ventricle without hydrocephalus
Moderate	Only 1 compartment or 1 lobe is involved with midline shift; **or** intraventricular hemorrhage of more than 1 ventricle without hydrocephalus
Severe	More than 1 lobe and more than 1 compartment is involved; **or** intraventricular hemorrhage with hydrocephalus
Source: Gupta SN, Kechli AM, Kanamalla US. Intracranial hemorrhage in term newborns: management and outcomes. Pediatr Neurol. Jan 2009;40(1):1–12	

Intracranial hemorrhages very often occur in **premature newborns** (25–40 % of all newborns weighting less then

2 000 g). They are germinal matrix hemorrhages, are classified as grade I, II, and III.

Table 5 – Radiological Appearance – Site of Hemorrhage

Grade	Radiological Appearance – Site of Hemorrhage
I	Subependymal region and/or germinal matrix
II	Subependymal hemorrhage with minimal filling (10–40 %) of lateral ventricles with no or little ventricular enlargement
III	Subependymal hemorrhage with significant filling of lateral ventricles (> 50 %) with significant ventricular enlargement
IV	Intraparenchymal haemorrhage

Grade I hemorrhages can be asymptomatic, often are diagnosed by ultrasonography.

In hard cases, hemorrhage manifests by sudden catastrophic onset of seizures, anemia and cardiovascular instability.

Epidural hemorrhage

Epidural hemorrhage is relatively rare in newborns, because the middle meningeal artery, the tearing of which is the usual cause of epidural hemorrhage, moves freely away from displacements of the skull in this age group.

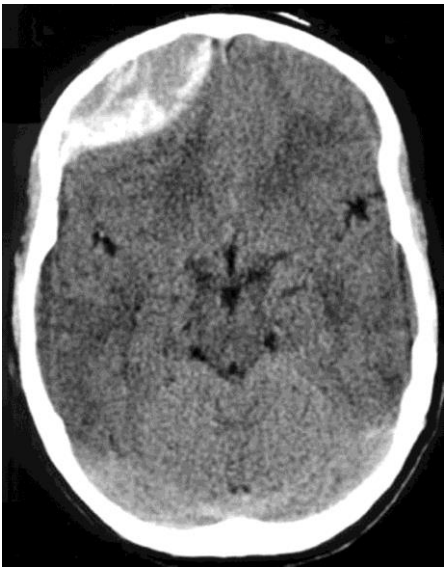


Figure 31 – Epidural hematoma

Subdural hemorrhage (SDH)

History. Traumatic delivery. Term or preterm infant w/breech delivery, face or brow presentation.

Signs. Excessive molding. Occipital diastasis w/ breech delivery. Neurologic signs vary w/ tentorial, posterior fossa or cerebral convexity & size of bleed.

– Tentorial laceration. More common in term infants. Acute neurological disturbance from birth. Decreased level of consciousness. Focal seizures. Asymmetric motor findings, hemiparesis. Deviation of eyes to side of lesion. Nuchal rigidity. Ataxic respirations, respiratory arrest as clot enlarges.

– Posterior fossa subdural. Initial signs appear from 24 hrs to 3–4 days as hematoma slowly enlarges. Signs of increased intracranial pressure: full fontanel, irritability, or lethargy, as CSF flow blocked in through the posterior fossa. **Brain stem signs**: respiratory abnormalities, oculomotor abnormalities, facial paresis; seizures.

– Cerebral convexity subdural: typically unilateral; 3 presentations: a) minimal/no clinical signs; hyper alert; b) focal cerebral disturbance at 24–48 hrs (i. e., hemiparesis, contralateral deviation of eyes, seizures); c) chronic subdural effusion over months w/ enlarging head, positive transillumination.

Tests. CBC, platelets; coagulation studies; lumbar puncture not recommended because of possibility of herniation; CT; MRI more effective in delineating posterior fossa hemorrhage; cranial US detection of subdural hemorrhage unreliable; skull radiographs to exclude fractures; subdural tap for diagnosis of cerebral convexity hemorrhage if CT unavailable.

Differential diagnosis. Other forms of intracranial bleeding: see intraventricular hemorrhage, cerebellar hemorrhage, subarachnoid hemorrhage.

Management. Close surveillance for progression of neurological symptoms in absence of major neurological signs. Treat seizures w/ anticonvulsant medication. Attn: to concomitant hypoxic ischemic cerebral injury, (see hypoxic ischemic encephalopathy). Correct coagulopathy.

Specific therapy. In severe tears of tentorium, falx, overt occipital osteodiastasis, treatment almost impossible. Surgical evacuation by subdural tap or craniotomy of convexity subdural hemorrhage, particularly if evidence of midline shift.

Follow-up. Reevaluation w/ CT or MRI required w/ changing neurological status. EEG if seizures at presentation.

Long-term: neurodevelopmental.

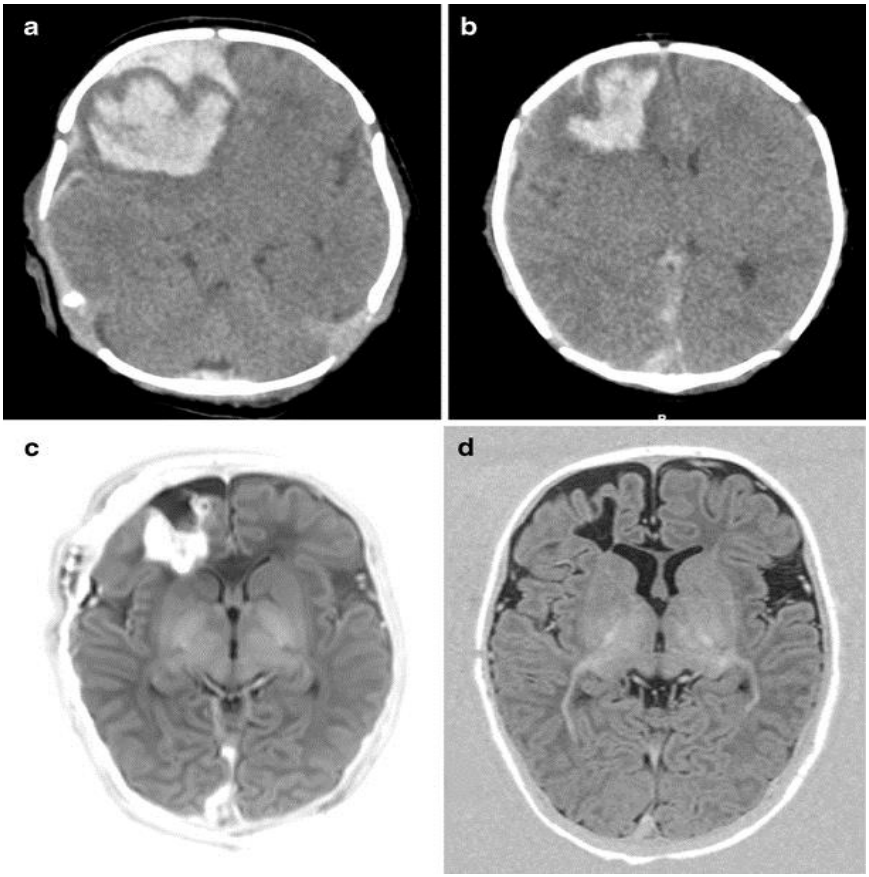


Figure 32 – Subdural hemorrhage

CT performed on day 2 (a, b), showing large intraparenchymal hemorrhage and SDH in the right frontal lobe, causing a shift in midline. MRI and IR axial view obtained on day 8 following craniotomy (c) showing resolution of the midline shift and reduction of subdural and intraparenchymal hematoma. A repeat MRI and IR axial view at 3 months (d) shows a small area of cavitation and mild atrophy of the right frontal lobe. Outcome was well within the normal range at 2 years of age.

Complications and prognosis

Poor prognosis for major lacerations of tentorium or falx: mortality rate ~40 %. Hydrocephalus frequently develops in survivors.

Lesser degrees of hemorrhage associated w/ > 50 % normal outcome.

Subarachnoid hemorrhage

History. Traumatic delivery, incl. vacuum & forceps extraction. Hypoxic-ischemic injury. Ruptured vascular lesion: arteriovenous malformation.

Signs. 3 presentations identified: a) minimal or no clinical features; b) seizures w/in 24 hrs, esp. in term; infant swell during interictal period; c) rapid neurol deterioration w/ massive subarachnoid hemorrhage.

Tests: CBC, platelets; coagulation studies; uniformly bloody CSF, elevated RBC, protein; CT: blood in superior longitudinal fissure, sulci; cranial US relatively insensitive; EEG w/ suspected seizures.

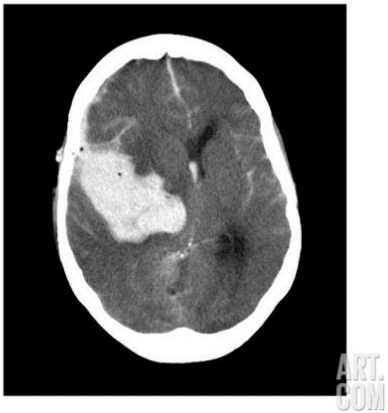


Figure 33 – Subarachnoid Haemorrhage, MRI Scan

Differential diagnosis. Other forms of intracranial hemorrhage producing abnl neurol signs: see intraventricular hemorrhage, cerebellar hemorrhage, subdural hemorrhage; CNS tumor.

Management. Treat seizures w/ anticonvulsant medication (see seizures). Correct coagulopathy prn.

Specific therapy: none.

Follow-up. Neurologic acutely.

Complications and prognosis. Subarachnoid bleeds generally of venous origin, self-limited: prognosis excellent in majority of infants – term infants w/ seizures have 90 % normal outcome. Hydrocephalus occurs rarely in severe cases secondary to adhesions at outflow of 4^{th} ventricle or over cerebral convexities. Death may follow massive subarachnoid hemorrhage.

Intraventricular hemorrhage (IVH)

Grades:

– grade I: germinal matrix hemorrhage (GMH);
– grade II: IVH ;
– grade III: IVH w/ ventricular dilatation ;
– grade IV: intraparenchymal hemorrhage (hemorrhagic infarct).

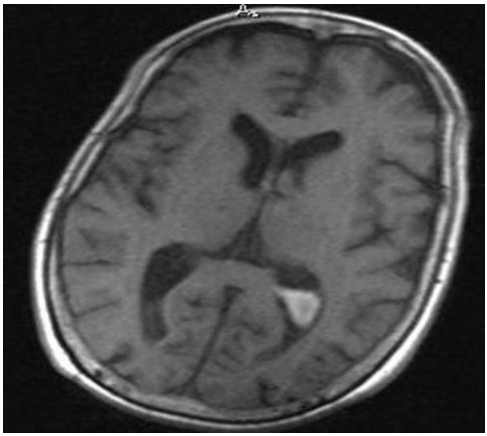


Figure 34 – Subacute intraventricular haemorrhage

History. Term infant: hypoxia-ischemia; 25 % w/o discernable pathogenesis; small minority: hemorrhagic infarction ruptured vascular lesion, tumor or coagulopathy.

Preterm infant: incidence of hemorrhage directly correlated w/ degree of prematurity; incidence of germinal matrix (GM) bleed/intraventricular hemorrhage
20–40 %; 50 % of GM/IVH originate on 1st day of life; 90 % of GM/IVH, before 4 days of life; periventricular hemorrhagic cerebral infarction in 15 %.

Signs

Term infant: seizures, focal or multifocal, 65 %; irritability, stupor; apnea, fever; full fontanel, vomiting w/ increased intracranial pressure.

Preterm infant (multiple presentations): asymptomatic, most common; neurologic deterioration over days; catastrophic presentation w/ coma, apnea, extensor posturing, brain stem dysfunction, flaccid quadriparesis.

Tests: cranial US (first US on day 4, if + repeat on day 7); CT scan; CBC; coagulation studies in term infants or w/ other excessive bleeding.

Differential diagnosis. Other types of intracranial hemorrhages (subarachnoid hemorrhage, subdural hemorrhage, cerebellar hemorrhage).

Management

Prevention: prevention of preterm delivery: prophylactic indomethacin (if prevalence of severe IVH > 10 %).

Supportive Rx: ABCs.

Specific therapy – N/A.

Follow-up.

Short-term: repeated cranial US at 1- to 2-wk intervals if hemorrhage is present on day 4 or 7 US for extension of hemorrhage, hydrocephalus.

Long-term: neurodevelopmental.

Complications and prognosis: 20–40 % of grade I/II hemorrhages extend in 1st wk of life.

Term infant:

– normal > 50 %;

– major neurologic deficit 40 %;

– hydrocephalus requiring shunting 50 %;

– mortality 5 %.

Preterm infant:

– acute increased intracranial pressure w/ major intraventricular hemorrhage;

– ventriculomegaly in 35 % of infants; may be static or spontaneously resolve in 65 %;

– post hemorrhagic hydrocephalus;

– major neurologic deficit: no increased risk w/ grades I/II, w/ grades III/IV 65–80 %.

Periventricular leukomalacia, highly predictive of CP. Mortality 10 %.

Table 6 – Grading of Germinal Matrix Hemorrhage in Preterm Neonates

Grade	Characteristics	Radiographic findings
I	Subependymal haemorrhage	Confined to germinal matrix where it originated
II	Intraventricular hemorrhage without ventricular dilatation	Hemorrhage in nondistended ventricle (blood fills < 50 % of ventricular diameter)
III	Intraventricular hemorrhage with ventricular dilatation	Lateral ventricle is distended by blood (blood fills > 50 % of ventricular diameter)
IV	Intraventricular hemorrhage with parenchymal hemorrhage	Haemorrhage into surrounding parenchyma

Parenchymal hemorrhagic

Parenchymal hemorrhagic lesions may co-exist with hemorrhage elsewhere in the cranium.

Parenchymal hemorrhage may be focal or multifocal and of any size. Multifocal small hemorrhages may be found in term infants presenting with convulsions during the first few days of life.

Thalamic hemorrhage is usually unilateral and associated with IVH. Primary

thalamic hemorrhage needs to be distinguished from the bilateral thalamic abnormalities seen in HIE. The thalamic lesions in HIE are focal, usually involving the lateral thalamic nuclei and sometimes the medial nuclei, these lesion have high signal intensity on T1-weighted images and low signal intensity on T2-weighted images due to capillary proliferation in region of infarction (not due to hemorrhage). However, infants with HIE may develop large intracranial hemorrhage.

Basal ganglia hemorrhage may occur as an isolated event in term newborn,

sometimes it is difficult to differentiate it from a hemorrhagic infarction involving a deep branch of middle cerebral artery.

Cerebellar hemorrhage may be primary, secondary to venous infarction or may complicate massive intraventricular or subarachnoid hemorrhage.

The MR appearance of parenchymal hemorrhage varies with time depending on the oxidation state of hemoglobin.

Diagnostic criterions of intracranial hemorrhages

Epidural and subdural hemorrhages:

- vomiting;
- seizures;
- breathing and cardiac arrhythmia;
- hypothermia;
- hypotonia of muscles;
- hypertension-hydrocephalus syndrome, which increases.

Subarachnoid hemorrhages:

- often apnea and secondary asphyxia;
- bradycardia;
- hypotonia of muscles, hyporephlexia;
- hyperesthesia;
- seizures;
- fixed glance;
- strained large fontanel.

Parenchymal hemorrhages:

- coma;
- severe breathing and cardiac disturbances ;
- tonic seizures, opistotonus;
- anisocoria, narrowing of ocular fissures, "swimming eye apples".

Hemorrhage into the brain

- anxiety;
- mimic muscles seizures;
- absence of unconditional reflexes.

The diagnosis of intracranial hemorrhages should be depend on: anamnestic data, clinical signs and symptoms, liquor investigation, neurosonography, ophthalmoscopy, computer tomography.

Table 7 – Differentials Apnea of Prematurity, Hypermagnesemia, Hypoglycemia, Neonatal Sepsis (more often meningitis), Periventricular Leukomalacia

Criterions	Intracranial birth injury	Meningitis
Anamnestic data	Abnormal delivery	Septic anamnesis
First signs appear	on 2–3h 1–3 days of life, continue 10–12 days	after 3 days of life up to one month
Intoxication	–	+++
Cerebral coma	develops rapidly	develops slowly
Blood count	anemia	anemia, leukocytosis, left shift of leukocyte formula
Liquor	contains erythrocytes	lymphocyte or neutrophil pleocytosis

General principles of treatment of intracranial hemorrhages

1. Guiet
2. Head fixation, craniocerebral hypothermia
3. Feeding through nasogastric tube
4. Hemostatics (fresh frozen plasma (FFP) – 10 ml/kg IV, vit K 1 % – 1 mgIM).
5. Dehydration therapy (lasix 1 % – 0.3 IV).
6. Microcirculation improvement (rheopolyglucini 10 ml/kg IV).
7. Treatment of seizures.
8. Treatment of secondary infections.
9. Correction of fluid, electrolytes, and acid-base disturbances.
10. Stabilizing and supporting the cardiovascular system.
11. Treatment of renal, gastrointestinal disturbances.
12. Symptomatic treatment.

13. For patients with progressive ventriculomegaly and hydrocephalus, ventricular drains and subsequent ventriculoperitoneal shunting are often required.

Prognosis:

– grade I and grade II hemorrhage: neurodevelopmental prognosis is excellent (i. e., perhaps slightly worse than infants of similar gestational ages without PVH-IVH);

– grade III hemorrhage without white matter disease: mortality is less than 10%. Of these patients, 30–40 % have subsequent cognitive or motor disorders;

– grade IV (severe PVH-IVH) IVH with either periventricular hemorrhagic infarction and/or periventricular leukomalacia: Mortality approaches 80 %. A 90 % incidence of severe neurological sequelae including cognitive and motor disturbances exists.

3. Premature infant

Figure 35 – Premature infant

Full-term gestation is 40 wk (range 38 to 42 wk). Infants born before 38 wk are preterm and have an increased incidence of complications and mortality roughly proportional to the degree of prematurity. Infants born < 34 wk are considered **moderate premature** and those born ≥ 34 wk and < 38 wk gestation are considered **late preterm.** Infants born < 32 wk are considered **very premature**, and those < 28 wk are considered **extremely premature**.

The rate of preterm birth was 12.8 % in 2017; 9.3 % were late preterm and 3.5 % were [premature], including 2 % who were very premature. Previously, any infant weighing < 2.5 kg was termed premature. This definition is inappropriate because many infants weighing < 2.5 kg are mature or postmature but **small for gestational age**; they have a different appearance and different problems. Infants < 2.5 kg at birth are considered **low-birth-weight infants (LBW)**, and those < 1 500 g are considered **very low-birth-weight infants (VLBW).**

Etiology

In a given patient, the specific cause of premature labor and delivery, whether preceded by premature rupture of the membranes or not, is usually unknown. There are many known maternal risk factors, which may involve

Socioeconomic factors:

low socioeconomic status;

mothers with less formal education;

unwed mothers;

cigarette smoking.

Past obstetric history:

prior premature births (previous preterm delivery due to preterm labor increases risk of future preterm deliveries; if the previous preterm neonate weighed < 1.5 kg, risk of preterm delivery in the next pregnancy is 50 %);

prior multiple pregnancies;

prior multiple therapeutic abortions and/or spontaneous miscarriages.

Current pregnancy-related factors:

pregnancy achieved by in vitro fertilization;

little or no prenatal care;

poor nutrition during gestation (and perhaps before);

untreated infections (eg, bacterial vaginosis, intra-amniotic infection [formerly chorioamnionitise]);

multiple gestation (e. g., twins, triplets);

cervical insufficiency (formerly cervical incompetence);

preeclampsia;

placental abruption.

However, most women who give birth preterm have no known risk factors.

Symptoms and Signs

The premature infant is small, usually weighing < 2.5 kg, and tends to have thin, shiny, pink skin through which the underlying veins are easily seen.

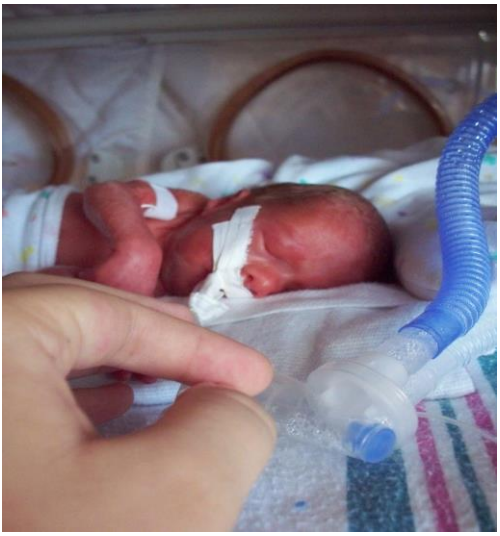


Figure 36 – Extreme prematurity

Little subcutaneous fat, hair, or external ear cartilage exists. Spontaneous activity and tone are reduced, and extremities are not held in the flexed position typical of term infants. In males, the scrotum may have few rugae, and the testes may be undescended. In females, the labia majora do not yet cover the labia minora. Reflexes develop at different times during gestation. The Moro reflex begins by 28 to 32 wks gestation and is well established by 37 wks. The palmar reflex starts at 28 wks and is well established by 32 wks. The tonic neck reflex starts at 35 wks and is most prominent at 1 mo postterm.

Complications

Most complications relate to dysfunction of immature organ systems. In some cases, complications resolve completely; in others, there is residual organ dysfunction.

Lungs

Pulmonary complications include:

respiratory distress syndrome;

bronchopulmonary dysplasia.

Surfactant production is often inadequate to prevent alveolar collapse and atelectasis, which result in **respiratory distress syndrome**. Surfactant replacement therapy is used to both prevent and treat respiratory distress syndrome. In spite of this therapy, many premature infants develop a chronic form of lung disease known as **bronchopulmonary dysplasia** with a prolonged need for ventilator therapy and supplemental O_2 therapy beyond 36 wks.

Palivizumab prophylaxis for **respiratory syncytial virus** is important for infants with chronic lung disease.

Cardiac.

The most common cardiac complication isPatent ductus arteriosus (PDA). The ductus arteriosus is more likely to fail to close after birth in premature infants. The incidence of PDA increases with increasing prematurity; PDA occurs in almost half of infants < 1 750 g birth weight and in about 80 % of those < 1 000 g. About one third to one half of infants with PDA have some degree of heart failure. Premature infants ≤ 29 wk gestation at birth who have respiratory distress syndrome have a 65 to 88 % risk of a symptomatic PDA. If infants are ≥ 30 wks gestation at birth, the ductus closes spontaneously in 98 % by the time of hospital discharge.

Central nervous system (CNS).

CNS complications include:

poor sucking and swallowing reflexes;

apneic episodes;

intraventricular hemorrhage;

developmental and/or cognitive delays.

Infants born before 34 wks gestation have inadequate coordination of sucking and swallowing reflexes and need to be fed intravenously or by gavage. Immaturity of the respiratory center in the brain stem results in apneic spells (central apnea). Apnea may also result from hypopharyngeal obstruction alone (obstructive apnea). Both may be present (mixed apnea).

The periventricular germinal matrix (a highly cellular mass of embryonic cells that lies over the caudate nucleus on the lateral wall

of the lateral ventricles of a fetus) is prone to hemorrhage, which may extend into the cerebral ventricles (intraventricular hemorrhage). Infarction of the periventricular white matter (periventricular leukomalacia) may also occur for reasons that are incompletely understood. Hypotension, inadequate or unstable brain perfusion, and BP peaks (as when fluid or colloid is given rapidly IV) may contribute to cerebral infarction or hemorrhage. Periventricular white matter injury is a major risk factor for cerebral palsy and neurodevelopmental delays.

Premature infants, particularly those with a history of sepsis, necrotizing enterocolitis, hypoxia, and intraventricular or periventricular hemorrhages, are at risk of developmental and cognitive delays. These infants require careful follow-up during the first year of life to identify auditory, visual, and neurodevelopmental delays. Careful attention must be paid to developmental milestones, muscle tone, language skills, and growth (weight, length, and head circumference). Infants with identified delays in visual skills should be referred to a pediatric ophthalmologist. Infants with auditory and neurodevelopmental delays (including increased muscle tone and abnormal protective reflexes) should be referred to early intervention programs that provide physical, occupational, and speech therapy. Infants with severe neurodevelopmental problems may need to be referred to a pediatric neurologist.

Eyes

Ocular complications include:

retinopathy of prematurity (ROP);

myopia and/or strabismus.

Retinal vascularization is not complete until near term. Preterm delivery may interfere with the normal vascularization process, resulting in abnormal vessel development and sometimes defects in vision including blindness (ROP). Incidence of ROP is inversely proportional to gestational age. Disease usually manifests between 32 wk and 34 wk gestational age.

Incidence of myopia and strabismus increases independently of ROP.

Gastrointestinal (GI) tract

GI complications include:

feeding intolerance, with increased risk of aspiration;

necrotizing enterocolitis.

Feeding intolerance is extremely common because premature infants have a small stomach, immature sucking and swallowing reflexes, and inadequate gastric and intestinal motility. These factors hinder the ability to tolerate both oral and NGT feedings and create a risk of aspiration. Feeding tolerance increases over time, particularly when infants are able to be given some enteral feedings.

Necrotizing enterocolitis usually manifests with bloody stool, feeding intolerance, and a distended, tender abdomen. Necrotizing enterocolitis is the most common surgical emergency in the premature infant. Complications of neonatal necrotizing enterocolitis include bowel perforation with pneumoperitoneum, intra-abdominal abscess formation, stricture formation, short bowel syndrome, septicemia, and death.

Infection

Infectious complications include:

sepsis;

meningitis.

Sepsis or meningitis is about 4 times more likely in the premature infant, occurring in almost 25 % of VLBW infants. The increased likelihood results from indwelling intravascular catheters and endotracheal tubes, areas of skin breakdown, and markedly reduced serum immunoglobulin levels.

Kidneys

Renal complications include:

metabolic acidosis;

growth failure.

Renal function is limited, so the concentrating and diluting limits of urine are decreased. Late **metabolic acidosis** and **growth failure** may result from the immature kidneys' inability to excrete fixed acids, which accumulate with high-protein formula feedings and as a result of bone growth. Na and HCO_3 are lost in the urine.

Metabolic problems

Metabolic complications include:

hypoglycemia;

hyperbilirubinemia;

hypoglycemia and hyperglycemia are discussed elsewhere.

Hyperbilirubinemia occurs more commonly in the premature as compared to the term infant, and kernicterus may occur at serum bilirubin levels as low as 10 mg/dL (170 μmol/L) in small, sick, premature infants. The higher bilirubin levels may be partially due to inadequately developed hepatic excretion mechanisms, including deficiencies in the uptake of bilirubin from the serum, its hepatic conjugation to bilirubin diglucuronide, and its excretion into the biliary tree. Decreased intestinal motility enables more bilirubin diglucuronide to be deconjugated within the intestinal lumen by the luminal enzyme β-glucuronidase, thus permitting increased reabsorption of unconjugated bilirubin (enterohepatic circulation of bilirubin). Conversely, early feedings increase intestinal motility and reduce bilirubin reabsorption and can thereby significantly decrease the incidence and severity of physiologic jaundice. Uncommonly, delayed clamping of the umbilical cord increases the risk of significant hyperbilirubinemia by allowing the transfusion of a large RBC mass, thus increasing RBC breakdown and bilirubin production.

Temperature regulation

The most common temperature regulation complication is **hypothermia.**

Premature infants have an exceptionally large body surface area to volume ratio. Therefore, when exposed to temperatures below the neutral thermal environment, they rapidly lose heat and have difficulty maintaining body temperature.

Diagnosis of premature newborn:

Gestational age estimated by new Ballard score.

Routine screening for metabolic, CNS, and ocular complications.

Findings on physical examination correlate with gestational age. Estimated date of delivery and prenatal ultrasonography, if done, also determine gestational age.

Initial testing:

Along with appropriate testing for any identified problems or disorders, routine evaluations include pulse oximetry, serum Ca and electrolytes, CBC, bilirubin level, blood culture, serum alkaline phosphatase and phosphorus levels (to screen for osteopenia of prematurity), hearing evaluation, cranial ultrasonography to screen for intraventricular hemorrhage and periventricular leukomalacia, and screening by an ophthalmologist for retinopathy of prematurity. Weight, length, and head circumference should be plotted on an appropriate growth chart at weekly intervals.

Subsequent screening:

If initial laboratory testing was done before the infant was taking full enteral feedings, some of the tests for metabolic disorders may be false-positive and should be repeated. In particular, positive screening tests for thyroid function and congenital adrenal hyperplasia (e. g., 17-hydroxyprogesterone) should be confirmed.

Preterm infants must be monitored for apnea and bradycardia until they are 34.5 to 35 wk adjusted age. Before discharge from the hospital, premature infants should undergo a car seat monitoring evaluation using pulse oximetry to make sure that they can maintain a patent airway and good O_2 saturation while positioned in the car seat. After discharge, premature infants should receive careful neurodevelopmental follow-up and appropriate early referral to intervention programs as needed for physical, occupational, and language therapy.

Prognosis:

Prognosis varies with presence and severity of complications, but usually mortality and likelihood of complications decrease greatly with increasing gestational age and birth weight.

Treatment

Supportive care

General supportive care of the premature infant is best provided in a neonatal ICU or special care nursery and involves careful attention to the thermal environment, using servo-controlled incubators. Scrupulous adherence is paid to handwashing before and after all patient contact. Infants are continually monitored for apnea, bradycardia, and hypoxemia until 34.5 or 35 wk gestation.

Parents should be encouraged to visit and interact with the infant as much as possible within the constraints of the infant's medical condition. Skin-to-skin contact between the infant and mother (kangaroo care) is beneficial for infant health and facilitates maternal bonding. It is feasible and safe even when infants are supported by ventilators and infusions.

Preterm infants should be transitioned to the supine sleeping position before hospital discharge. Parents should be instructed to keep cribs free of fluffy materials including blankets, quilts, pillows, and stuffed toys, which have been associated with an increased risk of SIDS.

Feeding

Feeding should be by NGT until coordination of sucking, swallowing, and breathing is established at about 34 wk gestation, **at which time breastfeeding is strongly encouraged**. Most premature infants tolerate breast milk, which provides immunologic and nutritional factors that are absent in cow's milk formulas. However, breast milk does not provide sufficient Ca, phosphorus, and protein for very low-birth-weight infants (i. e., < 1 500 g), for whom it should be mixed with a breast milk fortifier. Alternatively, specific premature infant formulas that contain 20 to 24 kcal/kg (2.8 to 3.3 joules/mL) can be used.

In the initial 1 or 2 days, if adequate fluids and calories cannot be given by mouth or NGT because of the infant's condition, IV parenteral nutrition with protein, glucose, and fats is given to prevent dehydration and undernutrition. Breast milk or preterm formula feeding via NGT can satisfactorily maintain caloric intake in

small, sick, premature infants, especially those with respiratory distress or recurrent apneic spells. Feedings are begun with small amounts (e. g., 1 to 2 mL q 3 to 6 h) to stimulate the GI tract. When tolerated, the volume and concentration of feedings are slowly increased over 7 to 10 days. In very small or critically sick infants, total parenteral hyperalimentation via a peripheral IV or a percutaneously or surgically placed central catheter may be required for a prolonged period of time until full enteral feedings can be tolerated.

Prevention

Although early and appropriate prenatal care is important overall, there is no good evidence that such care or any other interventions decrease the incidence of premature birth.

The use of tocolytics to arrest premature labor and provide time for prenatal administration of corticosteroids to hasten lung maturation is discussed elsewhere.

Key Points

There are many risk factors for premature birth but they are not present in most cases.

Complications include hypothermia, hypoglycemia, respiratory distress syndrome, apneic episodes, intraventricular hemorrhage, developmental delay, sepsis, retinopathy of prematurity, hyperbilirubinemia, necrotizing enterocolitis, and poor feeding.

Mortality and likelihood of complications decrease greatly with increasing gestational age and birth weight.

Treat disorders and support body temperature and feeding.

There is no evidence that improved prenatal care or other interventions decrease the incidence of premature birth.

Late Preterm Infant

A late preterm infant is an infant born ≥ 34 wk and < 37 wk gestation.

Full-term gestation is 40 wk (range 38 to 42 wk). Late preterm infants often appear to be the size of full-term infants but have increased morbidity due to their prematurity. Late preterm

births represent nearly three quarters of all preterm births. The rate of late preterm birth has increased in the past 2 decades from 7.2 % in 1990 to 8.3 % in 2017; many late preterm deliveries are medically indicated.

Etiology

Late preterm delivery is sometimes medically indicated (e. g., because of preeclampsia, placenta previa/placenta accreta, or premature rupture of membranes) and is often done using cesarean delivery.

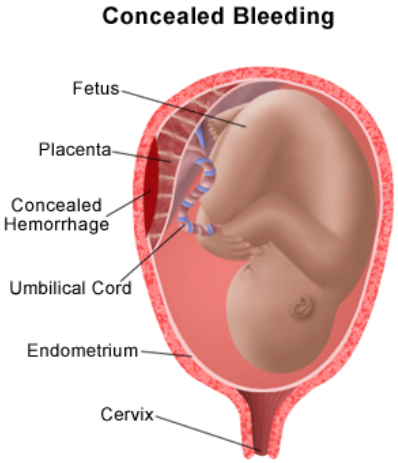


Figure 37 – Placental Abruption**:** premature separation of the placenta from the uterus during pregnancy

In a given patient, the cause of spontaneous late preterm labor and delivery is usually unknown. However, risk factors are similar to those of preterm birth in general and chronic chorioamnionitis may be associated with spontaneous late preterm deliveries.

Complications.

Although clinicians tend to focus on the more dramatic and obvious complications of premature infants born < 34 wk gestation, late preterm infants are at risk of many of the same disorders. They have longer hospital stays and higher incidence of readmission and diagnosed medical disorders than term infants. Most complications

relate to dysfunction of immature organ systems and are similar to, but typically less severe than, those of infants born more. However, some complications of prematurity (e. g., necrotizing enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia, intraventricular hemorrhage) are rare in late preterm infants. In most cases, complications resolve completely.

Complications include the following:

CNS: apneic episodes. Poor feeding due to delayed maturation of the suck and swallow mechanism (primary reason for prolonged hospital stay and/or readmission).

Hyperbilirubinemia: caused by immature mechanisms for hepatic bilirubin metabolism and/or increased intestinal reabsorption of bilirubin (e. g., if feeding difficulties cause decreased intestinal motility

Hypoglycemia: Caused by low glycogen stores.

Lungs: respiratory distress syndrome (caused by inadequate surfactant production; transient tachypnea of the newborn.

Temperature instability: Some degree of hypothermia in half of infants (caused by increased surface area to volume ratio, decreased adipose tissue, and ineffective thermogenesis from brown fat.

Diagnosis:

Gestational age estimated by new Ballard score.

Routine screening for metabolic complications.

Findings on physical examination correlate with gestational age.

Glucose monitoring is necessary for at least 24 h, particularly if regular feedings have not been well established. Routine evaluations include pulse oximetry, serum Ca and electrolytes, CBC, and bilirubin level.

Infants must be monitored for apnea and bradycardia until they are 34.5 to 35 wk adjusted age or until event free. Glucose levels are monitored for at least 24 h, particularly if regular feedings

have not been well established. Bilirubin levels are monitored clinically in the first week of life.

Prognosis

Prognosis varies with presence and severity of complications, but usually mortality and likelihood of complications decrease greatly with increasing gestational age and birth weight.

Most CNS problems resolve. Breathing control is usually mature by 37 to 38 wk gestation, and apneic events cease by 43 wk. However, some children have mild delays in development and school-related problems, so all should have neurodevelopmental follow-up and appropriate early referral to intervention programs as needed.

Lung problems usually resolve, but some infants develop pulmonary hypertension.

Treatment

Supportive care:

Identified disorders are treated. For infants without specific conditions, support focuses on body temperature and feeding.

Preterm infants can be stressed by the metabolic demands of maintaining core body temperature. Thus, they should be kept in a neutral thermal environment, which is the environmental temperature at which metabolic demands (and thus calorie expenditure) to maintain body temperature in the normal range are lowest. The neutral thermal environment has a narrow range from 36.7° C to 37.3° C.

Breastfeeding is strongly encouraged. Most late preterm infants tolerate breast milk, which provides immunologic and nutritional factors that are absent in cow's milk formulas. If infants do not suck and/or swallow adequately, feedings should be given by NGT beginning with small amounts and gradually increasing over time.

Key Points

Although late preterm infants (≥ 34 wk and < 37 wk gestation) may appear to be similar in size and appearance to term infants, they are at increased risk of complications.

Complications include hypothermia, hypoglycemia, respiratory distress syndrome, hyperbilirubinemia, and poor feeding.

Treat disorders and support body temperature and feeding.

Provide neurodevelopmental follow up to identify and address any disabilities.

Premature infants are at the same risk for developing **anemia of infancy**. This physiologic process occurs generally between the ages of 6 to 12 weeks. In addition, premature infants are at higher risk for protracted anemia, because they are born with lower body iron stores. This situation is further compounded by significant phlebotomy losses in the neonatal period related to hospitalization after birth.

Anemia of prematurity may at least partially be overcome by the use of erythropoietin, which is used to stimulate erythropoiesis. Nevertheless, it is important to replenish the body's iron stores and the provision of supplemental iron is critical until the hemoglobin levels reach normal values for age. In this respect, the iron supplementation during therapy should be at the levels used in the treatment of anemia at any other age (up to 6 mg/kg/d of elemental iron).

Premature infants are at higher **risk for infections**. This risk is multifactorial. The primary source of immunity for the neonate is passively derived antibodies from the mother and this tends to occur primarily in the third trimester. Thus, the relative amount of antibody transferred is affected by the duration of gestation. Additionally, a significant proportion of premature infants who are hospitalized in intensive care units, require interventions such as IV therapy, and placement of central vascular catheters for providing nutrition, and invasive monitoring. All of these factors contribute to the increased risk of infections in this population. Premature infants present with nonspecific signs and symptoms of infection. This mandates close monitoring for infectious complications, both during hospitalization, in the immediate neonatal period, and in subsequent months during the first year of life.

Given their propensity for infections, the American Academy of Pediatrics recommends that all childhood immunizations be administered to premature infants at the appropriate chronological age (PCA = weeks of age at birth + weeks of age since birth = 40 weeks).

Example: 25 weeks at birth + 15 weeks since birth = 40 weeks PCA. The only exception to this rule is the hepatitis B immunization, which should be initiated only after the infant's weight exceeds 2 kg. Despite lower titers of antibody response in these infants, there is no recommendation for additional doses of specific immunizations.

Passive prophylaxis for respiratory syncytial virus (RSV) infection is currently recommended during the cooler winter months for certain premature infants at highest risk for serious complications from RSV. These guidelines are evolving. The most current recommendation is published in the Red Book 2003 of the American Academy of Pediatrics. These infants will also benefit from receiving influenza immunization at 6 month chronological age during the cooler winter months.

The premature infant **is ready for discharge** when he/she is able to fulfill the following criteria: 1) ability to appropriately regulate their temperature without the need for technological support, 2) ability to ingest adequate calories to achieve consistent growth, and 3) to have demonstrated other parameters of global physiologic stability (the absence of clinically significant apnea, bradycardia, or hypoxemia). In addition, and most importantly, it is critical that the parents/caregivers feel comfortable with the care of the infant in the home environment. One of the issues that may alleviate some of the parental anxiety is training in infant CPR. Thus, the process of discharge of the infant is a continuum that begins several days to weeks prior to the actual discharge of the infant. Many of these infants will have additional needs and it is important that all of these needs and appropriate community resources are identified prior to discharge. At the time of discharge, the routine mandated screening

for hearing and metabolic diseases should be completed with the results forwarded to the primary care physician.

4. POST MATURE INFANT

A post mature infant is an infant born after 42 wks gestation.The cause of postmaturity is generally unknown, but previous post term delivery increases the risk 2- to 3-fold. Postmaturity may be caused by abnormalities that affect the fetal pituitary-adrenal axis (eg, anencephaly, adrenal gland hypoplasia, congenital adrenal hyperplasia) and by x-linked ichthyosis associated with placental sulfatase deficiency.

Pathophysiology

In most cases, continued fetal growth between 39 and 43 wk gestation results in a macrosomic infant. However, sometimes the placenta involutes, and multiple infarcts and villous degeneration cause placental insufficiency syndrome. In this syndrome, the fetus receives inadequate nutrients and O_2 from the mother, resulting in a thin (due to soft-tissue wasting), small-for-gestational-, undernourished infant with depleted glycogen stores. Post term, the amniotic fluid volume eventually decreases (oligohydramnios).

Complications

Post mature infants have higher morbidity and mortality than term infants. During labor, post mature infants are prone to develop:

asphyxia;

meconium aspiration syndrome;

hypoglycemia.

Asphyxia may result from cord compression secondary to oligohydramnios. Meconium aspiration syndrome may be unusually severe because amniotic fluid volume is decreased and thus the aspirated meconium is less dilute. Neonatal hypoglycemia is caused by insufficient glycogen stores at birth. Because anaerobic metabolism rapidly uses the remaining glycogen stores, hypoglycemia is exaggerated if perinatal asphyxia has occurred.

Symptoms and Signs

Post mature infants are alert and appear mature but have a decreased amount of soft-tissue mass, particularly subcutaneous fat. The skin may hang loosely on the extremities and is often dry and peeling. The fingernails and toenails are long. The nails and umbilical cord may be stained with meconium passed in utero.

Diagnosis

Clinical evaluation. Diagnosis is by clinical appearance and estimated date of delivery.

Treatment

Treatment of complications.

Prognosis and treatment depend on complications. Neonates with meconium aspiration may have chronic respiratory insufficiency and secondary pulmonary hypertension if untreated; surfactant replacement therapy is frequently helpful.

Large-for-Gestational-Age (LGA) Infant

Infants whose weight is > the 90^{th} percentile for gestational age are classified as large for gestational age (LGA). Macrosomia is birth weight > 4 000 g in a term infant. The predominant cause is maternal diabetes. Complications include birth trauma, hypoglycemia, hyperviscosity, and hyperbilirubinemia. The Fenton growth charts provide a more precise assessment of growth vs gestational age.

Etiology

Other than genetically determined size, maternal diabetes mellitus is the major cause of large-for-gestational-age (LGA) infants. The macrosomia results from the anabolic effects of high fetal insulin levels produced in response to excessive maternal blood glucose during gestation. The less well controlled the mother's diabetes during pregnancy, the more severe is the fetal macrosomia. Rare causes of macrosomia are Beckwith-Wiedemann syndrome (characterized by macrosomia, omphalocele, macroglossia, and hypoglycemia) and Sotos, Marshall, and Weaver syndromes.

Symptoms, Signs, and Treatment

LGA infants are large, obese, and plethoric. The 5-min Apgar score may be low. These infants may be listless and limp and feed poorly. Delivery complications can occur in any LGA infant. Congenital anomalies and some metabolic and cardiac complications are specific to LGA infants of diabetic mothers.

Delivery complications:

Because of the infant's large size, vaginal delivery may be difficult and occasionally results in birth injury, particularly including:

shoulder dystocia;
fracture of the clavicle or limbs;
perinatal asphyxia.

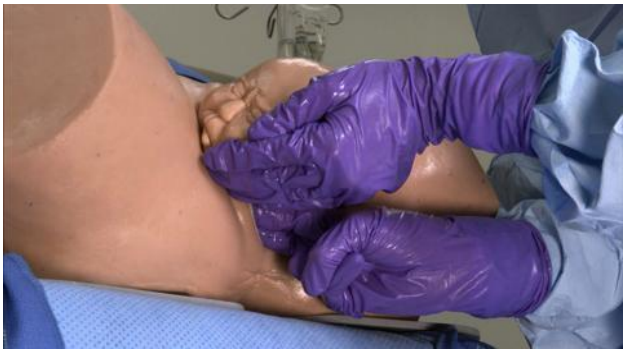


Figure 38 – How to deliver during shoulder dystocia

There fore, *operative delivery (cesarean delivery)* should be considered when the fetus is thought to be too large for the pelvis (true cephalopelvic disproportion).

Other complications occur when weight is > 4 000 g. There is a proportional increase in morbidity and mortality due to the following:

respiratory distress;
meconium aspiration;
hypoglycemia;

polycythemia.

Infants of diabetic mothers:

infants of diabetic mothers (IDMs) are at risk of:
hypoglycemia;
hypocalcemia and hypomagnesemia;
polycythemia;
hyperbilirubinemia;
respiratory distress syndrome;
certain congenital anomalies.

Hypoglycemia is very likely in the first few hours after delivery because of the state of hyperinsulinism and the sudden termination of maternal glucose when the umbilical cord is cut. Neonatal hypoglycemia can be decreased by close prenatal control of the mother's diabetes and early frequent feedings. Blood glucose levels should be closely monitored by bedside testing from birth through the first 24 h. If there is persistent hypoglycemia, parenteral IV glucose is given.

Hypocalcemia and hypomagnesemia may occur but are usually transient and asymptomatic; serum levels should be checked within the first 72 h after birth. Good prenatal glycemic control decreases the risk of neonatal hypocalcemia. Hypocalcemia typically does not require treatment unless there are clinical signs of hypocalcemia or levels < 7 mg/dL in term infants. Treatment is usually given with IV supplementation of Ca gluconate. Hypomagnesemia can interfere with the secretion of parathyroid hormone, so hypocalcemia may not respond to treatment until the Mg level is corrected.

Polycythemia is slightly more common among IDMs. Elevated insulin levels increase fetal metabolism and thus O_2 consumption. If the placenta is unable to meet the increased O_2 demand, fetal hypoxemia occurs, triggering an increase in erythropoietin and thus Hct.

Hyperbilirubinemia occurs for several reasons. IDMs have decreased tolerance for oral feedings (particularly when they are preterm) in the earliest days of life, which increases the enterohepatic

circulation of bilirubin. Also, if polycythemia is present, the bilirubin load increases.

Respiratory distress syndrome (RDS) may occur because elevated insulin levels decrease surfactant production; pulmonary maturation may thus be delayed until late in gestation. RDS may develop even if the infant is delivered late preterm or term. The lecithin/sphingomyelin ratio, and especially the presence of phosphatidyl glycerol, in amniotic fluid obtained by amniocentesis can evaluate fetal lung maturity and help determine the optimal time for safe delivery. Lung maturity can be assumed only if phosphatidyl glycerol is present. Good prenatal glycemic control decreases the risk of RDS. Treatment is discussed elsewhere. Transient tachypnea of the newborn is 2 to 3 times more likely in IDMs because of the delay in fetal lung fluid clearance.

Congenital anomalies are more likely in IDMs because maternal hyperglycemia at the time of organogenesis is detrimental. Specific anomalies include:

congenital heart disease (hypertrophic cardiomyopathy, ventricular septal defect, transposition of the great arteries, and aortic stenosis);

caudal regression syndrome;

spina bifida;

small left colon syndrome.

Persistently elevated insulin levels can also lead to increased deposition of glycogen and fat into cardiomyocytes. This deposition can cause transient hypertrophic cardiomyopathy, predominantly of the septum.

Key Points

Maternal diabetes mellitus is the major cause of LGA infants.

Large size itself increases risk of birth injury (e. g., clavicle or extremity long bone fracture) and perinatal asphyxia.

Infants of diabetic mothers (IDMs) also may have metabolic complications immediately after delivery, including hypoglycemia, hypocalcemia, and polycythemia.

IDMs are also at risk of respiratory distress syndrome and congenital anomalies.

Good control of maternal glucose levels minimizes risk of complications.

5. INTRAUTERINE GROWTH RESTRICTION (SMALL-FOR-GESTATIONAL-AGE (SGA) INFANT; DYSMATURITY)

Figure 39 – Prematurity, intrauterine fetal support (asymmetric)

Infants whose weight is < the 10th percentile for gestational age are classified as small for gestational age (SGA). Complications include perinatal asphyxia, meconium aspiration, and hypoglycemia.

The Fenton growth charts provide a more precise assessment of growth vs gestational age).

Growth Parameters in Neonates

(Length, Weight, and Head Circumference)

Growth parameters and **gestational age** help identify the risk of neonatal pathology. Growth is influenced by genetic and nutritional factors as well as intrauterine conditions. Growth parameters assessed at birth help predict subsequent growth and development and risk of disease. The parameters are length, weight, and head circumference.

By plotting weight vs gestational age, each infant is classified at birth as:

Small for gestational age: < 10^{th} percentile

Appropriate for gestational age: 10^{th} to 90^{th} percentile

Large for gestational age: > 90^{th} percentile

The Fenton growth charts provide a more precise assessment of growth vs gestational age for all three parameters.

Fenton Growth Chart for Preterm Boys

Fenton T, Kim J: A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatrics13:59, 2013; used with permission.

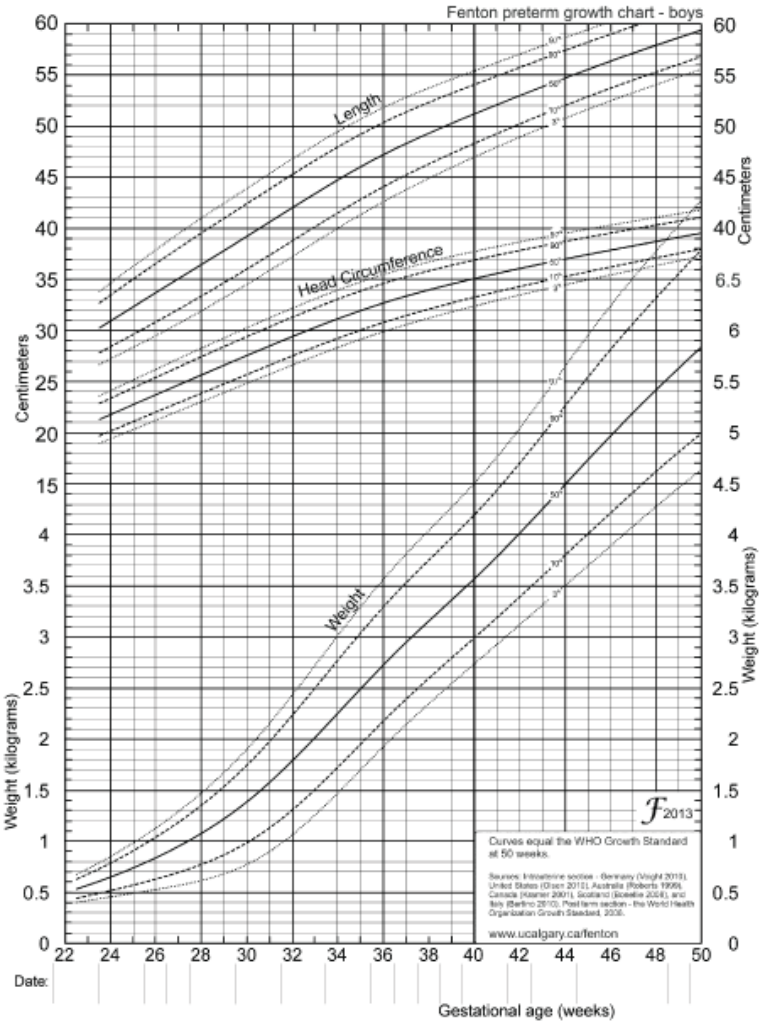


Figure 40 – Fenton growth chart for preterm boys

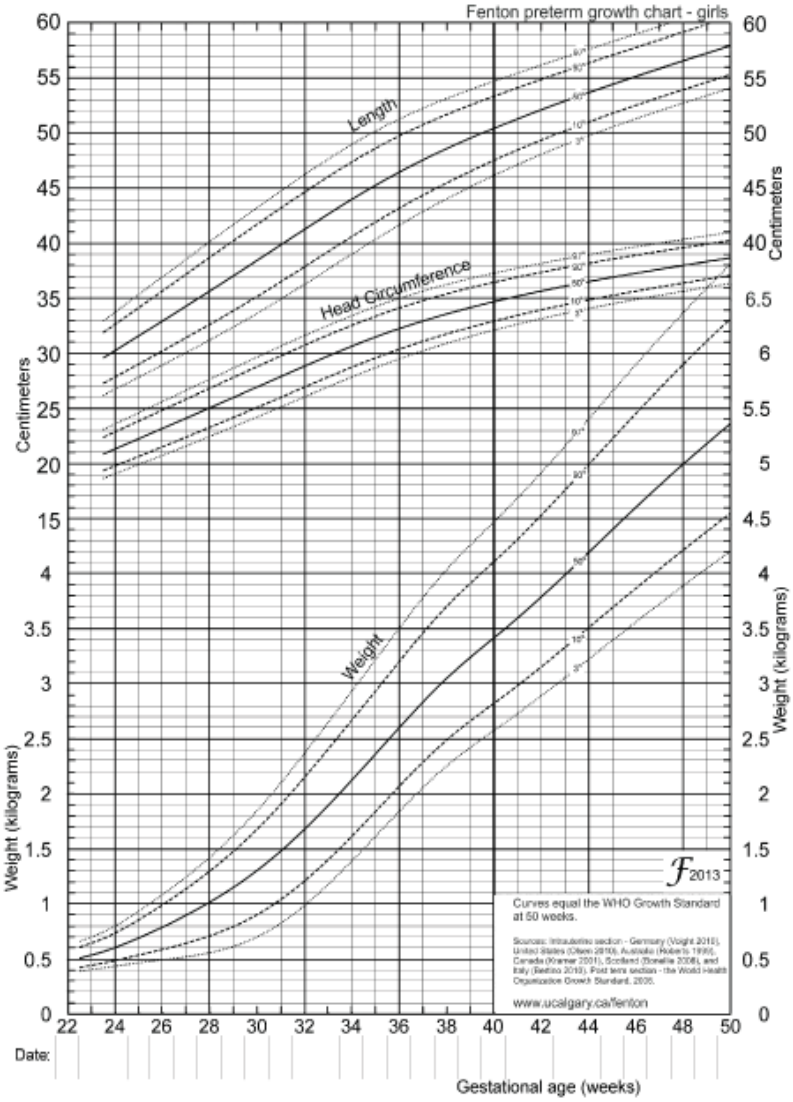


Figure 41 – Fenton growth chart for preterm girls

Etiology

Causes may be divided into those in which the growth restriction is:

Symmetric: height, weight, and head circumference are about equally affected.

Asymmetric: weight is most affected, with a relative sparing of growth of the brain, cranium, and long bones.

Symmetric growth restriction usually results from a fetal problem that begins early in gestation, often during the 1st trimester. When the cause begins relatively early in gestation, all of the body is affected, resulting in fewer cells of all types.

Common causes include:

many genetic disorders;

first-trimester congenital infections (e. g., with cytomegalovirus, rubella virus, or *Toxoplasma gondii*).

Asymmetric growth restriction usually results from placental or maternal problems that typically manifest in the late 2nd or the 3rd trimester. When the cause begins relatively late in gestation, organs and tissues are not equally affected, resulting in asymmetric growth restriction.

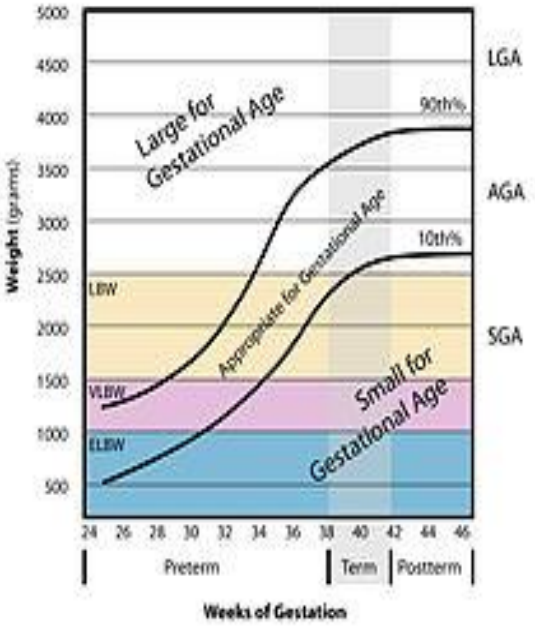


Figure 42 – Determination of gestational age

Common causes include:

Placental insufficiency resulting from maternal disease involving the small blood vessels (e. g., preeclampsia, hypertension in Pregnancy), renal disease, antiphospholipid antibody syndrome, long-standing diabetes

Relative placental insufficiency caused by multiple gestation.

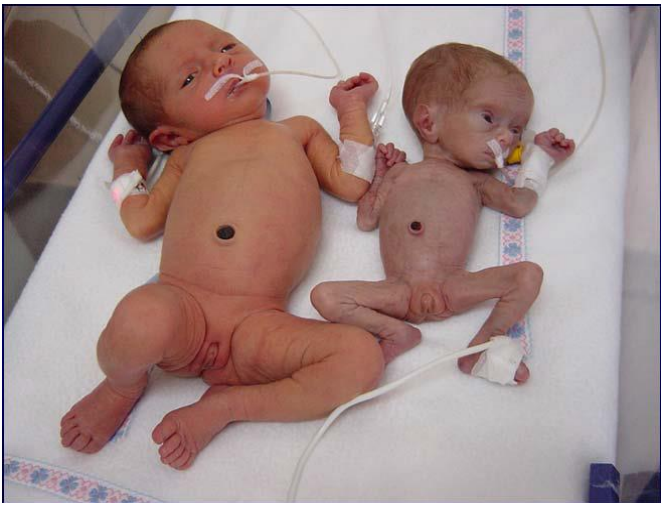


Figure 43 – Twins

Placental involution accompanying postmaturity

Chronic maternal hypoxemia caused by pulmonary or cardiac disease

Maternal malnutrition

Conception using assisted reproductive technology.

An infant may also have asymmetric growth restriction and be small for gestational age (SGA) if the mother is a heavy user of opioids, cocaine, alcohol, and/or tobacco during pregnancy.

Symptoms and Signs

Despite their size, SGA infants have physical characteristics (e. g., skin appearance, ear cartilage, sole creases) and behavior (e. g., alertness, spontaneous activity, zest for feeding) similar to those of normal-sized infants of like gestational age. However, they may appear thin with decreased muscle mass and subcutaneous fat tissue. Facial features may appear sunken, resembling those of an elderly person (“wizened facies”). The umbilical cord can appear thin and small.

Complications

Full-term SGA infants do not have the complications related to organ system immaturity that premature infants of similar size have. They are, however, at risk of:

perinatal asphyxia;

meconium aspiration;

hypoglycemia;

hypothermia.

Perinatal asphyxia during labor is the most serious potential complication. It is a risk if intrauterine growth restriction is caused by placental insufficiency (with marginally adequate placental perfusion) because each uterine contraction slows or stops maternal placental perfusion by compressing the spiral arteries. Therefore, when placental insufficiency is suspected, the fetus should be assessed before labor and the fetal heart rate should be monitored during labor. If fetal compromise is detected, rapid delivery, often by cesarean delivery, is indicated.

Meconium aspiration may occur during perinatal asphyxia. SGA infants, especially those who are postmature, may pass meconium into the amniotic sac and begin deep gasping movements. The consequent aspiration is likely to result in meconium aspiration syndrome (often most severe in growth-restricted or postmature infants, because the meconium is contained in a smaller volume of amniotic fluid and thus more concentrated).

Hypoglycemia often occurs in the early hours and days of life because of a lack of adequate glycogen synthesis and thus decreased glycogen stores and must be treated quickly with IV glucose.

Polycythemia may occur when SGA fetuses experience chronic mild hypoxia caused by placental insufficiency. Erythropoietin release is increased, leading to an increased rate of erythrocyte production. The neonate with polycythemia at birth appears ruddy and may be tachypneic or lethargic.

Hypothermia may occur because of impaired thermoregulation, which involves multiple factors including

increased heat loss due to the decrease in subcutaneous fat, decreased heat production due to intrauterine stress and depletion of nutrient stores, and increased surface to volume ratio due to small size. SGA infants should be in a thermoneutral environment to minimize O_2 consumption.

Prognosis

If asphyxia can be avoided, neurologic prognosis for term SGA infants is quite good. However, later in life there is probably increased risk of ischemic heart disease, hypertension, and stroke, which are thought to be caused by abnormal vascular development.

Infants who are SGA because of genetic factors, congenital infection, or maternal drug use often have a worse prognosis, depending on the specific diagnosis. If intrauterine growth restriction is caused by chronic placental insufficiency, adequate nutrition may allow SGA infants to demonstrate remarkable "catch-up" growth after delivery.

Treatment

Supportive care.

Underlying conditions and complications are treated. There is no specific intervention for the SGA state, but prevention is aided by prenatal advice on the importance of avoiding alcohol, tobacco, and illicit drugs.

Key Points

Infants whose weight is < the 10^{th} percentile for gestational age are small for gestational age (SGA).

Disorders early in gestation cause symmetric growth restriction, in which height, weight, and head circumference are about equally affected.

Disorders late in gestation cause asymmetric growth restriction, in which weight is most affected, with relatively normal growth of the brain, cranium, and long bones.

Although small, SGA infants do not have the complications related to organ system immaturity that premature infants of similar size have.

Complications are mainly those of the underlying cause but generally also include perinatal asphyxia, meconium aspiration, hypoglycemia, polycythemia, and hypothermia.

6. RESPIRATORY DISORDERS

Respiratory disorders are the most frequent cause of admission for neonatal intensive care in both term and preterm infants. Signs and symptoms include cyanosis, grunting, nasal flaring, retractions, tachypnea, decreased breath sounds with rales and/or rhonchi, pallor, and apnea.

A wide variety of pathologic lesions may be responsible for respiratory disturbances, including hyaline membrane disease (HMD; respiratory distress syndrome [RDS]), aspiration (meconium or amniotic fluid) syndrome, pneumonia, sepsis, congenital heart disease, heart failure, pulmonary hypertension, choanal atresia, hypoglycemia, hypoplasia of the mandible with posterior displacement of the tongue, macroglossia, malformation of the epiglottis, malformation or injury of the larynx, cysts or neoplasms of the larynx or chest, pneumothorax, lobar emphysema, pulmonary sequestration, cystic adenomatoid malformations, pulmonary agenesis or hypoplasia, congenital pulmonary lymphangiectasis, tracheoesophageal fistula, avulsion of the phrenic nerve, hernia or eventration of the diaphragm, intracranial lesions, neuromuscular disorders, and metabolic disturbances.

It is occasionally difficult to distinguish respiratory from cardiovascular causes or sepsis on the basis of clinical signs alone. Any sign of postnatal respiratory distress is an indication for immediate examination and diagnostic evaluation, including a blood gas or pulse oximetry determination and x-ray of the chest. Timely and appropriate therapy is essential to prevent ongoing injury and improve outcome. As a result of important advances in understanding the pathophysiology of respiratory disease, neonatal and infant deaths from early respiratory disease have declined markedly. The challenge is not only to continue to improve survival,

but also to reduce short- and long-term complications related to early lung disease.

Breathing patterns in newborns

During sleep in the 1st months of life, normal full-term infants may have infrequent episodes when regular breathing is interrupted by short pauses. This periodic breathing pattern, which shifts from a regular rhythmicity to cyclic brief episodes of intermittent apnea, is more common in premature infants, who may have apneic pauses of 5–10 sec followed by a burst of rapid respirations at a rate of 50–60/min for 10–15 sec. They rarely have an associated change in color or heart rate, and it often stops without apparent reason. Intermittent periodic breathing persists beyond 36 wks postconceptional age (PCA; gestational age at birth plus postnatal age) in the premature infant. The duration of periodic breathing, however, decreases between 33 and 35 wk PCA. If an infant is hypoxic, an increase in inspired oxygen concentration often converts periodic to regular breathing. Periodic breathing, a normal characteristic of neonatal respiration, has no prognostic significance.

Respiratory Distress Syndrome (Hyaline Membrane Disease)

Incidence

Infant respiratory distress syndrome (IRDS), also called neonatal respiratory distress syndrome (NRDS), respiratory distress syndrome of newborn, or increasingly surfactant deficiency disorder (SDD), and previously called hyaline membrane disease (HMD), is a syndrome in premature infants caused by developmental insufficiency of pulmonary surfactant production and structural immaturity in the lungs. It can also be a consequence of neonatal infection. It can also result from a genetic problem with the production of surfactant associated proteins. IRDS affects about 1 % of newborn infants and is the leading cause of death in preterm infants. The incidence decreases with advancing gestational age,

from about 50 % in babies born at 26–28 weeks, to about 25 % at 30–31 weeks. The syndrome is more frequent in males, Caucasians, infants of diabetic mothers, and the second born of premature twins.

*Respiratory Distress – clinical laboratory syndrome, characterized by violation of gas composition of blood (hypoxemia and /or hypercapnia)***.** RDS occurs primarily in premature infants; its incidence is inversely related to gestational age and birthweight. It occurs in 60–80 % of infants less than 28 wk of gestational age, in 15–30 % of those between 32 and 36 wk, in about 5 % beyond 37 wk, and rarely at term. The risk of developing RDS increases with maternal diabetes, multiple births, cesarean section delivery, precipitous delivery, asphyxia, cold stress, and a history of previously affected infants. The incidence is highest in preterm male or white infants. The risk of RDS is reduced in pregnancies with chronic or pregnancy-associated hypertension, maternal heroin use, prolonged rupture of membranes, and antenatal corticosteroid prophylaxis.

Etiology and pathophysiology

Surfactant deficiency (decreased production and secretion) is the primary cause of RDS. The failure to attain an adequate FRC and the tendency of affected lungs to become atelectatic correlate with high surface tension and the absence of pulmonary surfactant. The major constituents of surfactant are dipalmitoyl phosphatidylcholine (lecithin), phosphatidylglycerol, apoproteins (surfactant proteins SP-A, -B, -C, -D), and cholesterol. With advancing gestational age, increasing amounts of phospholipids are synthesized and stored in type II alveolar cells. These surface-active agents are released into the alveoli, where they reduce surface tension and help maintain alveolar stability by preventing the collapse of small air spaces at end-expiration. The amounts produced or released may be insufficient to meet postnatal demands because of immaturity.

Surfactant is present in high concentrations in fetal lung homogenates by 20 wk of gestation, but it does not reach the surface of the lungs until later. It appears in amniotic fluid between 28 and 32 wk. Mature levels of pulmonary surfactant are usually present

after 35 wk. Though rare, genetic disorders may contribute to respiratory distress. Abnormalities in surfactant protein B and C genes as well as a gene responsible for transporting surfactant across membranes (ABC transporter 3 *[ABCA3]*) are associated with severe and often lethal familial respiratory disease. Other familial causes of respiratory distress (not RDS) include alveolar capillary dysplasia, acinar dysplasia, pulmonary lymphangiectasia, and mucopolysaccharidosis.

Synthesis of surfactant depends in part on normal pH, temperature, and perfusion. Asphyxia, hypoxemia, and pulmonary ischemia, particularly in association with hypovolemia, hypotension, and cold stress, may suppress surfactant synthesis. The epithelial lining of the lungs may also be injured by high oxygen concentrations and the effects of respirator management, thereby resulting in a further reduction in surfactant.

Alveolar atelectasis, hyaline membrane formation, and interstitial edema make the lungs less compliant, so greater pressure is required to expand the alveoli and small airways. In affected infants, the lower part of the chest wall is pulled in as the diaphragm descends, and intrathoracic pressure becomes negative, thus limiting the amount of intrathoracic pressure that can be produced; the result is the development of atelectasis. The highly compliant chest wall of preterm infants offers less resistance than that of mature infants to the natural tendency of the lungs to collapse. Thus, at end-expiration, the volume of the thorax and lungs tends to approach residual volume, and atelectasis may develop.

Deficient synthesis or release of surfactant, together with small respiratory units and a compliant chest wall, produces atelectasis and results in perfused but not ventilated alveoli, which causes hypoxia. Decreased lung compliance, small tidal volumes, increased physiologic dead space, increased work of breathing, and insufficient alveolar ventilation eventually result in hypercapnia. The combination of hypercapnia, hypoxia, and acidosis produces pulmonary arterial vasoconstriction with increased right-to-left shunting through the foramen ovale and ductus arteriosus and within

the lung itself. Pulmonary blood flow is reduced, and ischemic injury to the cells producing surfactant and to the vascular bed results in an effusion of proteinaceous material into the alveolar spaces.

Pathology

The lungs appear deep purplish red and are liver-like in consistency. Microscopically, extensive atelectasis with engorgement of the interalveolar capillaries and lymphatics can be observed. A number of the alveolar ducts, alveoli, and respiratory bronchioles are lined with acidophilic, homogeneous, or granular membranes. Amniotic debris, intra-alveolar hemorrhage, and interstitial emphysema are additional but inconstant findings; interstitial emphysema may be marked when an infant has been ventilated. The characteristic hyaline membranes are rarely seen in infants dying earlier than 6–8 hrs after birth.

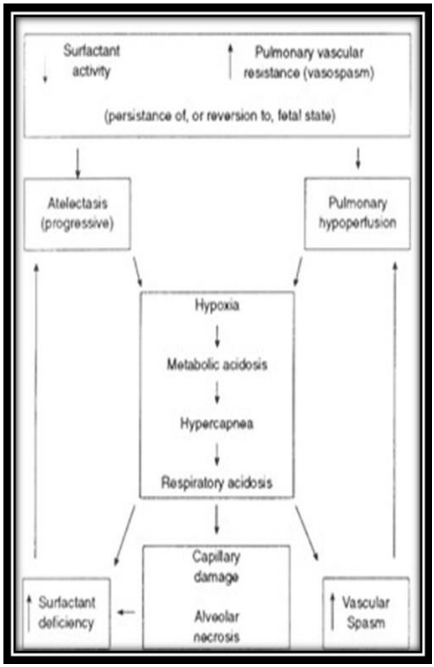


Figure 44 – RDS pathogenesis scheme

***Pathophysiology**: Surfactant deficiency. Decreased FRC Atelectasis. Increased R-L shunt. Increased W.O.B. Hypoxemia and eventually hypercapnia because of V/Q mismatch. Atelectasis keeps PVR high. Increased PAP. Lung hypoperfusion. R-L shunting may reoccur across the Ductus Arteriosus and the Foramen Ovale.*

Clinical manifestations

Signs of RDS usually appear within minutes of birth, although they may not be recognized for several hours in larger premature infants until rapid, shallow respirations have increased to 60/min or greater. A late onset of tachypnea should suggest other conditions. Some patients require resuscitation at birth because of intrapartum asphyxia or initial severe respiratory distress (especially with a birthweight <1 000 g). Characteristically, tachypnea, prominent (often audible) grunting, intercostal and subcostal retractions, nasal flaring, and duskiness are noted. Cyanosis increases and is often relatively unresponsive to oxygen administration. Breath sounds may be normal or diminished with a harsh tubular quality and, on deep inspiration, fine rales may be heard, especially posteriorly over the lung bases. The natural course of untreated RDS is characterized by progressive worsening of cyanosis and dyspnea. If the condition is inadequately treated, blood pressure may fall; fatigue, cyanosis, and pallor increase, and grunting decreases or disappears as the condition worsens. Apnea and irregular respirations occur as infants tire and are ominous signs requiring immediate intervention. Patients may also have a mixed respiratory-metabolic acidosis, edema, ileus, and oliguria. Respiratory failure may occur in infants with rapid progression of the disease. In most cases, the symptoms and signs reach a peak within 3 days, after which improvement is gradual. Improvement is often heralded by spontaneous diuresis and the ability to oxygenate the infant at lower inspired oxygen levels or lower ventilator pressures. Death is rare on the 1st day of illness, usually occurs between days 2 and 7, and is associated with alveolar air leaks (interstitial emphysema, pneumothorax), pulmonary hemorrhage, or

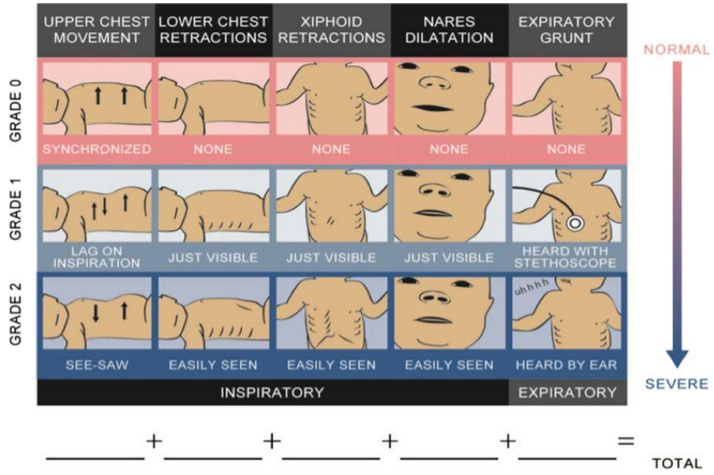
IVH. Mortality may be delayed weeks or months if BPD develops in mechanically ventilated infants with severe RDS.

Diagnosis

Diagnostic Test: ***Silverman-Andersen retraction score***

The Silverman-Andersen Retraction Score (SAs) is used to assess severity of respiratory distress in newborn and preterm infants without respiratory support. The score comprises 4 inspiratory categories of movements (thoraco-abdominal, intercostal, xiphoid, and chin movements) and one expiratory category (grunting).

Silverman-Andersen score a system for evaluation of breathing performance of premature infants. It consists of five items: (1) chest retraction as compared with abdominal retraction during inhalation; (2) retraction of the lower intercostal muscles; (3) xiphoid retraction; (4) flaring of the nares with inhalation; and (5) grunting on exhalation. Each of the five factors is graded 0, 1, or 2. The sum of these factors yields the score. Adequate ventilation is indicated by a 0, severe respiratory distress is indicated by a score of 10.



FEATURE	SCORE 0	SCORE 1	SCORE 2
Chest Movement	Equal	Respiratory Lag	Seesaw Respiration
Intercostal Retraction	None	Minimal	Marked
Xiphoid Retraction	None	Minimal	Marked
Nasal Flaring	None	Minimal	Marked
Expiratory Grunt	None	Audible w/ stethoscope	Audible

Figure 45 – Silverman-Andersen Retraction Score

The parameters assessed by inspection or auscultation of the upper and lower chest and nares on a scale of 0, 1 or 2 using this system are:

Chest movement

Synchronized vs. minimal lag or sinking of the upper chest as the abdomen rises. In the most extreme instances, a seesaw-like movement of the chest and abdomen is observed and would be given a score of 2.

Intercostal retractions

Retraction between the ribs is rated as none, minimal or marked.

Xiphoid retractions

Similarly retraction below the xiphoid process are rated as none, minimal or marked.

Nasal flaring

There should be no nasal flaring. Minimal flaring is scored 1 and marked flaring is scored 2.

Expiratory grunting

Grunting that is audible with a stethoscope is scored 1, and grunting that is audible without using a stethoscope is scored 2.

As you can see on the slide, the higher the score, the more severe the respiratory distress.

The clinical course, **x-ray of the chest, and blood gas and acid-base values help establish the clinical diagnosis.** On x-ray, the lungs may have a characteristic, but not pathognomonic appearance that includes a fine reticular granularity of the parenchyma and air bronchograms, which are often more prominent early in the left lower lobe because of superimposition of the cardiac shadow. The initial roentgenogram is occasionally normal, with the typical pattern developing at 6–12 hrs. Considerable variation in films may be seen, depending on the phase of respiration and the use of CPAP or positive end-expiratory pressure (PEEP); this variation often results in poor correlation between roentgenograms and the clinical course.

CXR: Normal

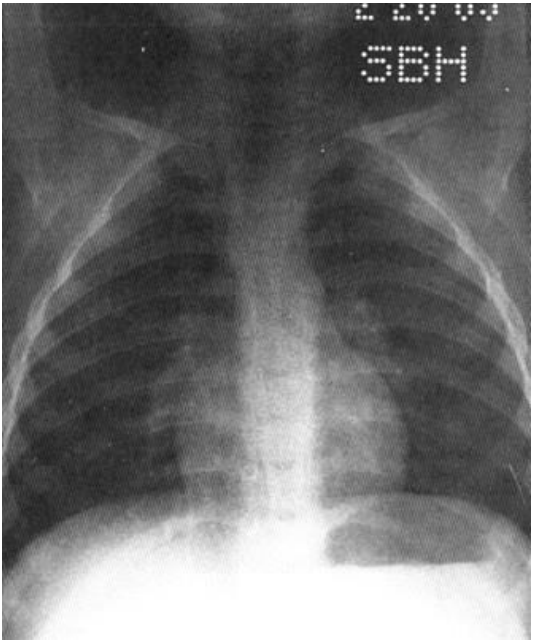


Figure 46 – RDS CXR: Ground Glass Effect

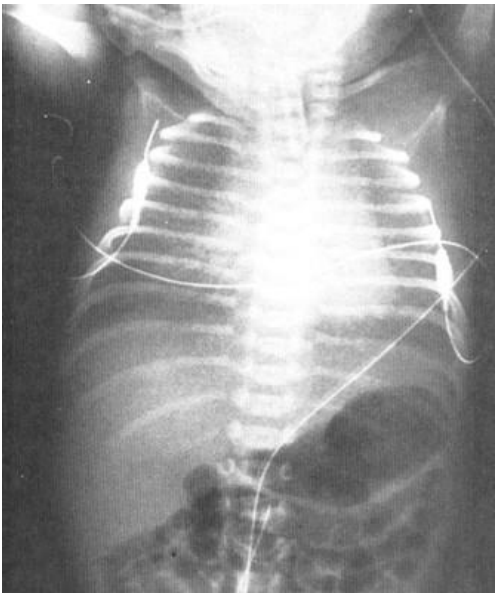
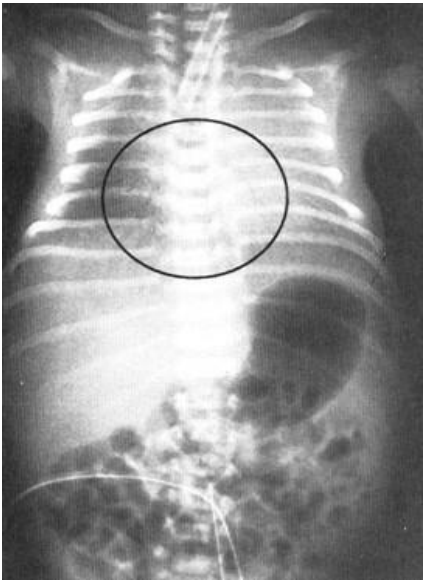


Figure 47 – RDS CXR: air bronchograms & hilar densities



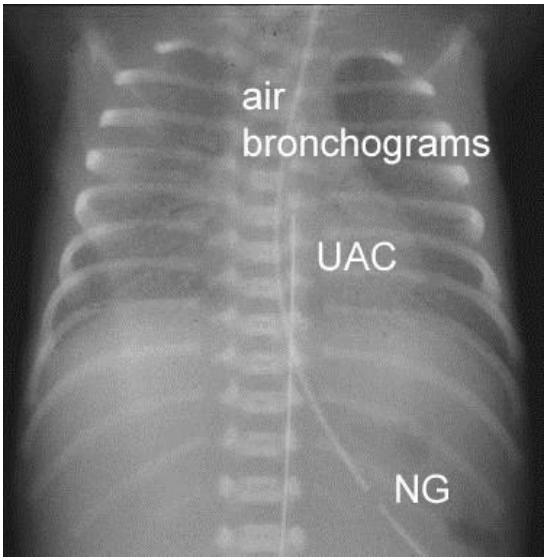


Figure 48 – air bronchogram

Laboratory findings are initially characterized by hypoxemia and later by progressive hypoxemia, hypercapnia, and variable metabolic acidosis.

In the **differential diagnosis,** early-onset sepsis may be indistinguishable from RDS. In pneumonia manifested at birth, the chest roentgenogram may be identical to that for RDS. Maternal group B streptococcal colonization, organisms on Gram stain of gastric or tracheal aspirates or a buffy coat smear, and/or the presence of marked neutropenia may suggest the diagnosis of early-onset sepsis. Cyanotic heart disease (total anomalous pulmonary venous return) can also mimic RDS both clinically and radiographically. Echocardiography with color flow imaging should be performed in infants who fail to respond to surfactant replacement to rule out cyanotic congenital heart disease as well as ascertain patency of the ductus arteriosus and assess pulmonary vascular resistance. Persistent pulmonary hypertension, aspiration (meconium, amniotic fluid) syndromes, spontaneous pneumothorax, pleural effusions, and congenital anomalies such as cystic

adenomatoid malformation, pulmonary lymphangiectasia, diaphragmatic hernia, and lobar emphysema must be considered, but can generally be differentiated from RDS by roentgenographic evaluation. Transient tachypnea may be distinguished by its short and mild clinical course. Congenital alveolar proteinosis (congenital surfactant protein B deficiency) is a rare familial disease that manifests as severe and lethal RDS in predominantly term and near-term infants. In atypical cases of RDS, a lung profile (lecithin: sphingomyelin ratio and phosphatidylglycerol level) performed on a tracheal aspirate can be helpful in establishing a diagnosis of surfactant deficiency.

Prevention

Avoidance of unnecessary or poorly timed cesarean section, appropriate management of high-risk pregnancy and labor, and prediction and possible in utero acceleration of pulmonary immaturity are important preventive strategies. In timing cesarean section or induction of labor, estimation of fetal head circumference by ultrasonography and determination of the lecithin concentration in amniotic fluid by the lecithin: sphingomyelin ratio (particularly useful with phosphatidylglycerol in diabetic pregnancies) decrease the likelihood of delivering a premature infant. Antenatal and intrapartum fetal monitoring may similarly decrease the risk of fetal asphyxia; asphyxia is associated with an increased incidence and severity of RDS.

Administration of betamethasone to women 48 hrs before the delivery of fetuses between 24 and 34 wks of gestation significantly reduces the incidence, mortality, and morbidity of RDS. Corticosteroid administration is recommended for all women in preterm labor (24–34 wks gestation) who are likely to deliver a fetus within 1 wk. Repeated weekly doses of betamethasone until 32 wks may reduce neonatal morbidities and the duration of mechanical ventilation. Prenatal glucocorticoid therapy decreases the severity of RDS and reduces the incidence of other complications of prematurity, such as IVH, patent ductus arteriosus (PDA), pneumothorax, and necrotizing enterocolitis, without adversely

affecting postnatal growth, lung mechanics or development, or the incidence of infection. Prenatal glucocorticoids may act synergistically with postnatal exogenous surfactant therapy. Prenatal dexamethasone may be associated with a higher incidence of periventricular leukomalacia than betamethasone. The relative risk of RDS, IVH and death is higher with antenatal dexamethasone treatment when compared with betamethasone.

Administration of a 1st dose of **surfactan**t into the trachea of symptomatic premature infants immediately after birth (prophylactic) or during the 1st few hours of life (early rescue) reduces air leak and mortality from RDS, but does not alter the incidence of BPD.

Treatment

The basic defect requiring treatment is inadequate pulmonary exchange of oxygen and carbon dioxide; metabolic acidosis and circulatory insufficiency are secondary manifestations. Early supportive care of LBW infants, especially in the treatment of acidosis, hypoxia, hypotension, and hypothermia may lessen the severity of RDS. Therapy requires careful and frequent monitoring of heart and respiratory rates, oxygen saturation, PaO_2, $PaCO_2$, pH, bicarbonate, electrolytes, blood glucose, hematocrit, blood pressure, and temperature. Arterial catheterization is frequently necessary. Because most cases of RDS are self-limited, the goal of treatment is to minimize abnormal physiologic variations and superimposed iatrogenic problems. Treatment of these infants is best carried out in a specially staffed and equipped hospital unit, the neonatal intensive care unit (NICU).

The general principles for supportive care of any LBW infant should be adhered to, including developmental care and scheduled "touch times." To avoid hypothermia and minimize oxygen consumption, infants should be placed in an isolette or radiant warmer and core temperature maintained between 36.5 and 37 °C. Use of an isolette is preferable in very low birthweight (VLBW) infants due to the high insensible water losses associated with radiant heat. Calories and fluids should initially be provided

intravenously. For the 1st 24 hrs, 10 % glucose and water should be infused through a peripheral vein at a rate of 65–75 mL/kg/24 hrs. Subsequently, electrolytes should be added and fluid volume increased gradually. Excessive fluids (> 140 cc/kg/day) contribute to the development of PDA and BPD.

Warm humidified oxygen should be provided at a concentration initially sufficient to keep arterial levels between 50 and 70 mm Hg (85–95 % saturation) to maintain normal tissue oxygenation while minimizing the risk of oxygen toxicity. If the Pa_{O_2} cannot be maintained above 50 mm Hg at inspired oxygen concentrations of 60 % or greater, applying ***continuous positive airway pressure (CPAP)*** at a pressure of 5–10 cm H_2O by nasal prongs is indicated and usually produces a sharp rise in Pa_{O_2}.

Early use of CPAP for stabilization of at-risk VLBW infants beginning in the delivery room is also common. CPAP prevents collapse of surfactant-deficient alveoli, improves FRC, and improves ventilation-perfusion matching.

Another approach is to intubate the VLBW infant, administer intratracheal surfactant, and then extubate to CPAP. The amount of CPAP required usually decreases abruptly at about 72 hrs of age, and infants can be weaned from CPAP shortly thereafter. If an infant managed by CPAP cannot maintain an arterial oxygen tension above 50 mm Hg while breathing 70–100 % oxygen, assisted ventilation is required.

Infants with severe RDS and those with complications that result in persistent apnea require assisted mechanical ventilation. Reasonable indications for its use are (1) arterial blood pH < 7.20, (2) arterial blood P_{CO_2} of 60 mm Hg or higher, (3) arterial blood P_{O_2} of 50 mm Hg or less at oxygen concentrations of 70–100 % and CPAP of 6–10 cm H_2O, or (4) persistent apnea.

Intermittent positive pressure ventilation delivered by time-cycled, pressure-limited, continuous flow ventilators is a common method of conventional ventilation for newborns. Other methods of conventional ventilation include synchronized intermittent mandatory ventilation (the set rate and pressure synchronized with

the patient's own breaths), pressure support (the patient triggers each breath and a set pressure is delivered), and volume guarantee (a mode in which a specific tidal volume is set and the pressure delivered varies). Assisted ventilation for infants with RDS should always include ***positive end-expiratory pressure (PEEP).*** When using high ventilatory rates in a mode without inspiratory flow termination, care should be taken to avoid the administration of inadvertent PEEP.

The **goals of mechanical ventilation** are to improve oxygenation and elimination of carbon dioxide without causing pulmonary barotrauma or oxygen toxicity. Acceptable ranges of blood gas values, after balancing the risks of hypoxia and acidosis against those of mechanical ventilation, vary between institutions and range between a Pa_{O_2} of 50–70 mm Hg, a Pa_{CO_2} of 45–65 mm Hg, and a pH of 7.20–7.35. During mechanical ventilation, **oxygenation** is improved by increasing either the F_{IO_2} or the mean airway pressure. The latter can be increased by increasing the peak inspiratory pressure, gas flow, the inspiratory: expiratory ratio, or PEEP. Excessive PEEP may impede venous return, thereby reducing cardiac output and decreasing oxygen delivery despite improvement in Pa_{O_2}. PEEP levels of 4–6 cm H_2O are usually safe and effective.

Carbon dioxide elimination is achieved by increasing the peak inspiratory pressure (tidal volume) or the rate of the ventilator. Many ventilated neonates receive sedation or pain relief with benzodiazepines or opiates (morphine, fentanyl), respectively. Midazolam is approved for use in neonates, and has demonstrated sedative effects. Adverse hemodynamic effects and myoclonus have been associated with its use in neonates. If used, a continuous infusion or administration of individual doses over at least 10 min is recommended to reduce these risks. Data are insufficient to assess the efficacy and safety of lorazepam. Diazepam is not recommended due to its long half-life, its long-acting metabolites, and concern about the benzyl alcohol content. Continuous infusion of morphine in VLBW neonates requiring mechanical ventilation does not improve mortality rates, severe intraventricular hemorrhage, or

periventricular leukomalacia. The need for additional doses of morphine is associated with poor outcome.

High-frequency ventilation (HFV) was developed to reduce lung injury and/or improve gas exchange in patients with severe respiratory disease. HFV achieves desired minute ventilation by using smaller tidal volumes and high rates (300–1 200 breaths/min or 5–20 Hz). HFV may improve the elimination of carbon dioxide, decrease the mean airway pressure, and improve oxygenation in patients who do not respond to conventional ventilators and who have severe RDS, interstitial emphysema, recurrent pneumothoraces, or meconium aspiration pneumonia. High-frequency jet ventilation may cause necrotizing tracheal damage, especially in the presence of hypotension or poor humidification, and high-frequency oscillator therapy has been inconsistently associated with an increased risk of air leaks, IVH, and periventricular leukomalacia. Both methods can cause gas trapping. High-frequency oscillation strategies that promote lung recruitment, combined with surfactant therapy, may improve gas exchange, but have not been shown to reduce the risk for BPD. Elective use of high-frequency oscillation or jet ventilation, when compared with conventional ventilation, does not offer advantages if used as the initial ventilation strategy to treat VLBW infants with RDS. There may be a small reduction in the rate of BPD with high-frequency oscillation, but the evidence is weakened by the inconsistency of this effect across trials and this finding is not statistically significant. Of concern is the increase in acute brain injury in one trial, which used a low-volume strategy during jet ventilation.

Multidose endotracheal instillation of **exogenous surfactant** to VLBW infants requiring 30 % oxygen and mechanical ventilation for the treatment **(rescue therapy)** of RDS dramatically improves survival and reduces the incidence of pulmonary air leaks, but it has not consistently reduced the incidence of BPD. Immediate effects include improved alveolar-arterial oxygen gradients, reduced ventilator mean airway pressure, increased pulmonary compliance,

and improved appearance of the chest roentgenogram. A number of surfactant preparations are available, including synthetic surfactants and natural surfactants derived from animal sources. Exosurf is a synthetic surfactant. Natural surfactants include Survanta (bovine), Infasurf (calf), and Curosurf (porcine). Although both synthetic and natural surfactants are effective in the treatment and prevention of RDS, natural surfactants appear to be superior, perhaps because of their surfactant-associated protein content. Natural surfactants have a more rapid onset and are associated with a lower risk of pneumothorax and improved survival. Surfaxin, formerly known as KL4 surfactant, is a novel synthetic lung surfactant containing phospholipids and an engineered peptide, sinapultide, designed to mimic the actions of human surfactant protein B (SP-B). Surfaxin use for the prevention and treatment of respiratory distress syndrome (RDS) demonstrates a lower all-cause mortality compared to Exosurf and equivalency to the natural surfactants Survanta and Curosurf. Rapid testing of pulmonary maturity soon after birth by examining tracheal aspirate secretions may reduce the number of unaffected infants treated with surfactant and permit early rescue therapy within the 1st 1–2 hrs of life.

Rescue treatment is initiated as soon as possible in the 1st 24 hrs of life. Repeated dosing is given via the endotracheal tube every 6–12 hrs for a total of 2 to 4 doses, depending on the preparation. Exogenous surfactant should be given by a physician who is qualified in neonatal resuscitation and respiratory management and who is able to care for the infant beyond the 1st hr of stabilization. Additional on-site staff support required includes nurses and respiratory therapists experienced in the ventilatory management of LBW infants. Appropriate monitoring equipment (radiology, blood gas laboratory, pulse oximetry) must also be available. Furthermore, each institution should have an approved protocol for the administration of surfactant. Complications of surfactant therapy include transient hypoxia, bradycardia and hypotension, blockage of the endotracheal tube, and pulmonary hemorrhage.

Weaning strategies from ventilators vary widely and are influenced by lung mechanics as well as the availability of ventilatory modes (pressure support). Once extubated, many infants transition to nasal CPAP to avoid postextubation atelectasis and hypoxia. Synchronized nasal intermittent ventilation has been shown to decrease the need for reintubation in VLBW infants. High flow (1–2 L/min) or warmed, humidified high flow (2–8 LPM) nasal cannula oxygen is commonly used to support term and near-term infants following extubation and to wean premature infants off nasal CPAP. Preloading with caffeine may enhance the success of extubation.

Metabolic acidosis in RDS may be a result of perinatal asphyxia and hypotension and is often encountered when an infant has required resuscitation. Sodium bicarbonate, 1–2 mEq/kg, may be administered over a 15–20 min period through a peripheral or umbilical vein, with the acid-base determination repeated within 30 min, or it may be administered over a period of several hours. Often, sodium bicarbonate is administered on an emergency basis through an umbilical venous catheter. Alkali therapy may result in skin slough from infiltration, increased serum osmolarity, hypernatremia, hypocalcemia, hypokalemia, and liver injury when concentrated solutions are administered rapidly through an umbilical vein catheter wedged in the liver. Sodium bicarbonate may exacerbate a severe respiratory acidosis, especially if ventilation is ineffective.

Because of the difficulty of distinguishing **group B streptococcal** or other bacterial infections from RDS, empirical antibiotic therapy is indicated until the results of blood cultures are available. Penicillin or ampicillin with an aminoglycoside is suggested; however, the choice of antibiotics is based on the recent pattern of bacterial sensitivity in the hospital where the infant is being treated.

Complications of RDS

Babies with RDS sometimes develop complications of the disease or problems as side effects of treatment. As with any disease,

more severe cases often have greater risks for complications. Some complications associated with RDS include the following:

Air leaks of the lung tissues such as:

Pneumomediastinum – this occurs when air leaks into the mediastinum (the space in the thoracic cavity behind the sternum and between the two pleural sacs containing the lungs).

Pneumothorax – this occurs when air leaks into the space between the chest wall and the outer tissues of the lungs.

Pneumopericardium – this occurs when air leaks into the sac surrounding the heart.

Pulmonary interstitial emphysema (PIE) – this occurs when air leaks and becomes trapped between the alveoli, the tiny air sacs of the lungs.

Chronic lung disease, sometimes called bronchopulmonary dysplasia

Some neonates with RDS may have clinically significant shunting through a **patent ductus arteriosus (PDA).** Delayed closure of the PDA is associated with hypoxia, acidosis, increased pulmonary pressure secondary to vasoconstriction, systemic hypotension, immaturity, and local release of prostaglandins, which dilate the ductus. There is a relationship between early adrenal insufficiency, ductal patency, airway inflammation, and the development of BPD. Shunting through the PDA may initially be bidirectional or right to left. As RDS resolves, pulmonary vascular resistance decreases, and left-to-right shunting may occur and lead to left ventricular volume overload and pulmonary edema. Manifestations of PDA may include (1) apnea for unexplained reasons in an infant recovering from RDS; (2) a hyperdynamic precordium, bounding peripheral pulses, wide pulse pressure, and a continuous or systolic murmur with or without extension into diastole or an apical diastolic murmur, multiple clicks resembling the shaking of dice; (3) carbon dioxide retention; (4) increasing oxygen dependence; (5) x-ray evidence of cardiomegaly and increased pulmonary vascular markings; and (6) hepatomegaly.

7. INTRAUTERINE INFECTIONS (TORCH)

Congenital (intrauterine) infectionsare a frequent and important cause of neonatal and infant morbidity and mortality. As many as 2 % of fetuses are infected in utero, and up to 10 % of infants have infections in the 1st mo of life. Neonatal infections are unique:

1) infectious agents can be transmitted from the mother to the fetus or newborn infant by diverse modes;

2) newborn infants are less capable of responding to infection because of 1 or more immunologic deficiencies;

3) coexisting conditions often complicate the diagnosis and management of neonatal infections;

4) the clinical manifestations of newborn infections vary and include subclinical infection, mild to severe manifestations of focal or systemic infection, and, rarely, congenital syndromes resulting from in utero infection. The timing of exposure, inoculum size, immune status, and virulence of the etiologic agent influence the expression of disease;

5) maternal infection that is the source of transplacental fetal infection is often undiagnosed during pregnancy because the mother was either asymptomatic or had nonspecific signs and symptoms at the time of acute infection;

6) a wide variety of etiologic agents infect the newborn, including bacteria, viruses, fungi, protozoa, and mycoplasmas;

7) immature, very low birthweight (VLBW) newborns have improved survival but remain in the hospital for a long time in an environment that puts them at continuous risk for acquired infections.

Terms

A vertically transmitted infection is an infection caused by bacteria, viruses, or in rare cases, parasites transmitted directly from the mother to an embryo, fetus, or baby during pregnancy or childbirth. It can occur when the mother gets an infection as an

intercurrent disease in pregnancy. Nutritional deficiencies may exacerbate the risks of perinatal infection.

The transmission can also be called **mother-to-child transmission**. A vertically transmitted infection can be called a perinatal infection if it is transmitted in the perinatal period, which is the period starting at a gestational age of 22 weeks to 28 (with regional variations in the definition) and ending seven completed days after birth.

The term **congenital infection** can be used if the vertically transmitted infection persists after childbirth.

The main routes of transmission of vertically transmitted infections are across the placenta (transplacental) and across the female reproductive tract during childbirth.

Transplacental

The embryo and fetus have little or no immune function. They depend on the immune function of their mother. Several pathogens can cross the placenta and cause (perinatal) infection. Often, microorganisms that produce minor illness in the mother are very dangerous for the developing embryo or fetus. This can result in spontaneous abortion or major developmental disorders. For many infections, the infant is more at risk at particular stages of pregnancy. Problems related to perinatal infection are not always directly noticeable.

During newbirth (intranatal)

Their mothers can also infect infants during birth. Some infectious agents may be transmit to the embryo or fetus in the uterus, while passing through the birth canal, or even shortly after birth. The distinction is important because when transmission is primarily during or after birth, medical intervention can help prevent infections in the infant.

During birth, babies are exposed to maternal blood, body fluids, and to the maternal genital tract without the placental barrier intervening. Because of this, blood-borne microorganisms (hepatitis B, HIV), organisms associated with sexually transmitted disease (e. g., Neisseria gonorrhoeae and Chlamydia trachomatis), and normal

fauna of the genitourinary tract (e. g. Candida albicans) are among those commonly seen in infection of newborns.

TORCH is an acronym for a group of congenitally acquired infections that may cause significant morbidity and mortality in neonates. TORCH stands for the following:

Toxoplasmosis;

Other: syphilis, hepatitis B, varicella zoster virus (VZV), human immunodeficiency virus (HIV), parvovirus B19, enteroviruses, lymphocyticchoriomeningitic virus;

Rubella;

Cytomegalovirus (CMV);

Herpes simplex virus (HSV);

While each of the congenital infections possesses distinct clinical manifestations and sequelae, some of these infections share characteristics.

It is important to think of one or more of these infections when a neonate presents with microcephaly, intracranial calcifications, rash, intrauterine growth restriction (IUGR), jaundice, hepatosplenomegaly, elevated transaminase concentrations, and thrombocytopenia. However, many congenital infections may be silent at birth, with symptoms manifesting years later.

Intrauterine infections are diagnosed by the isolation of microorganisms from the amniotic fluid, cervix, or vagina with standard culture techniques. It is often classified according to location into intra-amniotic or extra-amniotic infections. Although usually asymptomatic, it is the most commonly identified cause of preterm labor, with or without rupture of membranes. Preterm labor, characterized by uterine contraction or rupture of membranes before 37 weeks of gestation, increases morbidity and mortality rates of the fetus. Although rare, clinical symptoms of infection, as seen in figure 1 below, confer a poorer prognosis for the neonate. These symptoms must also be present in the absence of alternate foci of infection.

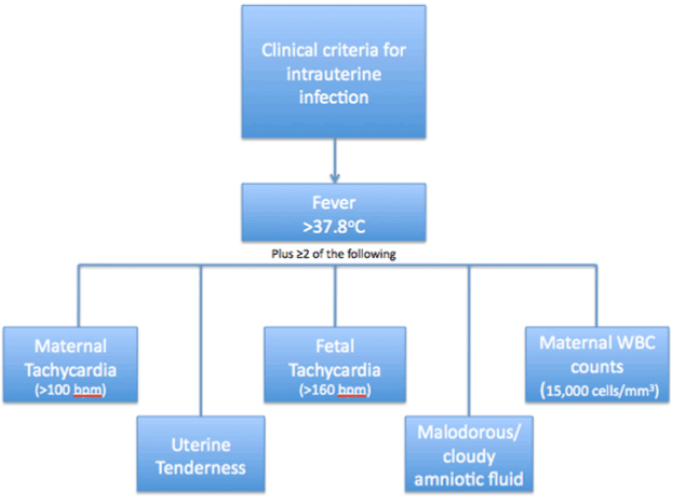


Figure 49 – Clinical criteria for the diagnosis of intrauterine infection

Chorioamnionitis is defined as inflammatory changes of the chorionic plate, chorioamniotic membranes, umbilical cord, and amniotic fluid. It was found by a recent study to be present in up to 70 % of all preterm births.

Risk factors for intrauterine infection are numerous and include prolonged rupture of membranes, prolonged labor, multiple vaginal exams, meconium stained amniotic fluid, smoking, alcohol, or drug abuse.

Routes of Transmission

Intrauterine infections occur by four main routes:

1) ascending infection from the vagina or cervix;

2) transplacental hematogenous spread;

3) retrograde seeding from the peritoneal cavity via fallopian tubes;

4) accidental introduction by invasive procedures such as chorionic villus sampling (CVS) or amniocentesis.

The most common pathway is the ascending route, which induces inflammation in each placental compartment and subsequent

intraamniotic, maternal, and fetal inflammatory responses. Ascending infection generally follows a four-stage processleading to infection.

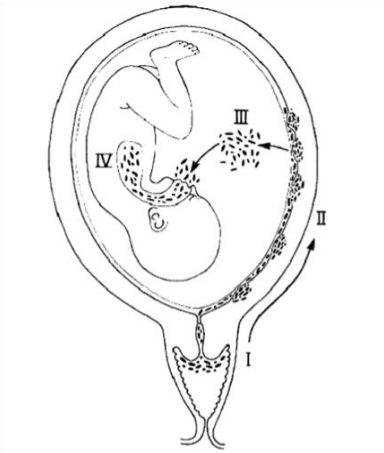


Figure 50 – The four stages of ascending infection

The process begins in Stage I with a change in the vaginal or cervical microbial flora. Stage II is characterized by microorganism entry into the intrauterine cavity followed by colonization of the decidua. The localized inflammatory reaction of the decidua leads to deciduitis and subsequent colonization of the chorion and amnion. Stage III proceeds to infection of the fetal vessels (choriovasculitis) or amnion (amnionitis) leading to intraamniotic infection. Once the bacteria gains access to the amniotic cavity, it may enter the fetus by several areas of entry. This represents the final stage, or stage IV, of infection. Outcomes of stage IV may include pneumonia, secondary to aspiration of infected fluid, otitis, conjunctivitis, and omphalitis. Seeding from any of these sites of infection may result in bacteremia of the fetus.

Microbiology

Intrauterine infections may result from bacterial, viral, or protozoal infections with bacterial colonization being the most common underlying cause. Preterm birth associated with infection is

thought to occur secondary to placental release of proinflammatory cytokines as a result of interaction with bacterial products. The most common microorganism associated with spontaneous preterm labor with intact membranes are Ureaplasma urealyticum, Mycoplasma hominis, Gardnerella vaginalis, peptostreptococci, and Bacteroides species. Another important, and common, risk factor is colonization of the vaginal canal with group B streptococcus (GBS). GBS is the most common congenital bacterial infection in developed nations. In a pregnant woman who tests positive for GBS, risk of transmission to the fetus is around 21 %.

Pregnancy outcomes

Intrauterine exposure of the fetus to infection and inflammation may lead to several adverse effects. Infection and inflammation may complicate greater than 30 % of premature deliveries. It is hypothesized to increase the risk of perinatal brain injury, and the gravity of the outcome, more than intrapartum hypoxia-ischemia (HI) induced brain damage. In term and preterm infants, intrauterine infections are a greater indicator of poor outcome than even perinatal asphyxia. Intrauterine infections are thought to affect the brain by increasing the local production of cytokines in the fetal brain, which may then damage the blood-brain barrier. Preterm birth and fetal infection were more highly correlated with infections involving the amnion and chorion rather than the amnion alone. This is likely secondary to invasion and inflammation being closer in proximity to the fetus.

Fetal Infection

The fetal inflammatory response syndrome (FIRS) is characterized by increased proinflammatory cytokines in cord blood. It involves the action of several different proinflammatory cytokines in addition to host defense mechanisms. It is believed to be FIRS rather than the maternal response to inflammation that causes fetal organ damage. Fetal infection (stage IV) is associated with a mortality rate between 25 % and 90 % and thus is important to focus on in prevention (fig. 51).

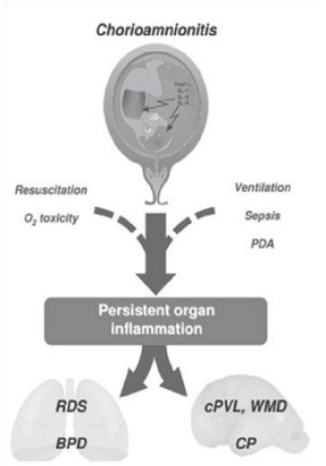


Figure 51 – The major results of FIRS in neonates exposed to chorioamnionitis in utero

Exposure of the fetus to chorioamnionitis while in utero stimulates proinflammatory cytokines, such as tumor necrosis factor (TNF) and interleukin (IL)-1 and 6. Subsequent to cytokine activation, a persistent inflammatory response may be seen in the fetus leading to respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD) in the lungs and cystic periventricular leukomalacia (cPVL), diffuse white matter disease (WMD,) developmental delay and the potential for cerebral palsy; retinopathy of prematurity,neonatal meningitis, intraventricular hemorrhage.

Symptoms of TORCH syndrome that may encourage testing include the following:

- Small size in proportion to length of the mother's pregnancy at time of delivery: small-for-gestational-age (SGA).
- Enlarged liver and spleen.
- Low level of platelets.
- Skin rash: the type of skin rash associated with the TORCH syndrome is usually reddish-purple or brown and is caused by the leakage of blood from broken capillaries into the baby's skin.

- Central nervous system impairment: this may include encephalitis, calcium deposits in brain tissue, or seizures.
- Jaundice: yellow-stained skin and whites of the eyes due to elevated levels of bilirubin, a substance normally filtered out by the liver. Jaundice may indicate liver dysfunction, although it can also be a normal result of red cell turnover in the newborn.

Toxoplasmosis

Causative Organism – **Toxoplasma gondii.**

Transmission:

1) transplacental;

2) fecal-oral route;

3) oocysts excreted in cat feces;

4) found in undercooked meat, contaminated water/soil, and unpasteurized goat milk;

5) risk of fetal infection increases with gestational age;

6) severity of fetal infection decreases with gestational age.

Clinical Manifestations:

1. First Trimester – often results in death.

2. Second Trimester – classic triad:

a) hydrocephalus;

b) intracranial calcifications;

c) chorioretinitis.

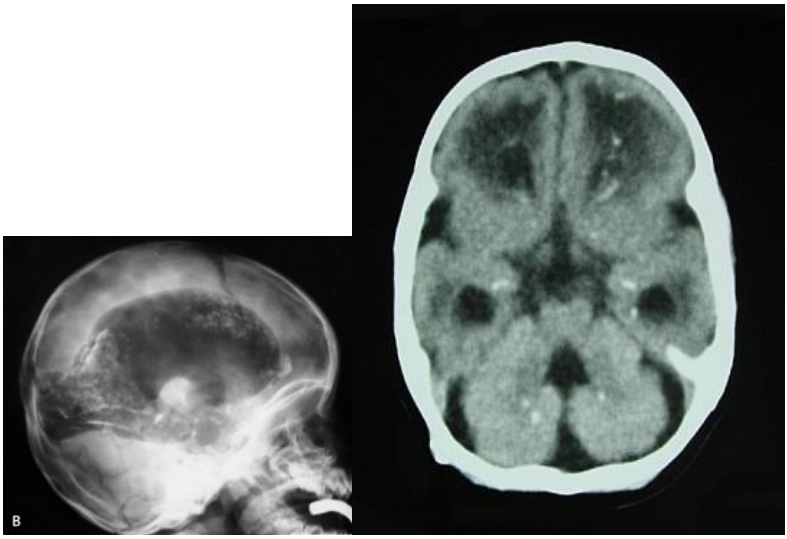


Figure 52 – Intracranial calcifications

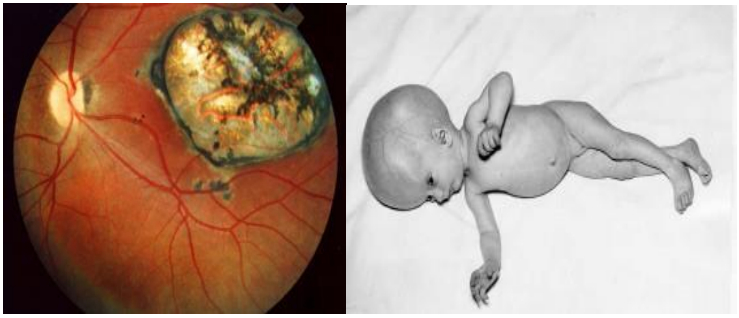


Figure 53 – Chorioretinitis Hydrocephalus

3. Third Trimester – often asymptomatic at birth.

4. Symptoms may also include fever, IUGR, microcepha-ly, seizure, hearing loss, maculopapular rash, jaundice, hepatosplenomegaly, anemia, and lymphadenopathy.

Diagnosis

Definitive – isolating organism from placenta, serum, or CSF.

Also available – PCR & IgM titer (IgG will be elevated if mother is infected regardless of transmission).

Differential diagnosis of chorioretinitis, intracranial calcifications, hydrocephalus, microcephaly; bacterial/viral sepsis; other congenital infections: CMV, syphilis, rubella, HSV.

Treatment

Pyrimethamine 2 mg/kg (maximum 50 mg/dose) once daily for two days; then 1 mg/kg (maximum 25 mg/dose) once daily for six months; then 1 mg/kg (maximum 25 mg/dose) every other day to complete one year of therapy, plus

Sulfadiazine 100 mg/kg per day divided in two doses every day for one year plus

Leucovorin 10 mg three times per week during and once a week after pyrimethamine therapy.

Infants should be weighed weekly and dosages adjusted accordingly.

Glucocorticoids (prednisone 0.5 mg twice per day) are added if CSF protein is > 1 g/dL or when active chorioretinitis threatens vision.

Syphilis

Causative Organism – *Treponema pallidum*

Transmission: transplacental; sexual activity.

Clinical Manifestations

Majority are symptomatic at birth.

Early congenital syphilis (symptoms at 1–2 months of age): *maculopapular rash, "snuffles," maculopapular rash, lymphadenopathy, hepatomegaly, thrombocytopenia, anemia, meningitis, chorioretinitis, osteochondritis.*

Late congenital syphilis (symptoms after 2 years of age)

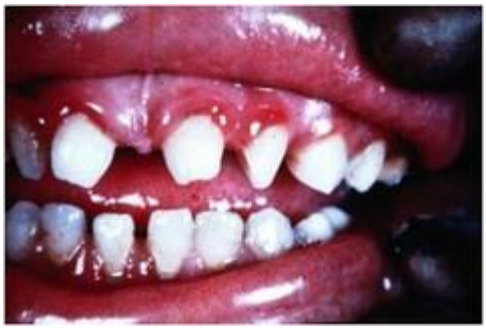
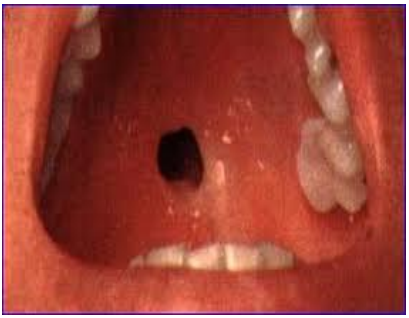



Figure 54 – Hutchinson teeth perforated hard palate

Figure 55 – Saber shins

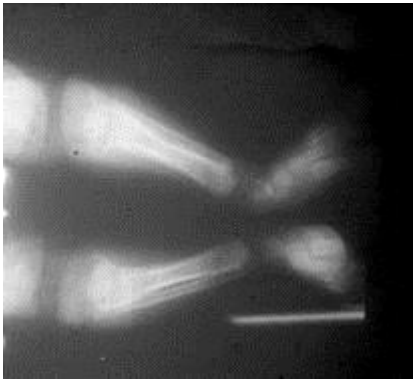


Figure 56 – Periostitis

Diagnosis

Dark field microscopy

FTA-Abs, RPR, VDRL

Treatment

Penicillin. For infants less than one month, either as a single dose of Benzathine Penicillin G (50 000 units/kg, intramuscularly [IM]), or as a ten day course (aqueous Penicillin G 50 000 units/kg intravenously (IV) every 12 hours (for infants ≤ 7 days of age); and every 8 hours (for infants > 7 days of age) for a total of 10 days; or Procaine Penicillin G 50 000 units/kg intramuscularly (IM) as a single daily dose for 10 days.

Single-dose therapy is contraindicated for asymptomatic infants born to women with inadequate/suboptimal treatment unless the infant has undergone appropriate evaluation (CSF quantitative VDRL, cell count, and protein; CBC with differential and platelet count; and long-bone radiographs) and has completely normal results.

For children diagnosed with congenital syphilis after one month of age (including those with late congenital syphilis) and children with acquired syphilis should be treated with aqueous Penicillin G (50 000 units/kg IV every 4–6 hours for 10 days). However, some experts suggest that the 10-day course of aqueous penicillin be followed with a single dose of Benzathine Penicillin (50 000 units/kg IM).

Rubella

Causative Organism **– Togavirus.** Rubella also known as **German measles.**

Transmission:

1) transplacental;

2) respiratory secretions.

Clinical Manifestations

1. "Blueberry muffin" – rash due to extramedullary hematopoiesis.

2. Cataracts.

3. "Salt and Pepper" retinopathy.

4. Radiolucent bone disease (long bones).

5. IUGR, glaucoma, hearing loss, pulmonic stenosis, ***patent ductus arteriosus***, lymphadenopathy, jaundice, hepatosplenomegaly, thrombocytopenia, interstitial pneumonitis, diabetes mellitus.

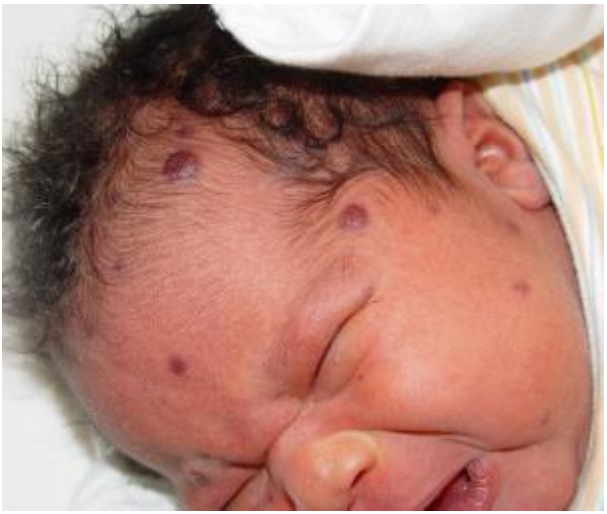


Figure 57 – “Blueberry muffin”

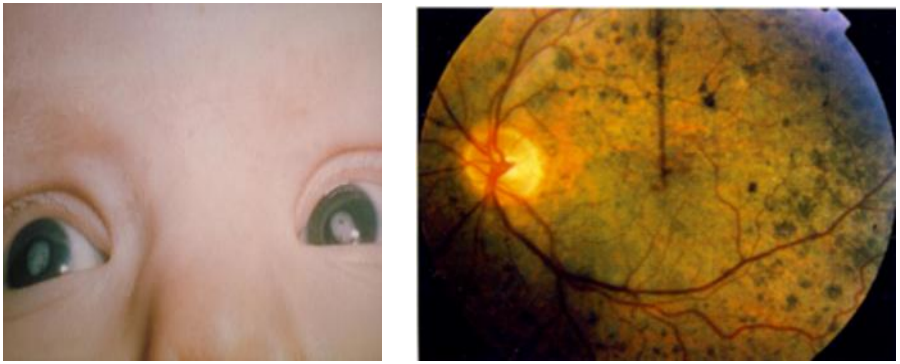


Figure 58 – Cataracts “Salt and Pepper” retinopathy

Diagnosis:

Culture from blood, urine, CSF, oral/nasal secretions IgM titer.

Treatment: supportive care.

Cytomegalovirus (CMV)

Causative Organism – **Human Herpesvirus 5**

Transmission:

1) transplacental;

2) perinatal (contact with vagina during delivery or breast milk after delivery);

3) contact with bodily fluids (urine/saliva);

4) transmission is possible through reactivation of latent virus (decreased risk of transmission).

Clinical Manifestations:

1) majority are asymptomatic at birth;

2) periventricular calcifications.

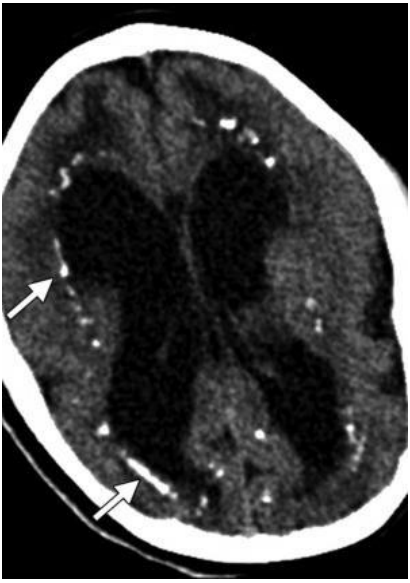


Figure 59 – Cytomegalovirus

3) IUGR, developmental delay, microcephaly, sensori-neural hearing loss, retinitis, jaundice, hepatosplenomegaly, thrombocytopenia, hypotonia, lethargy, poor suck;

4) preterm infants may appear septic – apnea, bradycardia, intestinal distension);

5) postnatal infections are generally asymptomatic.

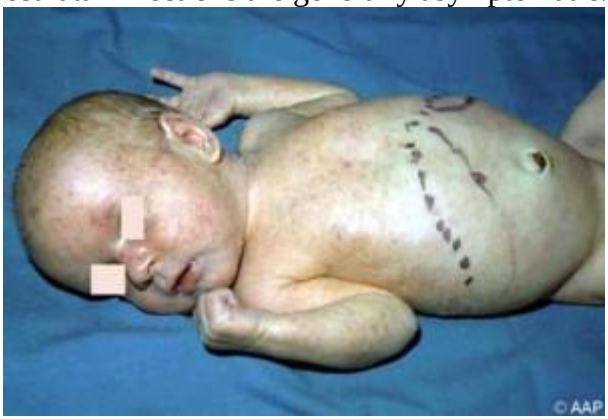


Figure 60 – Congenital CMV

Diagnosis

Culture (urine or pharyngeal secretions) PCR.

Treatment

Studies have shown that Ganciclovir can improve hearing loss and neurodevelopmental outcomes. One report showed 6 mg/kg per dose administered IV for six weeks in newborns with severe congenital CMV disease and neurologic impairment showed protection against hearing loss and head circumference growth in the first 6 to 12 months of life.

Supportive care.

Herpes

Herpes Simplex Virus

Causative Organism **– Human Herpesvirus 1 & 2**

Transmission:

1) perinatal (contact with vagina during delivery);
2) contact after rupture of membranes;
3) direct contact with affected areas.

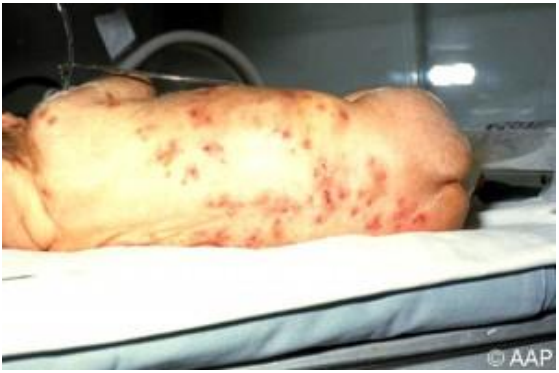


Figure 61 – Herpes

Clinical Manifestations

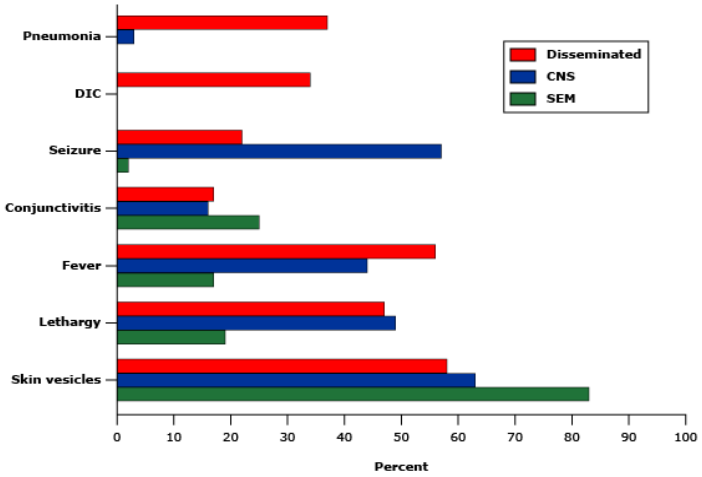


Figure 62 – Clinical manifestations of herpes of a newborn

1. SEM disease (Localized to skin, eyes, and mucosal):

- vesicular lesions on an erythematous base;

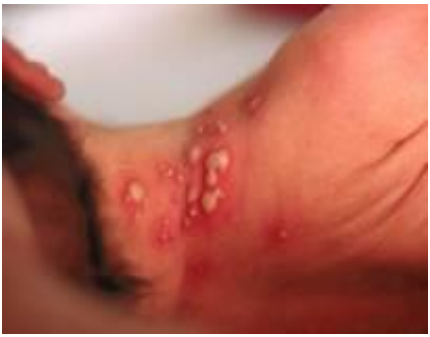


Figure 63 – Herpes rash

- keratoconjunctivitis, cataracts, chorioretinitis;
- ulcerative lesions of the mouth, palate, and tongue.

1. *CNS disease:*

- seizure, lethargy, irritability, tremor, poor feeding, temperature instability, full anterior fontanelle.

2. *Disseminated disease:*

- multiple organ involvement (CNS, skin, eye, mouth, lung, liver, adrenal glands);
- may appear septic – fever/hypothermia, apnea, irritability, lethargy, respiratory distress;
- hepatitis, ascites, direct hyperbilirubinemia, neutropenia, disseminated intravascular coagulation, pneumonia, hemorrhagic pneumonitis, necrotizing enterocolitis, meningoencephalitis, and skin vesicles.

Diagnosis: PCR of CSF, IgM titers, HSV culture of a lesion.

Treatment:

- acyclovir IV at a dose of 60 mg/kg per day IV divided every 8 h;
- treatment for localized SEM disease should be for a minimum of 14 days if disseminated and CNS disease have been excluded;
- treated for disseminated and CNS disease should be for a minimum of 21 days and repeat lumbar puncture is recommended to

make sure the HSV DNA PCR is negative and all CSF parameters have returned to normal before discontinuing therapy.

Human immunodeficiency virus (HIV)

HIV is an RNA virus belonging to the **Retroviride** family. There are two types of HIV: HIV-1 andHIV-2, with HIV-1 being the predominan virus found in the United States. Humans are the only known hosts of HIV-1 and HIV-2.

Route of infection

HIV is spread parenterally through exposure to infected blood, semen, vaginal and cervical secretions, contaminated needles or sharp objects, contaminated blood transfusions, and vertically. HIV can be transmitted to the infant at any time during pregnancy: transplacentally, during labor and delivery, or after birth through breastfeeding. The highest risk of neonatal infection occurs during delivery with exposure to maternal blood.

Clinical manifestations

Neonates suspected of having perinatally acquired HIV will be asymptomatic and have normal-for-age lymphocyte counts. As the infection volves, T-cell function declines. Depending on T-cell counts, various opportunistic infections can take hold, such as encapsulated bacteria, Pneumocystis jiroveci, VZV, CMV, and HSV, among others.

Diagnosis

The American Academy of Pediatrics and CDC recommend routine HIV-1 testing for all pregnant women. Knowledge of the maternal infection can prompt measures to decrease transmission, including HIV drug prophylaxis, cesarean section before rupture of membranes for women with a viral load of greater than 1 000 copies/mL at full term delivery, avoidance of breastfeeding,and early detection in the infant.

HIV serum DNA and RNA assays have low sensitivity shortly after birth. Either HIV-1 DNA or RNAPCR should be analyzed in the infant born to an HIV-infected mother at the

following times: 14 to 21 days after birth, 1 to 2 months of age, and 4 to 6 months of age.

An infant is considered uninfected if he or she meets either of the following laboratory criteria:

1) two negative HIV-1DNA or RNA assays, one obtaine dafter 1 month of age and the other at 4 months of age or older, OR

2) two negative HIV-1 antibody tests from separate specimens obtained at 6 months of age or older.

Some practitioners may follow antibodies until after 18 months of age because maternally derived antibodies rarely persist beyond this age.

Treatment

Infants suspected of having HIV infection are starting on **Zidovudine** until 6 weeks of age.

Infants with confirmed HIV infection are starting on further antiretroviral treatment.

Parvovirus B19

Parvovirus is a single **stranded DNA** virus.

Route of infection. Parvovirusis spread through respiratory tract secretions,exposure to contaminated blood, and transplacentally.

Clinical manifestations. Infants who are infected with parvovirus are at risk for hydrops, pleural and pericardial effusions, IUGR, and death.

Infection during the first half of pregnancy confers the greatest risk to the fetus. Infected infants demonstrate the extremes of outcomes withal most no middle ground: either life threatening infection or no residua.

Diagnosis. If congenital parvovirusis suspected, an IgM titer should be obtained from infant serum.

Treatment. Treatment is limited to supportive care. There is evidence that intravenous immunoglobulin may be beneficial.

Congenital Candidiasis

Transmission: intrauterine (hematogenous or ascending w/ROM) or intrapartum due to massive maternal vaginal colonization.

C. albicans most common etiologic species.

Risk factors: prolonged ROM, uterine foreign body

Presents w/in first 24 h of life as: widespread erythematous maculopapular rash evolving to vesicles/pustules; pneumonia, esp preterm infants.

Tests. *Nonspecific*: nodular or alveolar infiltrates on CXR w/pneumonia; w/ dissemination.

Specific: positive Gram stain of vesicle/pustule content, KOHprep of skinscrapings, culture of skin fold or vesicle/pustule content.

Differential diagnosis. Sepsis/pneumonia, early-onset.

Management. Supportive therapy. Infection control: none beyond universal precautions.

Specific therapy

Prevention: appropriate Dx & Rx of maternal vaginosis & UTI during pregnancy.

Treatment: cutaneous infection: topical anti-candidal agents (e.g., clotrimazole, ketoconazole, nystatin); in preterm infant or w/ pneumonia: systemic antifungal therapy.

Follow-up. Infection limited to cutaneous involvement: close surveillance for systemic infection.

W/ pneumonia, disseminated disease: serial blood/urine/CSF cultures; indirect ophthalmoscopy, echocardiogram, renal US, head US; serial CBC, serum electrolytes, Mg, creatinine, urine output, liver function tests for drug toxicity.

Long-term w/ recovery w/o dissemination: none.

Complications: extensive skin desquamation in the preterm infant may lead to fluid& electrolyte disturbances, secondary bacterial infection; hematogenous dissemination uncommon; more likely w/ prematurity, widespread cutaneous
involvement, central venous catheters.

Prognosis: good if limited to cutaneous involvement.

Table 8 – Congenital infections (TORCH)

Toxo-plasmosis	**Rubella**	**CMV = cytomegalo-virus**	**Herpes simplex**
Organism: Protozoan; toxoplasma gondii → inhabit cats' gut → oocytes in their stool → contaminate food, water in raw meat of infected cattle	Maternal infection with German measles especially in the 1st trimester	DNA virus infection can be: –trans-placental; – perinatal (via secretions) – breast milk	HSV type II; DNA virus infection occur either. * transplacental → rare. * contact with genital lesions during delivery → common
c. *Special features:* may be: hydrocephalus; microphthalmia	**CNS:** meningoencepha-litis Eye: cataract, glaucoma. CVS: – patent ductus arteriosus; – pulmonary stenosis. Mouth: – cleft palate (rare). Late signs: – sensorineural deafness; – mental retardation; – diabetes; – thyroid disease. Previous features are referred as: **congenital rubella syndrome**		In perinatal infection: • skin and mouth vesicles and ulcers. • kerato-conjunctivitis. • encephalitis • disseminated form: multi organ affection => septic shock like

Continuation of the table 8

Diffuse calcifications	No calcifications	Periventricular calcifications	Diffuse calcifications
Treatment Prevention: * Food hygiene * Spiramycin for infected pregnant.	* Rubella or MMR vaccine. * Pregnant female with german measles, either: – induction of abortion or – I.V. Immuno-globulin	* Hyperimmune anti-CMV Immunoglobulin. * Blood products screening for CMV	* Cesarean section for mothers with genital lesions. * Acyclovir for pregnants with primary HSV

8. SEPSIS/PNEUMONIA IN NEONATES

Sepsis *– generalized infectious acyclic disease, basis of which is make by the system inflammatory response of organism (SIRS), bacterial infection, which is manifested with generalized violation of the bloodstream, intoxication, disorders of hemostasis with DIC and development of multisystem insufficiency.*

Every year 1.6 million of newborn infants die from sepsis. The prevalence of sepsis, meningitis, and other confirmed bacterial infections has been estimated to range between 1 to 5/1000 live births. Preterm infants are 20 times more likely to get infection than term infants with a prevalence of 1/230. Very low birth weight infants, evaluated and treated for infections are around 50 % of all admissions to neonatal intensive care.

Sepsis is responsible for 30–80 % increased risk of neuro-developmental impairment and 30–100 % increase in odds for poor head growth and long-term morbidity.

45 % of late deaths in the (NICU) are caused by an infectious disease.

Septic shock in neonates is estimated to be around 1–5 % of all infants with proven severe sepsis, it reported in 1.3 % of

extremely low birth weight newborns with an associated mortality peaking at 71 %.

Neonatal sepsis may be categorized as **early or late** onset. Eighty-five percent of newborns with early-onset infection present within 24 hours, 5 % present at 24–48 hours, and a smaller percentage of patients present between 48 hours and 6 days of life. Onset is most rapid in premature neonates. *Early-onset sepsis syndrome* is associated with acquisition of microorganisms from the mother. Organisms that colonize in the mother's genitourinary tract may cause transplacental infection or an ascending infection from the cervix. The infant may acquire the microbe by passage through a colonized birth canal at delivery. The microorganisms most commonly associated with early-onset infection include group B Streptococcus (GBS), Escherichia coli, Haemophilus influenzae, and Listeria monocytogenes.

Late-onset sepsis syndrome occurs at 7–90 days of life and is acquired from the caregiving environment. Organisms that have been implicated in causing late-onset sepsis syndrome include coagulase-negative staphylococci, Staphylococcus aureus, E coli, Klebsiella, Pseudomonas, Enterobacter, Candida, GBS, Serratia, Acinetobacter, and anaerobes. The infant's skin, respiratory tract, conjunctivae, gastrointestinal tract, and umbilicus may become colonized from the environment, leading to the possibility of late-onset sepsis from invasive microorganisms. Vectors for such colonization may include vascular or urinary catheters, other indwelling lines, or contact from caregivers with bacterial colonization.

Pneumonia is more common in early-onset sepsis, whereas *meningitis and/or bacteremia are more common in late-onset sepsis.* Premature and ill infants have an increased susceptibility to sepsis and subtle nonspecific initial presentations; therefore, they require much vigilance so that sepsis can be identified and treated effectively.

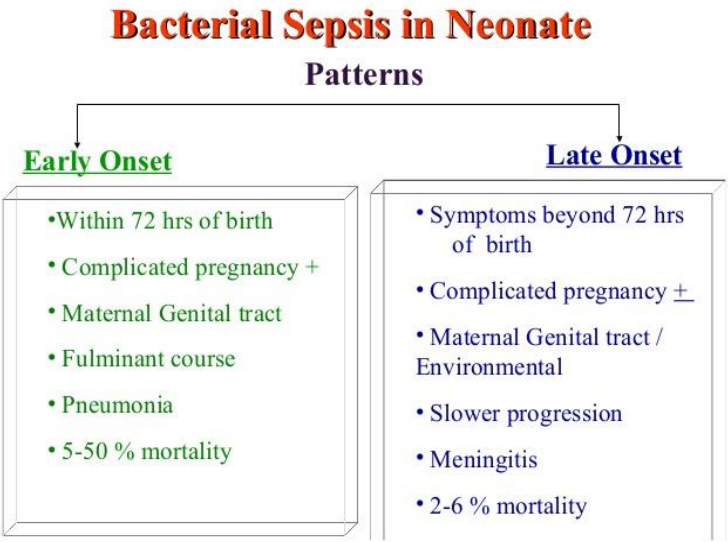


Figure 64 – Classification of neonatal sepsis

Etiology & risk factors

Infection, far from being a homogeneous condition, reflects a continuum from fetal Inflammatory response syndrome to sepsis, severe sepsis, septic shock, multiorgan failure, and death. The difficulty for the clinician is to define precisely the phase in which patient is at any given moment as the patient may move from one phase to another imperceptibly.

Definition of sepsis derives from the international consensus definitions that have been adapted for pediatric and neonatal use, including term neonates (0–7 days) and newborns (1 week to 1 month). Sepsis is a complex entity, with wide variations in clinical, laboratory parameters and outcome. *Septic shock is a severe sepsis and septic shock – understanding a serious killer condition of inadequate tissue perfusion secondary to cardiovascular dysfunction occurring in the course of suspected or certain systemic infection, requiring fluid resuscitation or inotropic support.*

Prenatal risk factors include maternal intrapartum fever, chorioamnionitis or prolonged rupture of membranes, treatment with steroids, group B Streptococci recto-vaginal colonization.

A few days after aspiration of infected amniotic fluid during the birth, the neonate may manifest with signs and symptoms of neonatal shock. Gram-positive germs as group B Streptococci are those most frequently described as causative agents in early neonatal sepsis, even if, more recently, some gram-negative agents have been frequently described (*Escherichia coli, Klebsiella spp., Enterobacter spp*.).

This probably is due to the intrapartum use of antibiotics directed against gram-positive pathogens that allows gram-negative flora's outbreak. Other microbes include *Listeria monocytogenes, coagulase-negative staphylococci (ConS) (22 %) and no pyogenic streptococci (9 %)* (2017).

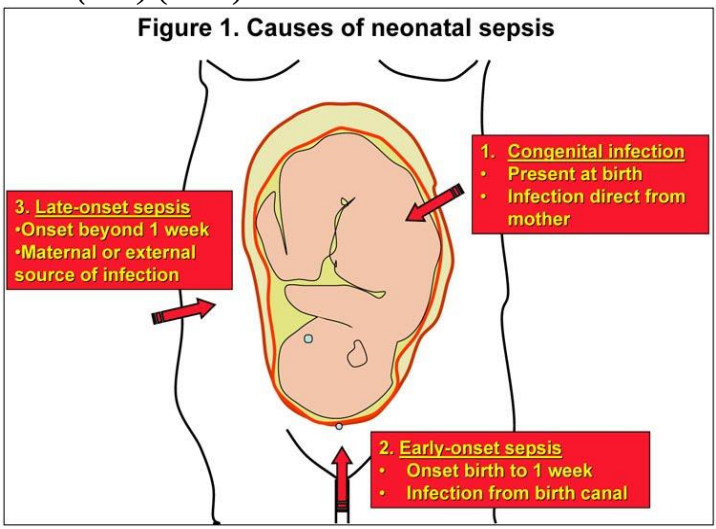


Figure 65 – Etiology of neonatal sepsis

Post-natal risk factors include male gender, birth weight less than 1000 g, hypogammaglobinemia, parenteral nutrition, central venous catheters, steroids or drugs that decrease gastric acidity, prolonged duration of mechanical ventilation, hand contamination of

health care personnel, mother and other family members, aspiration of feeds, and disruption of skin integrity.

Staphylococcus aureus is the most frequent germ in late sepsis. Gram negative and ConS, almost half the isolates (45 %), are the predominant pathogens associated with late severe sepsis or septic shock.

Also viruses (*herpes simplex*, *enteroviruses*) or fungi (*candida albicans*) have been associated with fulminant neonatal sepsis. Compared with ConS, Gram-negative infections are associated with a higher mortality: one-fifth of those infected by gram negatives die.

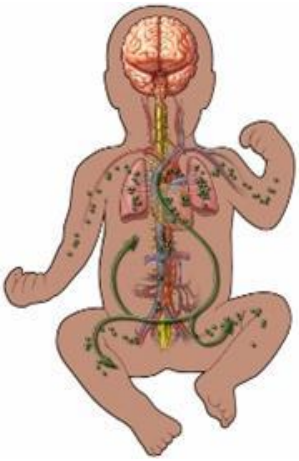


Figure 66 – Spread of Infection Via the Blood to the Entire Body in an Infant

Pathophysiology

The development of septic shock is associated with elevated levels of proinflammatory cytokines including IL-1β, IL-6, IL-8 and TNFα.

The inflammatory cytokine response to sepsis in neonates is more pronounced and faster than in adults and associated with an increase in early mortality (< 48 hours), while the compensatory antiinflammatory response system appears to be immature, with both

term and preterm infants demonstrating profoundly decreased IL-10 pro-duction and a lower amount of transforming growth factor beta-positive lymphocytes, than do adults, after lipopolysaccharide (LPS) stimulation.

In addition, in the neonate eosinophils, macrophages and polymorphonuclear neutrophils have reduced surface binding components and have defective opsonization, phagocytosis and antigen-processing capabilities, leading to a generally less robust response to pathogen exposure.

Mechanisms of sepsis include excessive activation of the coagulation cascade, inhibition of endogenous natural anticoagulants, and impaired fibrinolysis. Within the microcirculation, this leads to fibrin deposition, contributing to hypoperfusion that eventually results in tissue damage and organ dysfunction. On the other hand, consumption of coagulation factors and platelets promotes a bleeding tendency that may clinically manifest as petechiae, ecchymoses, and sometimes hemorrhages, all of which are associated to increased mortality.

The immune system and coagulation are closely related. Cytokines mediating neutrophils activation and migration to the tissues and extravascular compartment generate the thrombin and fibrin deposit formation, triggering tissue factor, that is considered the main both septic shock and diffuse tissue injury mediator. That is why, disseminated intravascular coagulation (DIC) is not so rare in septic shock, resulting from the sustained thrombin generation. Thrombin, in turn, stimulates more inflammatory mediators' formation. Fibrin formation stabilizes platelet plugs, in addition to its important role in pathogens' adhesion to the leukocyte surface, facilitating phagocytosis.

The *Toll-like receptors* (TLRs), found in immune system cells, have a fundamental role in the septic shock pathophysiology. They can interfere with the cardiovascular system depending on the systemic inflammatory response to pathogen. They are able to detect pathogens-associated molecular patterns (PAMPs), causing the

induction of proinflammatory and anti-inflammatory mediators, particularly cytokines.

TLRs, present in endothelial cells, alveolar epithelium cells, and cardiomyocytes, may induced TNFα and IL-1β production, responsible for the early myocardial dysfunction in gram-negative (TLR4) and gram-positive (TLR2) germs severe sepsis. Unlike in adults, TLRs genetic polymorphisms and signaling proteins (MYD88) regulating the host response to infection and different septic shock patterns, are less characterized in neonates.

In septic shock the action of inflammatory mediators leads to damage of the capillary wall with loss of vascular tone, resulting in vasodilatation and reduction of systemic vascular resistance with low to normal blood pressure and increased systemic blood flow. Thanks to the compensatory heart rate increase, skin is well perfused and warm (*warm shock*). In the late phase of shock there is a reduction of myocardial contractility that leads to vasoconstriction, decreased systemic blood flow, decreased pulse volume, cold periphery, prolonged capillary refill time, and increased vascular tone in an attempt to centralize the circulation (*cold shock*).

Shock, that is not recognized and treated, progresses from early to late stages, referred to as *compensated*, *uncompensated*, and *irreversible* shock.

The hemodynamic response to sepsis of a newborn is markedly different from that of an adults or an older child with relevant difference between the preterm and the term newborn owing to the different anatomical structure, the functional activity and excitation–contraction. In the neonates, the absence of hypotension does not precludes shock that is mainly related with blood flow rather than blood pressure as the mean blood pressure may be in the normal range due to compensatory mechanisms.

In the evaluation of blood pressure, the physiological variability with age and gestational age should be taken in account. Despite this, 30 mmHg should be considered the absolute minimum tolerable of in the extremely premature infants.

Furthermore in critically ill prematures, refractory hypotension may be related to patent ductus arteriosus, intraventricular hemorrhage and poor prognosis.

While in healthy prematures lower mean blood pressure levels may be accepted being associated with appropriate cerebral perfusion and normal cardiac output, in septic shock hypotension is not permissive and need a therapeutically interments.

The neonate is enable to increase the stroke volume or myocardial contractility in case of sepsis, due to different physiologic abnormalities: a relatively decreased left ventricular muscle mass, an impaired left ventricular diastolic function and alterations in mid-wall left ventricular fractional shortening. These differences may be mediated by alterations in calcium channel expression and activity, in ATP-sensitive potassium channel function and in receptor coupling. These developmental alterations make the neonates critically dependent on increasing the heart rate to generate increased cardiac output, but unable to compensate in this manner because of their relatively higher baseline heart rate. The development of cardiovascular dysfunction and septic shock make newborn infants susceptible to sudden cardiac deterioration, also performance is highly dependent on afterload. So the reopening of a patent ductus arteriosus and the development of persistent pulmonary hypertension may complicate the cardiovascular response to sepsis.

Classification

Table 9 – Classification of neonatal sepsis

Early onset sepsis (infection occurring in the first 5 days of life)	**Late onset sepsis** (infection occurring after 5 days of age)
Exposure to bacteria can occur: 1) before delivery due to infected amniotic fluid or occasionally following maternal sepsis; 2) during delivery when contact with organisms in the vagina can occur; 3) after delivery following exposure to organisms in the infants environment	Usually due to: 1) nosocomial infection, organisms acquired from the environment; 2) coagulase negative Staphylococci are the most common causative organisms; 3) VLBW infants with indwelling catheters, central lines, chest drains etc are at particular risk

Etiological factor of sepsis (gram+, gram- microorganisms, viral-bacterial associations, fungi).

Term of origin: intrauterine (antenatal, intranatal), postnatal (early, late), nosocomial.

Entrance gate: umbilical, dermic, pulmonary, intestinal, uroseptic, otogenic, cryptogenic (in 40 % an entrance gate is impossible to be determined).

Clinical forms: septicemia (sepsis without purulent metastases), septicopyemia (sepsis with purulent metastases).

Leading syndromes of sepsis: SIRS, bacteriemia, severe sepsis, septic shock, syndrome of multiple organ failure.

Duration: fulminant – few hours – 1–3 days; acute – 4–8 weeks; prolonged –more than 8 weeks.

Periods: initial, significant clinical signs, recovery, period of rehabilitation.

Complications: DIC-syndrome, thrombosis, hypotrophy, endomyocarditis, renal failure etc.

Sepsis leading syndromes

SIRS (systemic inflammatory response syndrome). For diagn. of SIRS – 2 or more of the following signs should be presented:

Clinical criteria of SIRS:

• disorders of temperature (hyperthermia > 38 °C, hypothermia < 36 °C);

• tachypnoea > 60/min;

• tachycardia > 160/min;

• depression of CNS and/or cramps;

• oliguria (< 1 ml/kg/hour in the first 3 days of life, < 2 ml/kg/hour in future) on background of adequate infusion therapy.

***Lab criteria of SIRS*:**

• metabolic lactate-acidosis;

• leukocytosis or leukopenia with a neutrophilia, or neutropenia;

• shift of leukocyte formula to left, the amount of immature forms > 2*109/l;

• toxic granularity in neutrophyles;

• thrombocytopenia;

• anaemia;

• increase of level of acute stage proteins;

• bacteriemia.

Bacteriemia - presence of viable bacteria in the blood confirmed bacteriologically (positive result of bacterial noculation of blood).

SIRS + bacteriemia = sepsis.

SIRS + local hearth of infection (omphalitis) = sepsis.

SIRS + clinic of infection = sepsis.

SIRS and bacteriemia can exist in the organism independently; unrelated to sepsis: local infection (pneumonia) + short-term bacteriemia – sepsis.

Multiple organ disorders – any combination of DIC-syndrome, RDS, acute kidney failure, hepatobiliary dysfunctions, dysfunction of CNS.

Criteria of neonatal sepsis:

- Presence of risk factors of the development of neonatal sepsis.
- Presence of respiratory dysfunctions (noisy breathing, intercostal retraction, BR > 60/min. or apnea > 15 sec.), circula-tory dysfunction (HR > 160/min. or < 100/min., oliguria, low perfusion of organs and tissues, hypotension – systolic AP < 35 mm Hg).
- Presence of early nonspecific clinical signs of infection (microsymptoms of sepsis): flabbiness, refuse of feeding, disturbance of thermoregulation, abdominal distension, dyspepsia, rash, gray skin, hepatomegaly) in combination with one of the laboratory criteria of SIRS.
- Combination of SIRS and pneumonia (lungs – main organ-target for causative agent).

Diagnosis example: late onset staphylococcal sepsis, septicopyemia: (omphalitis, bilateral pneumonia with cardiovascular syndrome, respiratory failure II gr.), acute duration, DIC-syndrome.

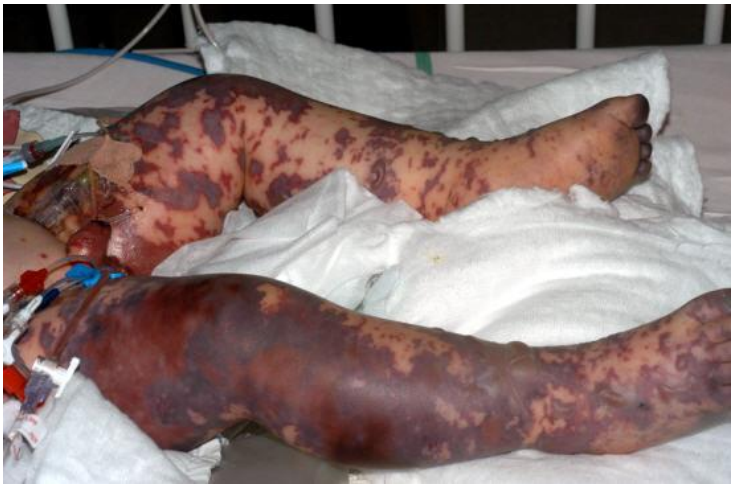


Figure 67 – DIC-syndrome

Sepsis/pneumonia, early-onset

Definition: clinical illness w/ positive bacterial blood culture at < = age 5 days

Prevalence: 1:2 000–1:5 000 live births.

Etiologic agent: 50 % gram positive, most commonly group B streptococcus (GBS); 50 % gram negative, most commonly E. coli.

Risk factors for early-onset bacterial sepsis*:* prematurity; rupture of membranes (> 18 hrs); maternal colonization w/ GBS; maternal UTI; signs or symptoms of chorioamnionitis:

– maternal fever (>3 7.8 ^{0}C);

– maternal leukocytosis (note: maternal WBC normally elevated in pregnancy, labor);

– maternal abdominal pain;

– cloudy or foul-smelling amniotic fluid.

Risk factors for early-onset bacterial sepsis: preterm, premature rupture of membranes; low socioeconomic status; male gender.

Signs*:* hypothermia, hyperthermia, respiratory distress, apnea, cyanosis, jaundice,

hepatomegaly, hypoglycemia, hyperglycemia, hyperbilirubinemia (total &/or direct), lethargy, irritability, hypotonia, vomiting, abdominal distention, diarrhea;

weak pulses, poor perfusion, hypotension w/ shock; petechiae/bleeding w/ thrombocytopenia, DIC.

Tests

No single laboratory test diagnostic of infection, other than positive culture result from deep body site (blood, urine, CSF, abscess, etc.). Best screening lab tests have <= 30–35 % pos predictive value. Sepsis screens – combined tests (WBC/differential count, C-reactive protein) most useful.

– Positive sepsis screen defined as 2 or more abnormal lab values obtained concurrently.

– If only a single value is abnormal it is considered a negative sepsis screen.

– Negative sepsis screen can exclude infection w/ a high degree of accuracy (99 %) if obtained 12–24 hrs following birth.

– *Abnormal values:*

• absolute neutrophil (PMN) count < = 1 750/mm^3;

• immature/total PMN ratio > = 0.2;

•absolute band count > = 2,000/mm^3;

• C-reactive protein > = 1mg/dL.

– *Recommended screening strategy:*

• asymptomatic infants w/ risk factors (PROM > = 18 hrs, maternal colonization w/GBS, signs consistent w/ maternal chorioamnionitis);

• sepsis screen age 12 hrs;

• symptomatic infants;

• sepsis screen at 12 hrs (do not delay cultures & empiric therapy).

Cultures (note: negative blood cultures do not exclude sepsis, pneumonia, meningitis, or UTI):

– < 72 hrs old: blood culture (optimal volume 1 mL);

– > = 72 hrs old: blood & urine cultures;

– repeat blood culture should be obtained in all infants w/ bacteremia after Rx initiated to ensure blood has been cleared.

Lumbar puncture indicated for:

• positive blood culture;

• persistently abnormal clinical signs (apnea, seizures, persistent lethargy, etc.)

Diarrhea: stool culture.

CXR w/ resp distress

Tests to narrow DDx or to detect complications:

– plasma glucose, plasma [Ca];

– blood gas;

– Hct, platelet count;

– PT, PTT, fibrinogen, D-dimers w/ petechiae, bleeding;

– CNS imaging w/ CNS signs;

– abdominal films (AP & left lateral decubitus w/ abd. signs).

Differential diagnosis

Other infections:

– urinary tract infection;

– herpes simplex infection;

– cytomegalovirus, congenital & cytomegalovirus, perinatal;

– toxoplasmosis, congenital;

– candidiasis, systemic.

Inborn errors of metabolism, metabolic disturbances (adrenal insufficiency and congenital adrenal hyperplasia; hypocalcemia and hypoglycemia).

CNS signs: asphyxia, hemorrhage, seizures (intraventricular hemorrhage and stroke, ischemic, perinatal and neonatal; hypotonia).

Primary or acquired coagulopathy (hemorrhagic disorders in the newborn).

Disorders causing resp. distress.

Disorders causing unconjugated/conjugated hyperbilirubinemia.

Disorders causing hepatomegaly.

Disorders causing shock.

Disorders causing abdominal signs.

Management

What to do first:

– ABCs (airway, breathing, circulation)

General measures:

– correct acid/base disturbances;

– establish IV access.

Specific therapy*:*

Antimicrobial therapy:

Indications for initiating treatment:

• persistent signs c/w sepsis in absence of clear etiology;

• positive sepsis screen w/ risk factors;

• GA < 35 wk w/ risk factors.

Choice of antibiotics depends on sensitivities of organisms causing sepsis in given nursery:

– caution: sensitivities must always be confirmed;

– empiric therapy must be appropriate for gram-positive and gram-negative pathogens;

– *ampicillin/aminoglycoside* or

– *ampicillin/cefotaxime* (note: rapid development of resistance may occur w/ use of cefotaxime as initial empiric therapy);

– once infecting organism is identified, usually treated w/ single antibiotic (see exceptions below);

– Streptococcus agalactiae (GBS): *penicillin or ampicillin;*

– E. coli: *Ampicillin* (for susceptible strains); *Kanamycin or Gentamicin* for resistant strains;

– Listeria monocytogenes: *ampicillin & gentamicin;*

– Enterococcus: *ampicillin &gentamicin; vancomycin* for resistant strains;

– Staphylococcus epidermidis resistant to oxacillin – *vancomycin;*

– Staphylococcus aureus:

• methicillin-sensitive: *methicillin, oxacillin,* or *nafcillin;*

• methicillin-resistant (MRSA): *vancomycin.*

– When Vancomycin or Aminoglycoside continues > 72 h, monitor serum level:

• vancomycin: trough < 10 mcg/mL;

• gentamicin: peak 5–10 mcg/mL; trough < 2 mcg/mL.

– Duration of treatment:

• discontinue antibiotic if blood culture is negative after 48 hrs w/o clinical signs/setting strongly suggestive of sepsis/pneumonia;

• consider treatment for 7–10 days in spite of negative blood culture w/ clinical setting strongly suggestive of sepsis/pneumonia;

• sepsis confirmed by blood culture w/o meningitis 7–10 days;

• meningitis.

Follow-up: hearing screen for all infants receiving aminoglycoside antibiotics, neurodevelopmental.

Complications:

– meningitis;

– DIC;

– shock.

Prognosis:

– mortality < 10 % in term infants w/ appropriate early therapy;

– mortality increases w/ decreasing gestational age;

– even w/o meningitis, confirmed bacterial sepsis associated w/increased risk of neurologic handicaps.

Late Onset Sepsis / Pneumonia(nosocomial)

Presents > 5 days of age (mean, 17 days)

Risk factors:

– prematurity, LBW (marked increase in incidence at < 30 wks & < 1 500 g);

– maternal Hx of pre-eclampsia w/ infant neutropenia in 1st wks of life;

– infants w/ pediatric surgical GI anomalies (e. g., congenital diaphragmatic hernia, necrotizing enterocolitis);

– male gender;

– indwelling central venous lines; assoc w/88 % of cases of coagulase-negative staphylococcal sepsis;

– CNS shunts;

– parenteral hyperalimentation;

– IV lipids;

– recurrent/prolonged antibiotic treatment;

– prolonged mechanical ventilation;

– H2 blockers for gastroesophageal reflux;

– steroid Rx for bronchopulmonary dysplasia;

– prolonged length of stay;

– overcrowding, understaffing, use of multiple-dose med vials in NICUs.

Signs:

– sudden onset, recurrence or increase in episodes of apnea, bradycardia, &/or O_2 desaturation;

– increasing req for resp support;

– feeding intolerance w/ emesis &/or increased volume of gastric aspirates;

– temp instability (hyperthermia > hypothermia);

– decreased activity &/or tone;

– hypotension; poor perfusion.

Tests

Basic tests

Blood cultures: simultaneous cultures from peripheral vein, all indwelling central lines:

– most commonly isolated organisms responsible for nosocomial sepsis: coagulase-negative staphylococci, Staphylococcus aureus, Enterococcus sp, Enterobacter sp, E. coli;

– Klebsiella sp, Pseudomonas sp, Candida sp more frequently isolated in "epidemic" outbreaks CBC w/ differential (calculate absolute neutrophil count, immature: total neutrophil ratio);

– lumbar puncture w/ CSF culture, cell count, Gram stain, protein, glucose (nosocomial sepsis assoc w/meningitis in 10 % of cases);

– urine culture (suprapubic tap procedure of choice; clean-catch urine if platelet count low);

– CXR w/ resp distress;

– W/ feeding intolerance: AP & left lateral decubitus abd films.

Other diagnostic tests

C-reactive protein (CRP):

– serial CRPs > 3 mg/dL at time of symptoms, 12–18 hrs later, > 24 hrs later have increasing sensitivities for identifying infants w/ nosocomial sepsis (35 %, 92 %, 97 %, respectively);

– CRP of value to determine whether to discontinue antibiotics at 48–72 hrs;

– persistently elevated CRP suggests further work-up required.

Differential diagnosis

Symptom-specific

Apnea, bradycardia, O_2 desaturations/increasing req for resp support:

– DDx: apnea of prematurity; worsening of primary lung disease or chronic lung disease; anemia of prematurity

– evaluation: consider, based on physical, lab findings: trial of caffeine; Initiating or augmenting mgt of chronic lung disease w/diuretics, systemic or inhaled steroids, or bronchodilators; PRBC transfusion.

Feeding intolerance/abdominal distention:

– DDx: necrotizing enterocolitis; intestinal obstruction due to stricture physiologic hypomotility; volvulus, etc.;

– evaluation: pediatric surgery consult; serial abdominal films; contrast studies as indicated.

Temp. instability:

– assess environmental temp control;

– consider CNS etiologies or drug effects (e. g., prosta-glandin E1) on temp control.

Management

What to do first:

After completion of sepsis evaluation, initiate empiric therapy w/vancomycin & gentamicin.

Note: Epidemics of nosocomial sepsis may require temporary changes in choice of agents for empiric therapy.

General measures:

– provide cardiorespiratory support as needed, incl O_2, ventilation, pressors;

– transfuse platelets, FFP, PRBC as indicated;

– place NPO; continue TPN;

– repeat blood cultures daily until sterile;

– remove all non-critical central lines, use peripheral IVs until blood cultures negative for at least 48 hrs:

• on occasion, nosocomial bacteremia can be treated by administering antibiotics through central line w/o removing it;

• central lines should always be removed with fungal or S. aureus sepsis.

– monitor vancomycin (trough levels) & gentamicin (trough levels) & adjust dose &/or administration interval as indicated.

Specific therapy:

– prevention: universal adherence to good handwashing practices prior to contact w/ any infant

Antibiotic therapy:

• if blood cultures positive, review sensitivities & narrow Rx to least toxic, effective antibiotic regimen [e. g., for coagulase negative staphylococci sensitive to oxacillin, d/c vancomycin & gentamycin, complete 10-day course of IV antibiotic Rx (from 1st day of neg cultures) w/ oxacillin]:

• consider 7-day course for coagulase-negative staphylococci sepsis that clears immediately w/ Rx;

• if blood cultures negative, infant clinically improved, d/c antibiotics at 48–72 hrs;

• lumbar puncture in all bacteremic infantswhen clinically stable.

Adjuvant therapy:

– IVIG – benefit marginal;

– WBC transfusions:

• reduce mortality in infants w/ documented bone marrow depletion of WBCs;

• more beneficial w/ gram-negative sepsis;

• should be used w/ caution in gram-positive infections due to increased incidence of WBC aggregation in lungs w/ deterioration in pulm status.

– ECMO: reduces mortality in infants w/ septic shock, pneumonia, persistent pulmonary hypertension of the newborn; higher incidence of morbidity compared to nonseptic infants treated w/ ECMO;

– G-CSF: Treatment w/ early-onset sepsis has no impact on mortality but reduces subsequent incidence of nosocomial sepsis;

– low-dose prophylactic vancomycin to reduce the incidence of catheter-related coagulase-negative staphylococci septicemia:

• does not affect overallmortality or length of stay;

• weigh against risk of development of vancomycin-resistant organisms;

• not currently recommended.

Follow-up

During treatment: serial CRPs; repeat blood cultures until negative; W/ persistent bacteremia (> = 2 + serial blood cultures 24–48 hrs apart) or failure of elevated CRP to decline:

– echocardiogram to r/o endocarditis or "fungus ball";

– serial limb exam for evidence of septic joints or osteomyelitis; radiographic studies as indicated;

– ophthal exam for evidence of septic emboli;

– renal US for fungal sepsis;

– neurol eval, imaging studies if supported by physical findings;

– serial CRP &/or ESR to monitor response to antibiotic treatment or follow bone infection if present.

Complications and prognosis:

– increased mortality;

– increased risk of recurrent bacterial infections, infections w/ resistant organisms, fungal systemic infections;

– prolonged length of stay;

– prolonged need for resp. support;

– increased incidence of bronchopulmonary dysplasia;

– increased risk of neurodevelopmental abnormalities.

Septic Shock

Septic shock should be suspected in any newborn with tachycardia, respiratory distress, poor feeding, poor tone, poor color, tachypnea, diarrhea or reduced perfusion particularly in the presence of prenatal risk factors like chorioamnionitis or prolonged rupture of membranes.

The predominant clinical sign is *circulatory failure* that can coexist with multiple organ damage, severe coagulopathy, metabolic acidosis and electrolyte alterations. During the compensated stage *blood pressure* remains normal and cardiac output is maintained. Clinical signs are pallor, increased capillary refill time (refill > 2), tachycardia, decreased urine output, mild agitation and confusion, signs of cerebral hypoperfusion.

When compensatory mechanisms fail, cardiac output falls resulting in a reduction of oxygenation and increase of anaerobic metabolic mechanisms. The toe/core temperature gap widens, and the peripheries become cool and mottled, the pulse becomes small and weak, oliguria worsens to the point of anuria. The further deterioration of *cerebral perfusion* leads to irritability, sleepiness and impairment of conscious state. Despite intense peripheral vasoconstriction, *hypotension* occurs. In the meantime, the clinical condition of the newborn becomes critical.

Newborn septic shock is typically accompanied by, *acidosis and hypoxia* that can lead to an increase in *pulmonary resistance* and persistence of the *patent ductus Botallo*, resulting in persistent fetal circulation which will result in right ventricle failure with right to left

shunting at the atrial and ductus arteriosus levels causing cyanosis, hepatomegaly and tricuspid regurgitation.

Diagnosis

Early recognition of neonatal shock allows to establish an adequate therapy and save lives. Ideally shock should be clinically diagnosed before hypotension occurs.

Laboratory diagnosis is mainly based on controlling the blood gases, CBC with differential, glucose, electrolytes, albumin, creatinine, urea, lactate, blood pyruvate, coagulation parameters, serum and urine osmolarity, cultures with susceptibility testing (blood culture, urine culture, culture catheters or drainage).

Research offers an increasing number of biological markers for early detection of sepsis, but many of them failed to differentiate between sepsis and other non septic critical illness.

Procalcitonine (PCT) revealed superior to C reactive protein (CRP) to differentiate children with sepsis from those with septic shock, mainly at admission and 12 h later. Increase of PCT levels relating to the severity, course and prognosis of disease. PCT values is significantly increased in neonates with septic shock (92.5 ng/mL) compared to those with SIRS (41 ng/mL), neonatal sepsis (10,26 ng/mL) and purulent meningitis (9,80 ng/mL). CRP is increasing without statistical differences in all stages.

Serum lactate level is considering an important biomarker to distinguish sepsis from septic shock. Normally a small amount of lactate is produced and all healthy tissue have the capacity to convert it, in aerobic condition, to pyruvate, used for cellular metabolism. When sepsis-associated multisystem organ failure occurs, this metabolic capacity, in anaerobic condition, is decreasing and lactate levels rise. In the past the lactate levels is used to distinguish between state of adequate perfusion and poor oxygen delivery. At present, as has been others factors like adrenergic stimuli and lung injury, it became important to consider the increase lactate levels in the general clinical context while a reduction of serum lactate is still advocating as a target for treatment could increase that lactate.

Among imaging techniques: chest X-ray, ECG, ultrasound scans of brain, heart and kidney are proposed.

Minimally invasive monitoring like central vein access and arterial pressure monitoring, and noninvasive tools like echocardiography are considered necessary in septic neonates.

Hemodynamic variables including (perfusion pressure mean arterial pressure [MAP], minus *central venous pressure* [CVP]), and cardiac output (CO) should guide resuscitation treatment.

The systemic circulation is represented by CO = (MAP – CVP)/SVR (systemic vascular resistance). This relationship is important for organ perfusion.

Measurement of urine output and creatinine clearance can be also used as an indicator of adequate blood flow and perfusion pressure. Because blood pressure does not necessarily reflect CO, it is recommended that normal CO and/or SVC (superior vena cava) flow, measured by Doppler echocardiography, be a primary goal as well.

Measurement of CO and O_2 consumption were proposed as being of benefit in patients with persistent shock because a cardiac index (CI) between 3.3 and 6.0 L/min/m2 and O_2 consumption > 200 mL/min/m^2 are associated with improved survival. Because low CO is associated with increased O2 extraction, $ScvO_2$ saturation can be used as an indirect indicator of whether CO is adequate to meet tissue metabolic demand. If tissue oxygen delivery is adequate, then assuming a normal arterial oxygen saturation of 100 %, mixed venous saturation is > 70 %.

In VLBW infants, SVC blood flow measurement was reportedly useful in assessing the effectiveness of shock therapies and prognostic value because approximates blood flow from the brain. It has been observed that a value > 40 mL/kg/min is associated with improved neurologic outcome and survival. $ScvO_2$ saturation can be used in low birth weight infants, but may be misleading in the presence of left to right shunting through the patent ductus arteriosus.

Shock should be diagnosed before blood pressure decrease by clinical signs like hypothermia, hyperthermia, vascular alterations,

tachycardia, bradycardia. Blood pressure should not be used as a marker of systemic blood flow in neonates because oxygen delivery to cells is dependent upon cardiac output and systemic blood flow than on blood pressure and a neonate may be hypotenisve but still have adequate oxygen delivery.

E-selectin, a protein expressed by the endothelium after activation at sites of acute inflammation, taking part in the first step of the adhesion cascade, shows plasma levels higher in nonsurvivors than in survivors and in patients with hemodynamic dysfunction than in those without hemodynamic dysfunction.

Management

In spite there are extensively studied multiple organ dysfunction scores and well-defined algorhythmic guidelines for treatment, there is a large amount of practice variability in neonatal septic shock.

In the onset of septic shock an early and aggressive management of septic shock is needed because for each hour of delay the risk of death increases by 2 times. The immediate objective is to optimize the perfusion and delivery of oxygen and nutrients to tissues.

According to the guidelines of the American College of Critical Care Medicine, 60 min is the average time needed to provide adequate circulatory support and block the development of shock. Recognize decreased perfusion, cyanosis and espiratory distress syndrome (RDS), establishing an airway for adequate ventilation and oxygenation and obtaining rapid peripheral or central venous access or intraosseus access are the first steps in managing a newborn in shock (0–5 min).

It is important to rember that all babies with shock and hepatomegaly, cyanosis or pressure gap between upper and lower limbs should begin treatment with prostaglandin within 10 min, until congenital heart disease is excluded.

A key element in the therapeutic management of septic shock is the early recognition of infection. One of the most important

factors in progression from infection to septic shock is the use of inappropriate or delayed antibiotic therapy.

Antibiotics

After appropriate blood cultures, tests for biomarkers of sepsis, glucose and ionized calcium are made, the empirical antibiotic therapy must be established.

A term neonate or a late pre-term infant ≤ 7 days of age with sepsis should be treated with *ampicillin and gentamicin within 60 min from the suspected diagnosis.*

The empiric therapy for late onset sepsis (LOS) in term or late preterm infants admitted from the community after 7 days, is a combination of ampicillin and gentamicin too. In case of meningitis, cefotaxime is administered every 8 hrs instead of gentamicin. If there is history of prolonged hospitalization or the newborn infant has a central venous catheter (CVC) vancomycin is preferable to ampicillin. In this case, vancomycin and gentamicin/cefotaxime is preferable empiric coverage because provides additional coverage for S. aureus and CONS.

Afterwards, once the causative organism has been identified, antibiotics can be targeted only against that organism. As Herpes simplex virus Type I is one of the causes of intractable 'shock', anti-viral (acyclovir) medication, should be initiated, even in the absence of history of maternal infection with herpes virus, in infants who either does not respond to standard therapy or has persistent signs and symptoms of infection with negative bacterial or fungal cultures or present in septic shock.

Therapeutic plasma levels should be monitored because renal and hepatic dysfunction may lead to abnormal volumes and levels of distribution of drugs.

The decision to continue or stop antibiotic therapy must be based on clinical signs plus biomarkers of sepsis and not only on negative blood culture results, that are frequently negative. Intravascular access devices potential source of severe sepsis or septic shock should be promptly removed after establishing other vascular access.

Mechanical ventilation

Respiratory failure in severe sepsis and septic shock, due to low functional residual capacity may require elective intubation and ventilation to garantee oxygenation and tissue perfusion, trying to avoid hyperoxemia and over distention of alveoli, which is a potent inducer of IL-6 release.

Volume replacement

Septic prematures microcirculation evaluation shows that changes are already detectable 24 hours before the systemic sepsis parameters are apparent. The damage of vascular endothelium, caused by inflammatory mediators, results in vasodilation and fluid shifts into the interstitial space resulting in intravascular volume decrease. So neonates in shock often require volume replacement to maintain and/or restore adequate tissue perfusion. A significant reduction in mortality has been obtained if hemodynamic function is optimized in a few time. The underlying importance is the maintenance of preload and tissue perfusion.

Volume expansion could be carried with crystalloids, colloid or blood products, if hemorrhage.

Crystalloids have been used more extensively because they are inexpensive and fluid retention and the incidence of adverse effects (e. g., intraventricular hemorrhage and infection transmission) may be lower. Normal saline and lactated ringers are 2 examples of crystalloid solutions used for volume expansion.

Colloid solutions contain minerals and electrolytes. They increase oncotic pressure, do not easily cross semipermeable membranes, may remain in the intravascular space longer than crystalloids and allow to use small volumes with less incidence of pulmonary edema. The colloid most commonly used for volume expansion is 5 % albumin.

In term infants or older preterm infants, aggressive volume expansion (push boluses of 10–40 mL/kg up to 60 mL/kg over 20 to 30 minutes should be considered. To prevent reperfusion injury it is preferable to increase the total volume and rate of fluid infusion rather than give repeated boluses of fluids.

Those infants who after adequate fluid resuscitation do not self-diurese may need diuretics to prevent fluid overload. For very preterm neonates there is insufficient evidence to support early volume expansion because of a significant risk of intracranial hemorrhage associated with rapid volume expansion from fluctuations in cerebral perfusion and developing heart failure and/or pulmonary overcirculation from resultant left to right flow through a patent ductus arteriosus, specially in case of anemia. In the septic shock, when hemoglobin levels are below 12 g/dL (Hb < 12 g/dL), packed red blood cells transfusion is recommended.

Cardiovascular agents

Inotropes are indicated when myocardial contractility remains compromised despite adequate volume replacement. They should be administered through a peripheral or intraosseous line before central access is available. A delay in administration of inotropes is associated with a 20-fold increased mortality risk.

Medications in this group include *dopamine, dobutamine, epinephrine, and norepinephrine*.

Both dopamine and epinephrine are efficacious in improving the mean arterial blood pressure but epinephrine is associated with more short-term adverse effects such as enhanced chronotropic response, hyperglycemia requiring insulin treatment, increased plasma lactate levels and inadequate gastric mucosa perfusion.

Dobutamine increases systemic blood flow more effectively than dopamine.

Anyhow dopamine remains the first-line agent in neonates, and epinephrine may be used in dopamine-resistant septic shock. Dopamine: is a natural precursor of both epinephrine and norepinephrine, stimulates the dopaminergic receptors β and α, in this order, with increasing dose. The initial dose of 5–10 mcg/kg/min is recommended and incremented by 2.5 mcg/kg/min steps every 10–15 minutes. Prematures may be resistant to its action due to deficient deposit of norepinephrine.

A dose ≥ 10 mcg/kg/min dopamine may reduce TSH release, and producing relevant adverse effects such as tachycardia,

arrhythmias, bradycardia, nausea and vomiting. If low cardiac output and high systemic vascular resistance persist, dobutamine and/or a type III phosphodiesterase inhibitor may be indicated.

Adrenergic (inotropic) dose dopamine is indicated between 5–9 mcg/kg/min associated with dobutamine 2.5–10 mcg/kg/min, already during the first man-agement hour. If the patient does not adequately respond to these interventions, then epinephrine (0.05–0.3 μg/kg/min) can be infused.

It is very important to have service procedures standardized to control for the results. Dopamine use is safe in patients. A combination of dopamine at low dosage and dobutamine is initially recommended. Epinephrine at a low dose < 0.03 mg/kg/min acts as a potent inotrope, chronotrope, and both systemic and pulmonary vasodilatator.

Corticosteroids

Corticosteroids are often used to treat shock when volume expansion and inotropes are ineffective to raise blood pressure. They may act by improving the vessel wall sensitivity to circulating cathecolamines or to exogenous vasoactive drugs, inhibiting the nitric oxide synthase enzyme expression, or suppressing immune responses. Additionally, septic newborns may develop relative adrenal insufficiency, manifested by low stress cortisol levels.

Hydrocotisone and dexamethasone are the most used steroids. There are no specific recommendations for neonates regarding the use of dexametasone, conversely *hydrocotison* is life saving and should be reserved for refractory shock patients, or in services missing inodilators, in epinephrine-resistant shock, when adrenal insufficiency is suspected. The dose of hydrocortisone ranged from the "stress-dose" used in adrenal insufficiency of 1–2 mg/kg to the empirical shock dose of 50 mg/kg.

Nutrition

Severe illness causes a catabolic process, increases an infant's metabolic requirements, especially in preterm infants owing to poor muscle mass and energy reserves. Appropriate quantities of energy, minerals, and vitamins can be provided rather by enteral feedings to

reduce bacterial translocation from the gut mucosa into the circulation and preserve gut mucosal function.

9. ANTIBIOTICS TREATMENT OF NEONATES INFECTIONS

Table 10 – Antibiotics treatment of neonatal infections

		DOSAGE (MG/KG) AND INTERVAL OF ADMINISTRATION				
		Weight < 1 200 g	Weight 1 200–2 000 g		Weight > 2000 g	
ANTIBIOTIC	ROUTE	*Age 0–4 wks*	*Age 0–7 days*	*Age > 7 days*	*Age 0–7 days*	*Age > 7 days*
Amikacin[†] (SDD)	IV, IM	7.5 q 12 h	7.5 q 12 h	7.5 q 8 h	10 q 12 h	10 q 8 h
Amikacin[†] (ODD)	IV, IM	18 q 48 h	16 q 36 h	15 q 24 h	15 q 24 h	15 q 24 h
Ampicillin	IV, IM					
Meningitis		50 q 12 h	50 q 12 h	50 q 8 h	50 q 8 h	50 q 6 h
Other infections		25 q 12 h	25 q 12 h	25 q 8 h	25 q 8 h	25 q6h
Aztreonam	IV, IM	30 q 12 h	30 q 12 h	30 q 8 h	30 q8h	30 q 6 h
Cefazolin	IV, IM	20 q 12 h	20 q 12 h	20 q 12 h	20 q 12 h	20 q 8 h
Cefepime	IV, IM	50 q 12 h	50 q 12 h	50 q 8 h	50 q 12 h	50 q 8 h

Continuation of the table 10

Cefotaxime	IV, IM	50 q 12 h	50 q 12 h	50 q 8 h	50 q 12 h	50 q 8 h
Ceftazidime	IV, IM	50 q 12 h	50 q 12 h	50 q 8 h	50 q 8 h	50 q 8 h
Ceftriaxone	IV, IM	50 q 24 h	50 q 24 h	50 q 24 h	50 q 24 h	75 q 24 h
Cephalothin	IV	20 q 12 h	20 q 12 h	20 q 8 h	20 q 8 h	20 q 6 h
Chloramphenicol[†]	IV, PO	25 q 24 h	25 q 24 h	25 q 24 h	25 q 24 h	25 q 12 h
Ciprofloxacin[§]	IV	—	—	10–20 q 24 h	—	20–30 q 12 h
Clindamycin	IV, IM, PO	5 q 12 h	5 q 12 h	5 q 8 h	5 q 8 h	5 q 6 h
Erythromycin	PO	10 q 12 h	10 q 12 h	10 q 8 h	10 q 12 h	10 q 8 h
Gentamicin[†] (SDD)	IV, IM	2.5 q 18 h	2.5 q 12 h	2.5 q 8 h	2.5 q 12 h	2.5 q 8 h
Gentamicin[†] (ODD)	IV, IM	5 q 48 h	4 q 36 h	4 q 24 h	4 q 24 h	4 q 24 h
Imipenem	IV, IM	—	20 q 12 h	20 q 12 h	20 q 12 h	20 q 8 h
Linezolid	IV	—	10 q 12 h	10 q 8 h	10 q 12 h	10 q 8 h

Continuation of the table 10

Methicillin	IV, IM					
Meningitis		50 q 12 h	50 q 12 h	50 q 8 h	50 q 8 h	50 q 6 h
Other infections		25 q 12 h	25 q 12 h	25 q 8 h	25 q 8 h	25 q 6 h
Metronidazole[[‡]]	IV, PO	7.5 q 48 h	7.5 q 24 h	7.5 q 12 h	7.5 q 12 h	15 q 12 h
Mezlocillin	IV, IM	75 q 12 h	75 q 12 h	75 q 8 h	75 q 12 h	75 q 8 h
Meropenem[[**]]	IV, IM	—	20 q 12 h	20 q 12 h	20 q 12 h	20 q 8 h
Nafcillin	IV	25 q 12 h	25 q 12 h	25 q 8 h	25 q 8 h	37.5 q 6 h
Netilmicin[[†]] (SDD)	IV, IM	2.5 q 18 h	2.5 q 12 h	2.5 q 8 h	2.5 q 12 h	2.5 q 8 h
Netilmicin (ODD)				Same as for genta-micin		
Oxacillin	IV, IM	25 q 12 h	25 q 12 h	25 q 8 h	25 q 8 h	37.5 q 6 h
Penicillin G (units)	IV					
Meningitis		50 000 q 12 h	50 000 q 12 h	50 000 q 8 h	50 000 q 8 h	50 000 q 6 h
Other infections		25 000 q 12 h	25 000 q 12 h	25 000 q 8 h	25 000 q 8 h	25 000 q 6 h

Continuation of the table 10

Penicillin benzathine (units)	IM	—	50 000 (one dose)	50 000 (one dose)	50 000 (one dose)	50 000 (one dose)
Penicillin procaine (units)	IM		50 000 q 24 h	50 000 q 24 h	50 000 q 24 h	50 000 q 24 h
Piperacillin	IV, IM	—	50–75 q 12 h	50–75 q 8 h	50–75 q 8 h	50–75 q 6 h
Peperacillin/ tazobactam				Same as for pipe-racillin		
Rifampin	PO, IV	—	10 q 24 h	10 q 24 h	10 q24h	10 q24h
Ticarcillin	IV, IM	75 q 12 h	75 q 12 h	75 q 8 h	75 q8h	75 q6h
Ticarcillin-clavulanate				Same as for ticarcillin		
Tobramycin (SDD)	IV, IM	2.5 q 18 h	2 q 12 h	2 q 8 h	2 q 12 h	2 q 8 h
Tobramycin (ODD)				Same as for gen-tamicin		
Vancomycin	IV	15 q 24 h	10 q 12 h	10 q 12 h	10 q 8 h	10 q 8 h

Once the pathogen has been identified and antibiotic sensitivities determined, the most appropriate drug or drugs should be selected. For most gram-negative enteric bacteria, ampicillin and an aminoglycoside or a 3rd-generation cephalosporin (cefotaxime or

ceftazidime) should be used. Enterococci should be treated with both a penicillin (ampicillin or piperacillin) and an aminoglycoside because the synergy of both drugs is needed. Ampicillin alone is adequate for *L. monocytogenes*, and penicillin suffices for GBS. Clindamycin or metronidazole is appropriate for anaerobic infections.

Third-generation cephalosporins such as cefotaxime are valuable additions for treating documented neonatal sepsis and meningitis because (1) the minimal inhibitory concentrations needed for treatment of gram-negative enteric bacilli are much lower than those for the aminoglycosides, (2) excellent penetration into CSF occurs, and (3) much higher doses can be given. The end result is much higher bactericidal titers in serum and CSF than achievable with ampicillin-aminoglycoside combinations. The routine use of 3rd-generation cephalosporins for suspected sepsis in NICU patients is inappropriate because of the potential for rapid emergence of resistant organisms and a possible link with candida sepsis. The emergence of antibiotic resistance among pathogens that infect newborns is of great concern. Vancomycin-resistant enterococci and vancomycin-insensitive *S. aureus* are worrisome. Guidelines to limit the use of vancomycin must be followed. Although vancomycin use cannot be avoided in neonatal units where methicillin-resistant *S. aureus* is endemic, use can be reduced by limiting empirical therapy to patients with a high suspicion of severe infection with coagulase-negative staphylococci (severely ill neonate with an indwelling intravascular catheter) and discontinuing therapy after 2–3 days when blood cultures are negative. The rational use of antibiotics in neonates involves using narrow-spectrum drugs when possible, treating infection and not colonization, and limiting the duration of therapy.

Therapy for most bloodstream infections should be continued for a total of 7–10 days or for at least 5–7 days after a clinical response has occurred. A blood culture taken 24–48 hrs after initiation of therapy should yield negative results. If the blood culture remains positive, the possibility of an infected indwelling catheter,

endocarditis, an infected thrombus, an occult abscess, subtherapeutic antibiotic levels, or resistant organisms should be considered. A change in antibiotics, longer duration of therapy, or removal of the catheter may be indicated. Treatment of newborn infants whose mothers received antibiotics during labor should be individualized. If early-onset sepsis is thought to be likely, treatment of the infant should be continued until it is shown that no infection has occurred (the infant remains asymptomatic for 24–72 hrs) or clinical and laboratory evidence of recovery is apparent. Furthermore, in the context of intrapartum antibiotic use, it is important to consider that the organism causing infection may be resistant to the antibiotic given to the mother, which may influence choice of antibiotic use in the infant.

For pneumonia developing in the 1st 7–10 days of life, a combination of ampicillin and an aminoglycoside or cefotaxime is appropriate. Nosocomial pneumonia, generally manifested after this time, can be treated empirically with methicillin or vancomycin and an aminoglycoside or a 3rd-generation cephalosporin. *Pseudomonas* pneumonia should be treated with an aminoglycoside combined with ticarcillin or ceftazidime. Pneumonia caused by *C. trachomatis* is treated with either erythromycin or trimethoprim-sulfamethoxazole; *U. urealyticum* infection is treated with erythromycin.

Presumptive antimicrobial therapy for bacterial meningitis should include ampicillin in meningitic doses and cefotaxime or gentamicin unless staphylococci are likely, which is an indication for vancomycin. Susceptibility testing of gram-negative enteric organisms is important because resistance to cephalosporins and aminoglycosides is common. Most aminoglycosides administered by parenteral routes do not achieve sufficiently high antibiotic levels in the lumbar CSF or ventricles to inhibit the growth of gram-negative bacilli. Therefore, some experts recommend a combination of intravenous ampicillin and a 3rd-generation cephalosporin for the treatment of neonatal gram-negative meningitis. Cephalosporins should not be used as empirical monotherapy because *L. monocytogenes* and enterococcus are resistant to cephalosporins.

Meningitis caused by GBS usually responds within 24–48 hrs and should be treated for 14–21 days. Gram-negative bacilli may continue to grow from repeated CSF samples for 72–96 hrs after therapy despite the use of appropriate antibiotics. Treatment of gram-negative meningitis should be continued for 21 days or for at least 14 days after sterilization of the CSF, whichever is longer. *P. aeruginosa*meningitis should be treated with ceftazidime. Metronidazole is the treatment of choice for infection caused by *B. fragilis.* Prolonged antibiotic administration, with or without drainage for treatment and diagnosis, is indicated for neonatal cerebral abscesses. CT scans are recommended for patients with suspected ventriculitis, hydrocephalus, or cerebral abscess (initial and follow-up assessments) and for those with an unexpectedly complicated course (prolonged coma, focal neurologic deficits, persistent or recurrent fever). Neonatal herpes meningoencephalitis should be treated with acyclovir, and empirical therapy should be considered in symptomatic infants with a CSF mononuclear pleocytosis. Pleconaril was the treatment of choice for severe enteroviral infections such as meningoencephalitis, carditis, or hepatitis.

Treatment of sepsis and meningitis may be divided into antimicrobial therapy for the suspected or known pathogen and supportive care. Careful attention to respiratory and cardiovascular status is mandatory. Adequate oxygenation of tissues should be maintained; ventilatory support is frequently necessary for respiratory failure caused by sepsis, pneumonia, pulmonary hypertension, or ARDS. Refractory hypoxia and shock may require extracorporeal membrane oxygenation, which has reduced mortality rates in full-term infants with respiratory failure. Shock and metabolic acidosis should be identified and managed with fluid resuscitation and inotropic agents as needed. Corticosteroids should be administered only for adrenal insufficiency. Fluids, electrolytes, and glucose levels should be monitored carefully with correction of hypovolemia, hyponatremia, hypocalcemia, and hypoglycemia. Hyperbilirubi-nemia should be monitored and treated aggressively

with phototherapy and/or exchange transfusion because the risk of kernicterus increases in the presence of sepsis and meningitis. Seizures should be treated with anticonvulsants. Parenteral nutrition is needed for any infant who cannot sustain enteral feeding. DIC may complicate neonatal septicemia. Platelet counts, hemoglobin, and clotting studies should be monitored. DIC is treated by management of the underlying infection, but if bleeding occurs, DIC may require fresh frozen plasma, platelet transfusions, or whole blood.

Because neutrophil storage pool depletion has been associated with a poor prognosis, a number of clinical trials of granulocyte transfusion therapy have been conducted, with variable results. The use of G-CSF or GM-CSF abolishes sepsis-induced neutropenia, but the effect of these cytokines on sepsis-related mortality is unclear. Modern leukapheresis techniques and the use of G-CSF to mobilize polymorphonuclear cells in healthy donors for use in granulocyte transfusion is a promising approach that needs further study. The use of intravenous immunoglobulin (IVIG) has been shown to decrease mortality in patients with sepsis; a meta-analysis of several trials recommended administration of a single dose of 500–750 mg/kg as adjunctive therapy. Selected IVIG preparations containing specific monoclonal antibodies are being studied.

10. HEMOLYTIC DISEASE OF THE NEWBORN (ERYTHROBLASTOSIS FETALIS)

Erythroblastosis fetalis is caused by the transplacental passage of maternal antibody active against paternal RBC antigens of the infant and is characterized by an increased rate of RBC destruction. It is an important cause of anemia and jaundice in newborn infants despite the development of a method of preventing maternal isoimmunization by Rh antigens. Although more than 60 different RBC antigens are capable of eliciting an antibody response, significant disease is associated primarily with the D antigen of the Rh group and with incompatibility of ABO factors. Rarely, hemolytic disease may be caused by C or E antigens or by other

RBC antigens such as C^W, C^X, D^U, K (Kell), M, Duffy, S, P, MNS, Xg, Lutheran, Diego, and Kidd. Anti-Lewis antibodies do not cause disease.

Hemolytic disease of the newborn caused by Rh incompatibility

The Rh antigenic determinants are genetically transmitted from each parent, determine the Rh type, and direct the production of a number of blood group factors (C, c, D, d, E, and e). Each factor can elicit a specific antibody response under suitable conditions; 90 % are due to D antigen and the remainder to C or E.

Pathogenesis. Isoimmune hemolytic disease from D antigen is approximately three times more frequent among white persons than among blacks. When Rh-positive blood is infused into an Rh-negative woman through error or when small quantities (usually more than 1 mL) of Rh-positive fetal blood containing D antigen inherited from an Rh-positive father enter the maternal circulation during pregnancy, with spontaneous or induced abortion, or at delivery, antibody formation against D antigen may be induced in the unsensitized Rh-negative recipient mother. Once sensitization has taken place, considerably smaller doses of antigen can stimulate an increase in antibody titer. Initially, a rise in IgM antibody occurs, which is later replaced by IgG antibody; the latter readily crosses the placenta and causes hemolytic manifestations

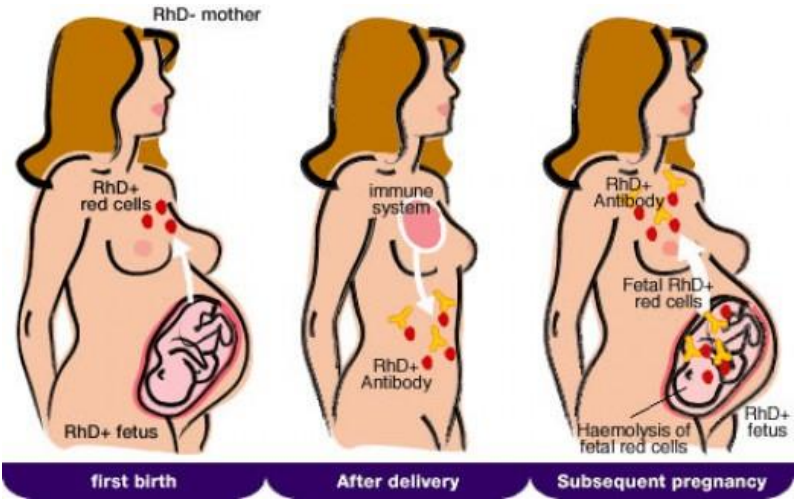


Figure 68 – Mechanism of development of rhesus conflict

Kernicterus

Kernicterus, or bilirubin encephalopathy, is a neurologic syndrome resulting from the deposition of unconjugated (indirect) bilirubin in the basal ganglia and brainstem nuclei. The pathogenesis of kernicterus is multifactorial and involves an interaction between unconjugated bilirubin levels, albumin binding and unbound bilirubin levels, passage across the blood-brain barrier, and neuronal susceptibility to injury. Disruption of the blood-brain barrier by disease, asphyxia, and other factors and maturational changes in blood-brain barrier permeability affect risk.

The precise blood level above which indirect-reacting bilirubin or free bilirubin will be toxic for an individual infant is unpredictable, but kernicterus is rare in healthy term infants and in the absence of hemolysis if the serum level is < 430 μmol/L. In previously healthy, predominantly breast-fed term infants, kernicterus has developed when bilirubin levels exceed 516 μmol/L, although the range is wide (361.2 –860 μmol/L). Onset is usually in the 1st wk of life, but may be delayed to the 2nd–3rd wks. The risk in infants with hemolytic disease is directly related to serum

bilirubin levels. The duration of exposure needed to produce toxic effects is unknown. Little evidence suggests that a level of indirect bilirubin < 430 μmol/L affects the IQ of healthy term infants without hemolytic disease. Nonetheless, the more immature the infant is the greater the susceptibility to kernicterus.

Signs and symptoms of kernicterus usually appear 2–5 days after birth in term infants and as late as the 7th day in premature infants, but hyperbilirubinemia may lead to encephalopathy at any time during the neonatal period. The early signs may be subtle and indistinguishable from those of sepsis, asphyxia, hypoglycemia, intracranial hemorrhage, and other acute systemic illnesses in a neonate. Lethargy, poor feeding, and loss of the Moro reflex are common initial signs. Subsequently, the infant may appear gravely ill and prostrated, with diminished tendon reflexes and respiratory distress. Opisthotonos with a bulging fontanel, twitching of the face or limbs, and a shrill high-pitched cry may follow. In advanced cases, convulsions and spasm occur, with affected infants stiffly extending their arms in an inward rotation with the fists clenched (Table 11). Rigidity is rare at this late stage.

Table 11 – Clinical Features of Kernicterus

ACUTE FORM
Phase 1 (1st 1–2 days): poor sucking, stupor, hypotonia, seizures
Phase 2 (middle of 1st wk): hypertonia of extensor muscles, opisthotonos, retrocollis, fever
Phase 3 (after the 1st wk): hypertonia
CHRONIC FORM
First year: hypotonia, active deep tendon reflexes, obligatory tonic neck reflexes, delayed motor skills
After 1st yr: movement disorders (choreoathetosis, ballismus, tremor), upward gaze, sensorineural hearing loss

Many infants who progress to these severe neurologic signs die; the survivors are usually seriously damaged, but may appear to recover and for 2–3 mo show few abnormalities. Later in the 1st yr of life, opisthotonos, muscle rigidity, irregular movements, and convulsions tend to recur. In the 2nd yr, the opisthotonos and seizures abate, but irregular, involuntary movements, muscle rigidity, or, in some infants, hypotonia increase steadily. By 3 yr of age, the complete neurologic syndrome is often apparent and consists of bilateral choreoathetosis with involuntary muscle spasms, extrapyramidal signs, seizures, mental deficiency, dysarthric speech, high frequency hearing loss, squinting, and defective upward eye movements. Pyramidal signs, hypotonia, and ataxia occur in a few infants. In mildly affected infants, the syndrome may be characterized only by mild to moderate neuromuscular incoordination, partial deafness, or "minimal brain dysfunction," occurring singly or in combination; these problems may be inapparent until the child enters school (see Table).

Pathology

The surface of the affected brain is usually pale yellow. On pathologic section, certain regions are characteristically stained yellow by unconjugated bilirubin, particularly the corpus subthalamicum, hippocampus and adjacent olfactory areas, striate bodies, thalamus, globus pallidus, putamen, inferior clivus, cerebellar nuclei, and cranial nerve nuclei. Nonpigmented areas may also be damaged, characterized by neuronal loss, reactive gliosis, and atrophy of involved fiber systems in late disease. The pattern of injury has been related to the development of oxidative enzyme systems in various regions of the brain and overlaps with that found in hypoxic brain damage. Evidence favors the hypothesis that bilirubin interferes with oxygen utilization by cerebral tissue, possibly by injuring the cell membrane; antecedent hypoxic injury increases the susceptibility of brain cells to injury. Gross bilirubin staining without the specific microscopic changes of kernicterus may not be the same entity.

Incidence and prognosis

By pathologic criteria, kernicterus will develop in ⅓ of infants (all gestational ages) with untreated hemolytic disease and bilirubin levels > 430–516 μmol/L. The incidence at autopsy in hyperbilirubinemic premature infants is 2–16 %. Reliable estimates of the frequency of the clinical syndrome are not available because of the wide spectrum of manifestations. Overt neurologic signs have a grave prognosis; more than 75 % of such infants die, and 80 % of affected survivors have bilateral choreoathetosis with involuntary muscle spasms. Mental retardation, deafness, and spastic quadriplegia are common.

Prevention

Although kernicterus has been thought to be a disease of the past, there are recent reports of neurotoxic effects of bilirubin in term and near-term infants discharged as healthy newborns. Some experts recommend universal screening for hyperbilirubinemia in the 1st 24–48 hrs of life to detect infants at high risk for severe jaundice and bilirubin-induced neurologic dysfunction.

Effective prevention requires ongoing vigilance and a practical, system-based approach in order to distinguish infants with benign newborn jaundice from those whose course may be less predictable and potentially harmful. Protocols using the hour-specific bilirubin nomogram, physical examination and clinical risk factors have been successful in identifying patients at risk for hyperbilirubinemia and candidates for targeted management. The American Academy of Pediatrics (AAP) has identified potentially preventable causes of kernicterus:

1) early discharge (< 48 hrs) with no early follow-up (within 48 hrs of discharge); this problem is particularly important in near-term infants (35–37 wks gestation);

2) failure to check the bilirubin level in an infant noted to be jaundiced in the 1st 24 hrs;

3) failure to recognize the presence of risk factors for hyperbilirubinemia;

4) underestimation of the severity of jaundice by clinical (visual) assessment;

5) lack of concern regarding the presence of jaundice;

6) delay in measuring the serum bilirubin level despite marked jaundice or delay in initiating phototherapy in the presence of elevated bilirubin levels; and

7) failure to respond to parental concern regarding jaundice, poor feeding, or lethargy. The AAP subcommittee on hyperbilirubinemia provided an evidence-based management guideline for infants at least 35 wks.

They further recommend determining before discharge each infant's risk factors from established protocols (see Table). The following is further recommended:

1) any infant who is jaundiced before 24 hrs requires measurement of the serum bilirubin level and, if it is elevated, the infant should be evaluated for possible hemolytic disease and

2) follow-up should be provided within 2–3 days of discharge to all neonates discharged earlier than 48 hrs after birth.

Early follow-up is particularly important for infants younger than 38 weeks' gestation. The timing of follow-up depends on the age at discharge and the presence of risk factors. In some cases, follow-up within 24 hrs is necessary. Post-discharge follow-up is essential for early recognition of problems related to hyperbilirubinemia and disease progression. Parental communication with regard to concerns about infant's skin color and behavioral activities should be addressed early and frequently, including education about potential risks and neurotoxicity. Ongoing lactation promotion, education, support, and follow-up services are essential throughout the neonatal period. Mothers should be advised to nurse their infant every 2–3 hrs and avoid routine supplementation with water or glucose water in order to ensure adequate hydration and caloric intake.

11. HEMORRHAGIC DISEASE OF THE NEWBORN

Vitamin K Deficiency

Deficiency of vitamin K, which is necessary for the synthesis of clotting factors II, VII, IX, and X, may result in clinically significant bleeding. This typically affects infants, who experience a transient deficiency related to inadequate intake, or patients of any age who have decreased vitamin K absorption. Mild vitamin K deficiency may affect long-term bone and vascular health.

Pathogenesis

Vitamin K is a group of compounds that have a common naphthoquinone ring structure. Phylloquinone, called vitamin K_1, is present in a variety of dietary sources, with green leafy vegetables, liver, and certain legumes and plant oils having the highest content. Vitamin K_1 is the form used to fortify foods and as a medication in the USA. Vitamin K_2 is a group of compounds called *menaquinones*, which are produced by intestinal bacteria. There is uncertainty regarding the relative importance of intestinally produced vitamin K_2. Menaquinones are also present in meat, especially liver, and cheese. A menaquinone is used pharmacologically in some countries.

Vitamin K is a cofactor for γ-glutamyl carboxylase, an enzyme that performs post-translational carboxylation, converting glutamate residues in proteins to γ-carboxyglutamate (Gla). The Gla residues, by facilitating calcium binding, are necessary for protein function.

The classic Gla-containing proteins involved in blood coagulation that are decreased in vitamin K deficiency are factors II (prothrombin), VII, IX and X. In addition, vitamin K deficiency causes a decrease in proteins C and S, which inhibit blood coagulation, and protein Z, which also has a role in coagulation. All of these proteins are made only in the liver, except for protein S, a product of various tissues.

Gla-containing proteins are also involved in bone biology (e. g., osteocalcin and protein S) and vascular biology (matrix Gla protein and protein S). Based on the presence of reduced levels of Gla, these proteins appear more sensitive to subtle vitamin K deficiency than the coagulation proteins. There is evidence suggesting that mild vitamin K deficiency may have a deleterious effect on long-term bone strength and vascular health.

Because it is fat-soluble, vitamin K requires the presence of bile salts for its absorption. Unlike other fat-soluble vitamins, there are limited body stores of vitamin K. In addition, there is high turnover of vitamin K and the vitamin K-dependent clotting factors have a short half-life. Hence, symptomatic vitamin K deficiency may develop within weeks when there is inadequate supply due to low intake or malabsorption.

There are 3 forms of **vitamin K-deficiency bleeding (VKDB)** of the newborn Early VKDB, formerly called *classic hemorrhagic disease of the newborn*, occurs at 1–14 days of age. Early VKDB is secondary to low stores of vitamin K at birth due to the poor transfer of vitamin K across the placenta and inadequate intake during the 1st few days of life. In addition, there is no intestinal synthesis of vitamin K_2 because the newborn gut is sterile. Early VKDB occurs mostly in breast-fed infants due to the low vitamin K content of breast milk (formula is fortified). Delayed feeding is an additional risk factor.

Late VKDB most commonly occurs at 1–6 mo of age, although cases can occur up to 6 mo after birth. Almost all cases are in breast-fed infants due to the low vitamin K content of breast milk. An additional risk factor is occult malabsorption of vitamin K, such as occurs in children with undiagnosed cystic fibrosis or cholestatic liver disease (e. g., biliary atresia, α_1 antitrypsin deficiency). Without vitamin K prophylaxis, the incidence is 4–10/100 000 newborns.

Table 12 – Hemorrhagic Disease of the Newborn

	EARLY ONSET	CLASSIC DISEASE	LATE ONSET
Age	0–24 hrs	2–14 days	1–6 mo
Site of hemorrhage	Cephalohematoma	Gastrointestinal	Intracranial
	Subgaleal	Ear-nose-throat–mucosal	Gastrointestinal
	Intracranial	Intracranial	Cutaneous
	Gastrointestinal	Circumcision	Ear-nose-throat–mucosal
	Umbilicus	Cutaneous	Injection sites
	Intra-abdominal	Gastrointestinal	Thoracic
		Injection sites	
Etiology/risks	Maternal drugs (phenobarbital, phenytoin, warfarin, rifampin, isoniazid) that interfere with vitamin K	Vitamin K deficiency	Cholestasis – malabsorption of vitamin K (biliary atresia, cystic fibrosis, hepatitis)
	Inherited coagulopathy	Breast-feeding	Abetalipoprotein deficiency
			Idiopathic in Asian breast-fed infants
			Warfarin ingestion
Prevention	Posible vitamin K at birth or to mother (20 mg) before birth	Prevented by parenteral vitamin K at birth. Oral vitamin K regimens require repeated dosing over time	Prevented by parenteral and high-dose oral vitamin K during periods of malabsorption or cholestasis
	Avoid high-risk medications		
Incidence	Very rare	≈ 2 % if not given vitamin K	Dependent on primary disease

Vitamin K – deficiency bleeding due to fat malabsorption may occur in children of any age. Potential etiologies include

cholestatic liver disease, pancreatic disease, and intestinal disorders (celiac sprue, inflammatory bowel disease, short-bowel syndrome). Prolonged diarrhea, especially in breast-fed infants, may cause vitamin K deficiency. Children with cystic fibrosis are most likely to have vitamin K deficiency if they have pancreatic insufficiency and liver disease.

Beyond infancy, low dietary intake by itself never causes vitamin K deficiency. However, the combination of poor intake and the use of broad-spectrum antibiotics that eliminate the intestine's vitamin K_2 – producing bacteria can cause vitamin K deficiency. This is especially common in the intensive care unit. Vitamin K deficiency may also occur in patients who receive total parenteral nutrition without vitamin K supplementation.

Clinical manifestations

In early VKDB, the most common sites of bleeding are the gastrointestinal tract, mucosal and cutaneous tissue, the umbilical stump, and the post-circumcision site; intracranial bleeding is less common. Gastrointestinal blood loss can be severe enough to require a transfusion. In contrast, the most frequent site of bleeding in late VKDB is intracranial, although cutaneous and gastrointestinal bleeding may be the initial manifestation. Intracranial bleeding may cause convulsions, permanent neurologic sequelae, or death. In some cases of late VKDB, the presence of an underlying disorder may be suggested by jaundice or failure to thrive. Older children with vitamin K deficiency may present with bruising, mucocutaneous bleeding, or more serious bleeding.

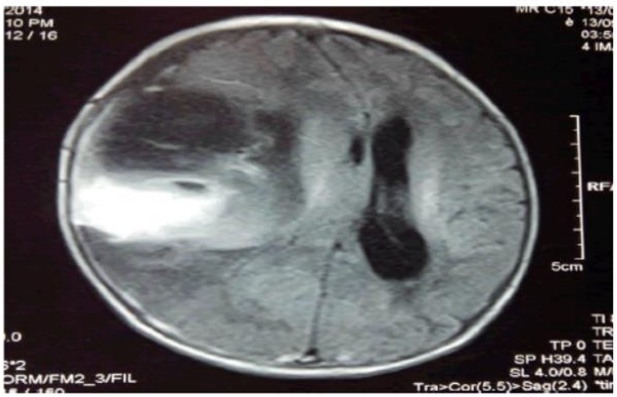


Figure 2. *Magnetic resonance imaging (axial view) brain showing massive right intracerebral hemorrha with midline shift*

Laboratory findings

In patients with bleeding due to vitamin K deficiency, the prothrombin time (PT) is prolonged. The PT must be interpreted based on the patient's age because it is normally prolonged in newborns (see Chapter 475.2). The partial thromboplastin time (PTT) is usually prolonged, but may be normal in early deficiency because factor VII has the shortest half-life of the coagulation factors (isolated factor VII deficiency does not affect the PTT). The platelet count and fibrinogen level are normal.

When there is mild vitamin K deficiency, the PT is normal, but there are elevated levels of the undercarboxylated forms of the proteins that are normally carboxylated in the presence of vitamin K. These undercarboxylated proteins are called *proteins induced by vitamin K absence* (PIVKA). Measurement of undercarboxylated factor II (PIVKA-II) can be used to detect mild vitamin K deficiency. Determination of blood vitamin K levels is less useful because of significant variation based on recent dietary intake; levels are not always reflective of tissue stores.

Diagnosis and differential diagnosis

The diagnosis is established by the presence of a prolonged PT that corrects rapidly after administration of vitamin K. This also stops the active bleeding. Other possible causes of bleeding and a prolonged PT include **disseminated intravascular coagulation** (DIC), liver failure, and rare hereditary deficiencies of clotting factors. DIC, which is most commonly secondary to sepsis, is associated with thrombocytopenia, low fibrinogen, and elevated D-dimers. In addition, most patients have hemodynamic instability that does not correct with restoration of blood volume. Severe liver disease results in decreased production of clotting factors; the PT does not fully correct with administration of vitamin K. Children with a hereditary disorder have a deficiency in a specific clotting factor (I, II, V, VII, X).

Coumarin derivatives inhibit the action of vitamin K by preventing its recycling to an active form after it functions as a cofactor for γ-glutamyl carboxylase. Bleeding can occur with overdosage of the commonly used anticoagulant warfarin or with ingestion of rodent poison, which contains a coumarin derivative. High doses of salicylates also inhibit vitamin K regeneration, potentially leading to a prolonged PT and clinical bleeding.

Treatment

Infants with VKDB should receive 1 mg of parenteral vitamin K. The PT should decrease within 6 hrs and normalize within 24 hrs. For rapid correction in adolescents, the parenteral dose is 2.5–10 mg. In addition to vitamin K, a patient with severe, life-threatening bleeding should receive an infusion of fresh frozen plasma, which corrects the coagulopathy rapidly. Children with vitamin K deficiency due to malabsorption require chronic administration of high doses of oral vitamin K (2.5 mg twice/wk–5 mg/day). Parenteral vitamin K may be necessary if oral vitamin K is ineffective.

Prevention

Administration of either oral or parenteral vitamin K soon after birth prevents early VKDB of the newborn. In contrast, a single

dose of oral vitamin K does not prevent a substantial number of cases of late VKDB. However, a single intramuscular injection of vitamin K (1 mg), the current practice in the USA, is almost universally effective, except in children with severe malabsorption. This increased efficacy of the intramuscular form is believed to be due to a depot effect. Concerns about an association between parenteral vitamin K at birth and the later development of malignancy are unsubstantiated.

Discontinuing the offending medications before delivery can prevent VKDB due to maternal medications. If this is not possible, administration of vitamin K to the mother may be helpful. In addition, the neonate should receive parenteral vitamin K immediately after birth. If this does not correct the coagulopathy rapidly, then the child should receive fresh frozen plasma.

Children at high risk for malabsorption of vitamin K should receive supplemental vitamin K and periodic measurement of the PT.

REFERENCES

1. Nelson Textbook of Pediatrics, 20th edition / Robert M. Kliegman, Bonita F. Stanton, Nina F. Schor et al. – London : Elsevier, 2016. – 3880 p.

2. Dyer J. Neonatal Respiratory Distress Syndrome: Tackling A Worldwide Problem / J. Dyer // Pharmacy and Therapeutics. – 2019. – № 44 (1). – P. 12–14.

3. David K. Stevenson. Neonatology: Clinical Practice and Procedures / David K. Stevenson, Ronald S. Cohen, Philip Sunshine. – Yayınevi : MC GRAW HILL, 2015.

4. Mhairi G. MacDonald. Avery's Neonatology. Patho-physiology and Mandgement of the Newborn. Seventh edition / Mhairi G. MacDonald, Mary M. K. Seshia. – Yayınevi : L.W.W, 2016.

5. Medical and Legal Aspects of Respiratory Care // Jonathan M. Fanaroff MD, JD, in Assisted Ventilation of the Neonate (6th edition). – 2017.

6. Jonathan M. Ventilation of the Neonate (Sixth Edition) / Jonathan M., Fanaroff M. D., 2017.

7. Alan H. Jobe. Pathophysiology of Respiratory Distress Syndrome / Alan H. Jobe // Fetal and Neonatal Physiology. – 5th edition. – 2017.

8. Chandra Rath. Pathophysiology Based Management of the Hemodynamically Significant Ductus Arteriosus in the Very Preterm Neonate / Chandra Rath, Martin Kluckow // Hemodynamics and Cardiology. – 3th edition. – 2019.

Навчальне видання

Редько Олена Костянтинівна,
Петрашенко Вікторія Олександрівна,
Лобода Андрій Миколайович

НЕОНАТОЛОГІЯ

Конспект лекцій

для студентів спеціальності *222 «Медицина»*
денної форми навчання

(Англійською мовою)

Відповідальний за випуск О. І. Сміян
Редактор І. А. Іванов
Комп'ютерне верстання О. К. Редько

Підписано до друку 12.10.2021, поз. 121.
Формат 60×84/16. Ум. друк. арк. 11,04. Обл.-вид. арк. 11,86. Тираж 20 пр. Зам. №

Видавець і виготовлювач
Сумський державний університет,
вул. Римського-Корсакова, 2, м. Суми, 40007
Свідоцтво суб'єкта видавничої справи ДК № 3062 від 17.12.2007.