Hypoxic Ischemic Encephalopathy

Scope Of The Problem

- occurs in up to 6 /1000 live term births
- a major cause of neurodevelopmental disability, with one-quarter of survivors sustaining permanent neurological deficits

Definitions

- **Hypoxia or Anoxia:** A partial (hypoxia) or complete (anoxia) lack of oxygen
- **Hypoxemia:** A partial (hypoxia) or complete (anoxia) lack of oxygen in the brain or blood

- **Asphyxia:** The state in which placental or pulmonary gas exchange is compromised or ceases altogether
- **Ischemia:** The reduction or cessation of blood flow to an organ which compromises both oxygen and substrate delivery to the tissue

Definitions

- **Perinatal Asphyxia** refers to a condition during the first and second stage of labor in which impaired gas exchange leads to fetal hypoxemia and hypercarbia
- identified by fetal acidosis as measured in umbilical arterial blood
- the most widely accepted definition of fetal acidosis is a pH <7.0, even with this degree of acidosis, the likelihood of brain injury is low.

Definitions

- **Perinatal Asphxia** is a combination of Hypoxia, Hypercarbia and Metabolic acidosis
- According to American Academy of Pediatrics, perinatal asphyxia is described as
- Cord umbilical PH < 7 with base deficit of <10 mEq/l
- Neonatal neurologic manifestation suggestive of HIE
- Evidences of multi organ failure (CVS, Renal etc)

WHO Definition

- **a "failure to initiate and sustain breathing at birth"**
- WHO/NNF – Apgar 0-3 at 1 minute – severe asphyxia,4-7 – moderate asphyxia
- In Community Settings NNF defines – asphyxia as absence of cry at 1 minute, severe asphyxia as absent or inadequate breathing at five minutes

The National Neonatal Perinatal Database (NNPD)

- Defined **moderate asphyxia** as slow gasping breathing or an Apgar score of 4-6 at 1 minute of age
- **Severe asphyxia** was defined as no breathing or an Apgar score of 0-3 at 1 minute of age

The National Neonatal Perinatal Database (NNPD)

- **Perinatal /neonatal depression** is a descriptive term that pertains to the condition of the infant on physical examination in the immediate postnatal period (i.e., in the first hour after birth).
- **clinical features**

- depressed mental status,
- muscle hypotonia,
- disturbances in spontaneous respiration and cardiovascular function.
- Term makes no association with the prenatal or later postnatal condition, physical exam, laboratory tests, imaging studies, or electroencephalograms (EEGs).

After the first hour

- **Neonatal encephalopathy** is a clinical and not an etiologic term that describes an abnormal neurobehavioral state consisting of decreased level of consciousness and usually other signs of brain stem and/or motor dysfunction
- does not imply a specific etiology, nor does it imply irreversible neurologic injury as it may be caused by such reversible conditions as maternal medications or hypoglycemia

Hypoxic-ischemic encephalopathy (HIE)

- describes encephalopathy as defined before, with objective data to support a hypoxic-ischemic mechanism as the underlying cause for the encephalopathy
- Hypoxic-ischemic (HI) brain injury refers to neuropathology attributable to hypoxia and/or ischemia as evidenced by
- biochemical (such as serum creatinekinase brain bound [CK-BB])
- electrophysiologic (EEG),
- neuroimaging (head ultrasonography [HUS], magnetic resonance imaging [MRI], computed tomog-raphy [CT]),
- pathologic (postmortem) abnormalities

Etiology

- In term newborns, asphyxia can occur in the antepartum or intrapartum period as result of impaired gas exchange across the placenta
- inadequate provision of oxygen (O2)
- removal of carbon dioxide (CO2) and hydrogen (H2) from the fetus.
- In the postpartum period, usually secondary to pulmonary, cardiovascular, or neurologic abnormalities

Factors that increase the risk of perinatal asphyxia

- Impairment of maternal oxygenation
- Decreased blood flow from mother to placenta

- Decreased blood flow from placenta to fetus
- Impaired gas exchange across the placenta or at the fetaltissue level
- Increased fetal O2 requirement

Etiologies may be multiple and include the following:

- Preconceptua
- Advanced maternal age
- IDDM
- Thyroid disease
- Fertility Treatments
- Maternal factors:
- hypertension (acute or chronic),
- hypotension,
- infection (including chorioamnionitis),
- hypoxia from pulmonary or cardiac disorders, diabetes, maternal vascular disease, and in utero exposure to cocaine

Etiologies may be multiple and include the following:

- Placental factors:

abnormal placentation,

abruption,

infarction,

fibrosis

- Uterine rupture
- Umbilical cord accidents:

prolapse,

entanglement,

true knot,

compression

- Abnormalities of umbilical vessels
- Instrumentation

Etiologies may be multiple and include the following:

- Fetal factors:

anemia,

infection,

cardiomyopathy,

hydrops,

severe cardiac/ circulatory insufficiency

- Neonatal factors:

cyanotic congenital heart disease,

persistent pulmonary hyper-tension of the newborn

(PPHN),

cardiomyopathy,

neonatal cardio-genic and/or septic shock

Pathophysiology

- Hypoxia-ischemia causes a number of physiologic and biochemical alterations
- The adverse consequences of cerebral ischemia include deprivation of energy substrates and oxygen, and an inability to clear accumulated, potentially toxic metabolites.

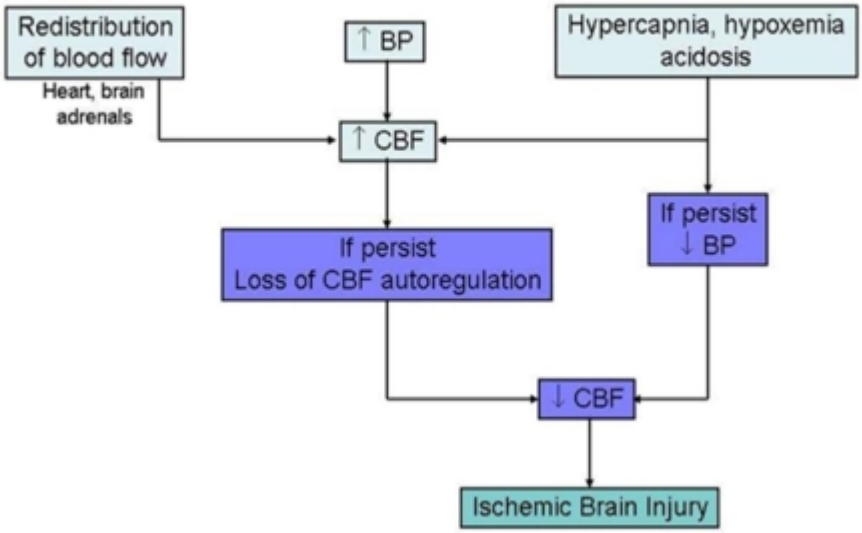
Pathophysiology

- Cerebral Blood Flow and Energy Metabolism
- Excitotoxicity
- Oxidative Stress
- Inflammation
- Apoptosis

Cerebral Blood Flow and Energy Metabolism

- Disruption of cerebrovascular autoregulation – important factor in the pathophysiology of neonatal hypoxic-ischemic brain injury

- Widely accepted that preterm infants have a “pressure-passive” cerebral circulation; however, term infants may remain at risk for impairment of cerebrovascular autoregulation and susceptibility to cerebral ischemia with fluctuations in systemic blood pressure



Cerebral Blood Flow and Energy Metabolism

- With brief asphyxia, there is
- a transient increase, followed by a decrease in heart rate (HR)
- mild elevation in blood pressure (BP)
- an increase in central venous pressure (CVP)
- and essentially no change in cardiac output (CO)
- Accompanied by a redistribution of CO with an increased proportion going to the brain, heart, and adrenal glands (diving reflex)

Cerebral Blood Flow and Energy Metabolism

- With prolonged asphyxia, there can be a loss of pressure autoregulation and/or CO_2 vasoreactivity
- This, in turn, may lead to further disturbances in cerebral perfusion, particularly when there is cardiovascular involvement with hypotension and/or decreased cardiac output

Cerebral Blood Flow and Energy Metabolism

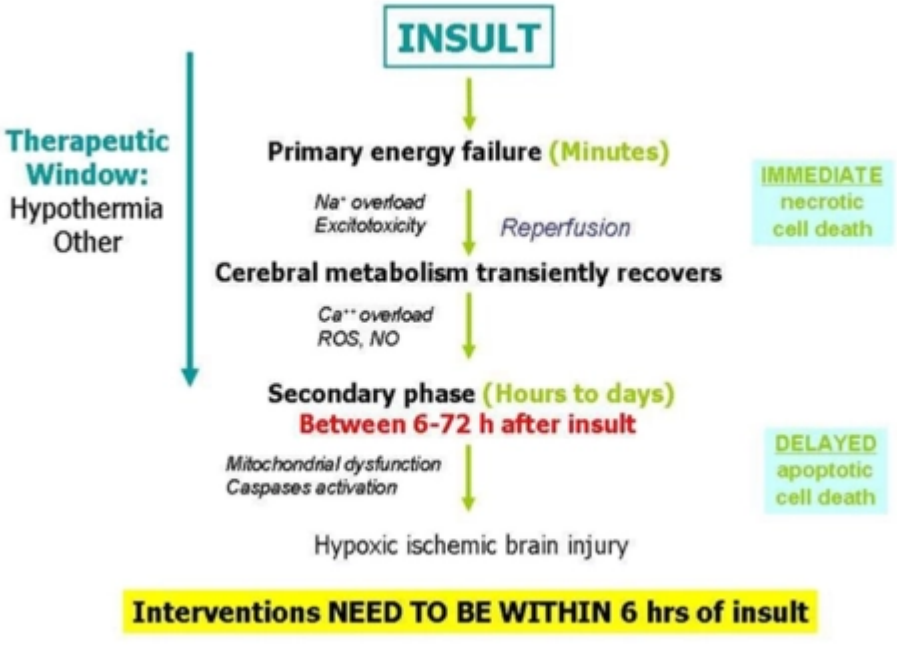
- An inadequate supply of glucose or alternate substrates plays a pivotal role in hypoxic-ischemic neuronal cell death
- Although overall metabolic demands are lower in the neonatal than in the adult brain, during periods of rapid brain growth, particularly the perinatal period, metabolic needs rise

Cerebral Blood Flow and Energy Metabolism

- Brain development is associated with a transition from the ability to use glucose and ketones as energy substrates in the neonate to an absolute requirement for glucose in the adult
- The immature brain can use lactate as an alternate fuel source to some degree, and the deleterious effects of lactate accumulation after hypoxia-ischemia therefore may be attenuated in the neonate compared with the adult

Cerebral Blood Flow and Energy Metabolism

- A decrease in cerebral blood flow results in anaerobic metabolism and eventual cellular energy failure due to increased glucose utilization in the brain and a fall in the concentration of glycogen, phosphocreatine, and adenosine triphosphate (ATP)



Excitotoxicity

- Glutamate can activate a variety of excitatory amino acid receptors

- Excitatory amino acid neurotransmission plays a pivotal role in brain development and in learning and memory
- Substantial body of data has emerged over the past 30 years documenting the fact that overactivationof excitatory amino acid receptors (i.e., excitotoxicity) contributes to neurodegeneration in a broad range of acute and chronic neurologic disorders

Excitotoxicity

- Two closely linked mechanisms contribute to ischemia-induced increases in synaptic glutamate:
- increased efflux from presynaptic nerve terminals
- impaired reuptake by glia and neurons
- initial increase in efflux is mediated by a calcium dependent process through activation of voltage-dependent calcium channels
- later, calcium-independent efflux is thought to be mediated primarily by functional reversal of glutamate transporters

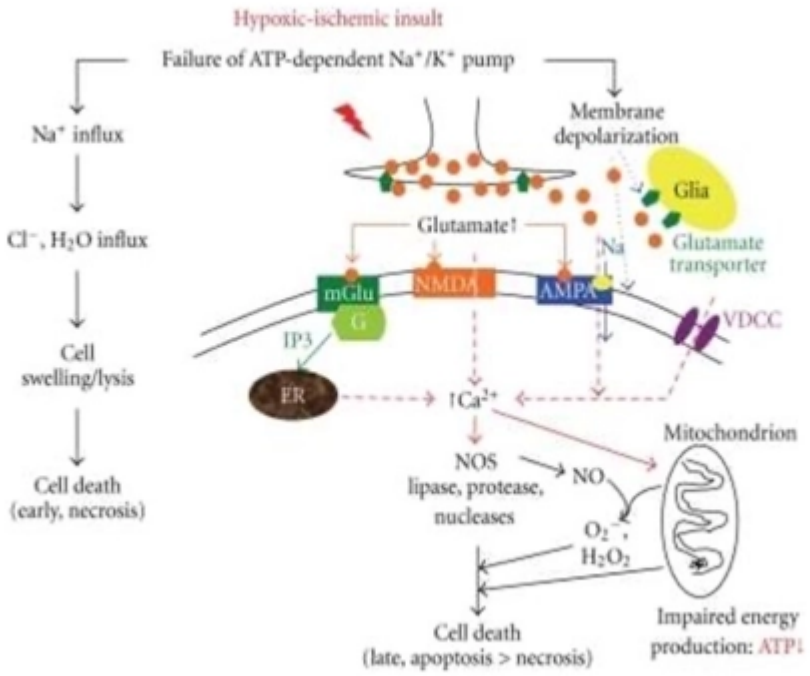
Excitotoxicity

- Removal of glutamate from the synaptic cleft depends primarily on energy-dependent glutamate transporters, which are predominantly glial
- Any pathophysiologic process that depletes energy supply (e.g., hypoxia-ischemia, hypoglycemia, prolonged seizures) disrupt these mechanisms and result in increased synaptic glutamate accumulation

Excitotoxicity

- The NMDA receptor is relatively overexpressed in the developing brain compared with the adult brain
- In the setting of hypoxia-ischemia, NMDA receptor overactivationleads to:
- massive sodium and water influx
- cell swelling
- elevated intracellular calcium and its associated mitochondrial
- dysfunction,
- increased nitric oxide production,
- increased phospholipid turnover
- accumulation of potentially toxic free fatty acids,
- cell death by apoptotic or necrotic mechanisms.

- However, ischemia and energy failure also result in cation influx by non-NMDA-mediated mechanisms



Oxidative Stress

- Oxidative stress describes the alterations in cellular milieu that result from an increase in free radical production as a result of oxidative metabolism under pathologic conditions
- consequence of mitochondrial dysfunction is an accumulation of superoxide

Oxidative Stress

- Excitotoxicity causes energy depletion, mitochondrial dysfunction, and cytosolic calcium accumulation, lead to the generation of free radicals, such as superoxide, nitric oxide derivatives, and the highly reactive hydroxyl radical
- With reoxygenation, mitochondrial oxidative phosphorylation is overwhelmed and reactive oxygen species accumulate
- Intrinsic antioxidant defensesare depleted, and free radicals directly damage multiple cellular constituents (lipids, DNA, protein) and can activate pro-apoptotic pathways

Oxidative Stress

- Nitric oxide metabolism provides critical link between excitotoxicity and oxidative injury in the hypoxic ischemic injured brain
- Hypoxic-ischemic increases in nitric oxide production have multiple potential beneficial and detrimental effects
- Early endothelial NO is protective by maintaining blood flow, but early neuronal NO and late inducible NO are neurotoxic by promoting cell death

Inflammation

- Cytokines that have been strongly implicated as mediators of brain inflammation in neonates include interleukin (IL)-1b, tumor necrosis factor (TNF)a, IL-6,and membrane co-factor protein-1
- After an asphyxial episode, there are many potential sources of plasma cytokines,
- injured endothelium
- acutely injured organs, e.g brain by means of a disrupted
- blood–brain barrier

Apoptosis

- Apoptosis is critical for normal brain development, but it is also an important component of injury following neonatal hypoxia-ischemia and stroke
- Immediate neuronal death (necrosis) can occur due to intracellular osmotic overload

Apoptosis

- Delayed neuronal death (apoptosis) occurs secondary to uncontrolled activation of enzymes and second messenger systems within the cell
- Ca2+-dependent lipases, proteases, and caspases);
- perturbation of mitochondrial respiratory electron chain transport;
- generation of free radicals and leukotri-enes;
- generation of nitric oxide (NO) through NO synthase; and depletion of energy stores.

Neurological Patterns of HIE

- **Premature**
- Selective subcortical neuronal necrosis
- Periventricular leukomalacia
- Focal/Multifocal ischemic necrosis

- Periventricular hemorrhage/infarction
- **Term**
- Selective Subcortical Neuronal necrosis
- Status Marmoratusof basal ganglia and thalamus
- Parasagittal cerebral injury
- Focal/Multifocal Ischemic cerebral necrosis

Diagnosis

- Assessment
- Low Apgar scores and need for resuscitation in the delivery room are common but nonspecific Findings
- Many features of the Apgar score relate to cardiovascular integrity and not neurologic dysfunction resulting from asphyxia.

Diagnosis

- the differential diagnosis for a term newborn with
- an Apgar score <3 for >10 minutes includes
- depression from maternal anesthesia or analgesia
- trauma
- Infection
- cardiac or pulmonary disorders
- Neuromuscular
- other central nervous system disorders or malformations
- If the Apgar score is >6 by 5 minutes, perinatal asphyxia is not likely.

Umbilical cord or first blood gas

- The specific blood gas criteria that define asphyxia causing brain damage are uncertain
- The pH and base deficit on the cord or first blood gas is helpful
- In the randomized clinical trials of hypothermia for neonatal HIE, severe acidosis was defined as pH <7.0 or base deficit <16 mmol/L

Clinical Suspicion

- Suspect HIE in encephalopathic newborns with a history of fetal and neonatal distress and laboratory evidence of asphyxi
- Diagnosis not be overlooked in scenarios such as

- meconium aspiration,
- pulmonary hypertension,
- birth trauma
- fetal–maternal hemorrhage

Clinical Suspicion

- **Consider Asphyxia/HIE if:**

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

Neurologic Signs

- The clinical spectrum of HIE is described as mild, moderate, or severe (Sarnat stages of HIE).
- EEG is useful
- Encephalopathy
- must have depressed consciousness by definition, whether mild, moderate, or severe
- An initial period of well-being or mild HIE may be followed by sudden deterioration, suggesting ongoing brain cell dysfunction, injury, and death; during this period, seizure intensity might increase

Table 17-1 The Encephalopathy Score

Sign	Score = 0	Score = 1
Feeding	Normal	Gavage feeds, gastrostomy tube, or not tolerating oral feeds
Alertness	Alert	Irritable, poorly responsive, or comatose
Tone	Normal	Hypotonia or hypertonia
Respiratory status	Normal	Respiratory distress (need for continuous positive airway pressure or mechanical ventilation)
Reflexes	Normal	Hyperreflexia, hyporeflexia, or absent reflexes
Seizure	None	Suspected or confirmed clinical seizure

(From Miller et al. Clinical signs predict 30-month neurodevelopmental outcome after neonatal encephalopathy. Am J Obstet Gynecol 2004;190(1):93–99.)

Table 55-1 Sarnat and Sarnat Stages of Hypoxic-Ischemic Encephalopathy*

Stage	Stage 1 (Mild)	Stage 2 (Moderate)	Stage 3 (Severe)
Level of consciousness	Hyperalert; irritable	Lethargic or obtunded	Stuporous, comatose
Neuromuscular control:	Uninhibited, overreactive	Diminished spontaneous movement	Diminished or absent spontaneous movement
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive, disinhibited	Decreased or absent
Segmental myoclonus	Present or absent	Present	Absent
Complex reflexes:	Normal	Suppressed	Absent
Suck	Weak	Weak or absent	Absent
Moro	Strong, 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	Midposition, often unequal; poor light reflex
Respirations	Spontaneous	Spontaneous; occasional apnea	Periodic; apnea
Heart rate	Tachycardia	Bradycardia	Variable
Bronchial and salivary secretions	Sparse	Profuse	Variable
Gastrointestinal motility	Normal or decreased	Increased, diarrhea	Variable
Seizures	None	Common focal or multifocal (6–24 hours of age)	Uncommon (excluding decerebration)
Electroencephalographic findings	Normal (awake)	Early: generalized low-voltage, slowing (continuous delta and theta)	Early: periodic pattern with isopotential phases
		Later: periodic pattern (awake); seizures focal or multifocal; 1.0–1.5 Hz spike and wave	Later: totally isopotential
Duration of symptoms	<24 hours	2–14 days	Hours to weeks
Outcome	About 100% normal	80% normal; abnormal if symptoms more than 5–7 days	About 50% die; remainder with severe sequelae

Levene Staging

Feature	Mild	Moderate	Severe
Consciousness	rritability	Lethargy	omatose
Tone	Hypotonia	Marked Hypotonia	Severe Hypotonia
Seizures	No	Yes	Prolonged
Sucking/Respiration	Poor Suck	Unable to Suck	Unable to sustain spontaneous respiration

Neurologic Signs

- Mild encephalopathy can consist of an apparent hyperalertor jittery state, but the newborn does not respond appropriately to stimuli, and thus consciousness is abnormal
- Moderate and severe encephalopathies are characterized by more impaired responses to stimuli such as light, touch, or even noxious stimuli

Neurologic Signs

- Brain stem and cranial nerve abnormalities manifest as abnormal or absent brain stem reflexes
- Pupillary/corneal/oculocephalic/cough/gag
- Abnormal eye movementsgaze preference/ocular bobbing/absence of visual fixation or blink to light
- Newborns may show facial weakness (usually symmetric) and have a weak or absent suck and swallow with poor feeding
- They can have apnea or abnormal respiratory patterns

Neurologic Signs

- Motor abnormalities. With greater severity of encephalopathy, there is generally greater hypotonia
- Weakness
- Abnormal posture with lack of flexor tone, which is usually symmetric
- A unilateral, focal infarct, especially one involving
- the middle cerebral artery, causes contralateral
- hemiparesis and focal seizures

Neurologic Signs

- With severe HIE, primitive reflexes such as the Moro or grasp reflex may be diminished
- Over days to weeks, the initial hypotonia may evolve into spasticity and hyperreflexia if there is significant HI brain injury
- If a newborns how significant hypertonia within the first day or so after birth, the HI insult may have occurred earlier in the antepartum and have already resulted in established HI brain injury

Neurologic Signs - Seizures

- Seizures occur in up to 50% of newborns with HIE, and usually start within 24 hours after
- the HI Insult
- Seizures indicate that the severity of encephalopathy is moderate or severe, not mild

Neurologic Signs - Seizures

- Seizures may be subtle, tonic, or clonic
- Its difficult to differentiate seizures from jitteriness or clonus, although the latter two are usually suppressible with firm hold of the affected limb(s)
- Subtle manifestations of neonatal seizures are confirmed on EEG and include apnea; tonic eye deviation; sustained eye opening; slow, rhythmic, tongue thrusting; and boxing, bicycling, and swimming movements

Neurologic Signs - Seizures

- Being subclinical, EEG remains the gold standard for diagnosing neonatal seizures, particularly in HIE
- Seizures may compromise ventilation and oxygenation, especially in newborns who are not receiving mechanical ventilation

Increased intracranial pressure (ICP)

- Resulting from diffuse cerebral edemain HIE often reflects extensive cerebral necrosis rather than swelling of intact cells and indicates a poor prognosis
- Treatment to reduce ICP does not affect outcome

Multiorgan Dysfunction

- In a minority of cases (<15%), the brain may be the only organ exhibiting dysfunction following asphyxia
- The kidney is the most common organ to be affected
- acute tubular necrosis with oliguria
- water and electrolyte imbalances

Multiorgan Dysfunction

- Cardiac dysfunction
- caused by transient myocardial ischemia.
- In severely asphyxiated newborns, dysfunction more commonly affects the right ventricle.
- reduced myocardial contractility
- severe hypotension
- passive cardiac dilatation
- tricuspid regurgitation
- A fixed HR may raise suspicion of severe brain stem injury.
- Gastrointestinal
- bowel ischemia
- necrotizngenterocolitis

Multiorgan Dysfunction

- Hematologic effects
- disseminated intravascular coagulation
- damage to blood vessels
- poor production of clotting factors due to liver dysfunction
- poor production of platelets by the bone marrow.
- Liver dysfunction
- manifested by isolated elevation of hepatocellular enzymes
- DIC

- inadequate glycogen stores with resultant hypoglycemia
- altered metabolism
- Pulmonary effects include
- PPHN
- pulmonary hemorrhage
- pulmonary edemadue to cardiac dysfunction
- meconium aspiration

Assessment Tools in HIE

- Amplitude-integrated EEG (aEEG)
- Most useful in infants who have moderate to severe encephalopathy
- Marginally abnormal or normal aEEG is very reassuring of good outcome
- Severely abnormal aEEG in infants with moderate HIE raises the probability of death or severe disability from 25% to 75%
- **Evoked Potentials**
- Brainstem auditory evoked potentials, visual evoked potentials and somatosensory evoked potentials can be used in full-term infants with HIE
- More sensitive and specific than aEEG alone

Neuroimaging

- Cranial ultrasound:
- Not the best in assessing abnormalities in term infants. Echogenicitydevelops gradually over days
- most useful for detection of PVL
- Less useful in assessing edema, subtle midline shift & posterior fossahemorrhage & ventricular compression
- CT: Less sensitive than MRI for detecting changes in the central gray nuclei
- MRI: Most appropriate technique and is able to show different patterns of injury. Presence of signal abnormality in the internal capsule later in the first week has a very high predictive value for neurodevelopmental outcome

Acid – base measurements

- Assessed by umbilical artery pH measurement are correlated with neonatal seizures & death when pH < 7.04
- Low umbilical – pH may be due to sepsis
- Association of low pH & long term outcome is weak

Cardiac evaluation

- Cardiac troponin (CTNI) & troponinT (CtnT).
- Cardiac regulatory proteins and are markers of myocardial damage
- Elevated levels in asphyxia
- Serum creative kinase myocardial bound:
- (CK-MB) fraction of > 5% to 10% may indicate myocardial injury

Others

- Brain Injury
- CK-BB infants within 12 hrs of the insult.
- No specific relation with long term neurodevelopmental outcome.
- CK-BB also expressed in placenta, lungs, GITand kidneys.
- Renal Evaluation
- BUN and serum creatinine may be elevated in perinatal asphyxia
- in 2-4 days after the insult
- Urine levels of ß2-microglobulin is used as an indicator of proximal tubular dysfunction

Prevention

- Perinatal management of high-risk pregnancies
- Fetal HR and rhythm abnormalities may provide supporting evidence of asphyxia, especially if accompanied by presence of thick meconium
- Measurement of fetal scalp pH is a better determinant of fetal oxygenation than PO2

Prevention

- Close monitoring of progress of labor with awareness of other signs
- of in utero stress is important
- The presence of a constellation of abnormal findings may indicate the need to mobilize the perinatal team for a newborn that could require immediate intervention

Postnatal management

- Ventilation. CO2 should be maintained in the normal range.
- Hypercapniacan cause cerebral acidosis and cerebral vasodilation.
- Excessive hypocapnia (CO2 <25 mm Hg) may decrease CBF

- Oxygenation. Oxygen levels should be maintained in the normal range
- although poor peripheral perfusion may limit the accuracy of continuous non-invasive monitoring
- Hypoxemia should be treated with supplemental O2 and/or ventilation
- Hyperoxia may cause decreased CBF or exacerbate free radical damage

Metabolic

- Maintain physiologic metabolic state
- Hypocalcemia
- Hypoglycemia
- Hyperglycemia
- increases brain lactate, damage to cellular integrity, cerebral edema,
- or further disturbance in vascular autoregulation

Temperature

- Temperature. Passive cooling by turning off warming lights is an effective way to initiate therapeutic hypothermia as soon as possible after the HI insult.
- Hyperthermia should always be avoided

Cardiovascular

- Fluid restriction may aid in minimizing cerebral edema
- Judicious fluid management
- Fluid overload and inadequate circulating volume to be avoided
- Fluid overload in asphyxiated newborns
- SIADH secretion hyponatremia and hypoosmolarity in combination with low urine output and inappropriately concentrated urine (elevated urine specific gravity, osmolarity, and Na+)
- Perfusion, cardiovascular stability and adequate mean systemic arterial BP are to be maintained (Dopamine, Milnirone)

Control of seizures

- Start within 12 hours of birth, increase in frequency, and then usually resolve within days, although may persist in severe cases.
- Can be extremely difficult to control and may not be possible to eliminate completely with currently available anticonvulsants

- Not yet been proven that improved seizure control results in improved neurologic outcome

Acute anticonvulsant management

- Phenobarbital is the initial drug of choice
- Phenytoin may be added when seizures are not controlled by phenobarbital. Fosphenytoin can be used
- Benzodiazepines are considered third-line drugs
- Levetiracetamhas been used recently because of its availability in IV form and relative safety and efficacy for various types of childhood epilepsy

Long-term anticonvulsant management

- Anticonvulsants can be weaned when the clinical exam and EEG indicate that the newborn is no longer having seizures
- If a newborn is receiving more than one anticonvulsant, weaning should be in the reverse order of initiation, with phenobarbital being weaned last

Prognosis
A. Overall mortality is 10% to 30% Neurodevelopment sequelae 15% to 45%.

B. Risk of CP in survivors of perinatal asphyxia is 5% to 10% compared to 0.2% in general population

- Most CP is not related to perinatal asphyxia & most perinatal asphyxia does not cams CP
- Only 3%-13% of infants with CP have evidence of intrapartum asphyxia

Prognosis

According to Sarnat staging:

a)Stage 1 – 90% to 1=0% (N) neurologic outcome < 10% mortality.

b)Stage - 2 – 20% to 37% die or have abnormal neurodevelopmental outcomes.

- Infants who exhibit stage 2 sign for > 7 days have poorer outcomes

Prognosis

c)Stage 3 HIE-50% to 89% die and all survivors have major neurodevelopment

d)Prognosis is good if an infant does not progress to &/or remain in stage 3 & if total duration of stage 2<5 days

e)Term baby not breast feeding by Day 10 of life

f)Seizures on Day 1 requiring multiple drugs to control

Outcomes

- depend on the pattern and severity of the brain injury
- involve motor, visual, and cognitive functions
- follow-up of these newborns should include assessment of motor function, vision and hearing, cognition,behavior, and quality of life, through infancy and childhood

Motor Functions

- The risk of cerebral palsy or severe disability may involve more than one third of affected newborns
- More in those with severe encephalopathy
- Spastic quadriparesis is the most common type of CP

Vision and Hearing

- Injury to the posterior visual pathway, including the primary visual cortex, results in “cortical visual impairment”
- Injuries to the basal nuclei may also affect acuity, visual fields, or stereopsis (depth perception)
- SNHL, likely secondary to brainstem injury, is also seen following neonatal encephalopathy affecting 18 percent of survivors of moderate encephalopathy without cerebral palsy

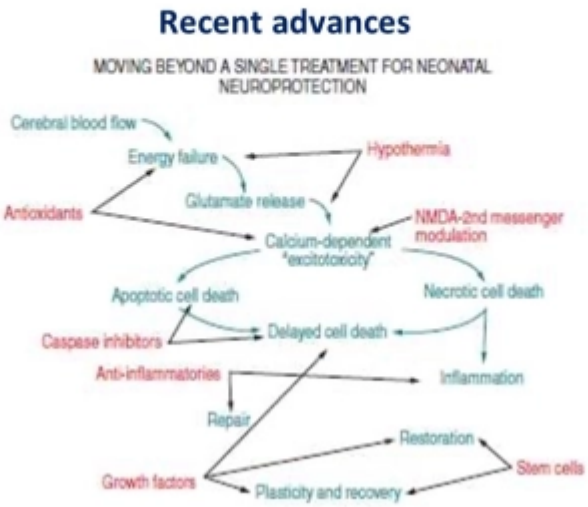
Cognition

- Cognitive deficits are seen in 30–50 percent of childhood survivors
- Cognitive deficits, such as those in language and memory, may be seen, even when IQ scores are normal

Investigations For Prognosis

- EEG – background burst suppression,low voltage or electrocerebralsilence
- = poor prognosis
- CT/MRI – Diffuse decrease in density on CT scan at 2-4 weeks of life

- indicates poor prognosis
- Early MRI – basal ganglia and thalamic enhancment = poor prognosis



Strategies	Interventions
↓ cerebral metabolic rate	Hypothermia
Block NMDA receptor channel	Magnesium
↓ glutamate release	Adenosine Adenosine agonists Adenosine uptake inhibitors
Inhibit voltage-sensitive Ca++ channels	Calcium channel blockers
↓ free radical reactions	Free radical scavengers Allopurinol Vitamin C, E Super oxide dismutase (SOD)
Prevent free radical formation	Indomethacin Iron chelators Allopurinol NOS inhibitors
↓ inflammatory response	Allopurinol Inflammatory antagonists (blocking IL-1 and TNF-α, steroids)
Attenuate apoptosis pathway	Caspase inhibitors

Therapeutic Cooling

- 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
- reduced metabolic rate and energy depletion;
- decreased excitatory transmitter release;
- reduced alterations in ion flux;
- reduced apoptosis due to hypoxic-ischemic encephalopathy
- reduced vascular permeability, edema, and disruptions of blood-brain barrier functions.

Therapeutic Cooling

- Criteria from the larger trials (NICHD, CoolCap, and TOBY) are summarized as follows:
- Near-term infants born at 36 weeks' gestation or more with birth weight of 1800-2000 g or more, younger than 6 hours at admission
- Evidence of acute event around the time of birth
- Apgar score of 5 or less at 10 minutes after birth
- severe acidosis, defined as pH level of less than 7 or base deficit of 16 mmol/L or less (cord blood or any blood gas obtained within 1 h of birth)
- continued need for resuscitation at 10 minutes after birth
- Evidence of moderate to severe encephalopathy at birth

Erythropoetin

- Epogen receptors are present in the developing human embryo
- higher levels of Epogen in cerebral spinal fluid have been correlated with improved neurodevelopmental outcomes.
- May benefit infants with HIE through protection from neuronal apoptosis, neural regeneration, decreased inflammation, and decreased susceptibility to glutamate toxicity

Erythropoetin

- Term infants with HIE treated with Epogen show decreased seizure activity, improved EEG results, and enhanced neurologic outcome
- Although additional clinical trials are needed, epogen appears to be effective in the treatment of infants with HIE if administered within 48 hours after delivery

Magnesium sulfate

- Magnesium sulfate is an N-methyl-D-aspartate receptor antagonist important in cell proliferation, differential, and survival in the developing brain
- Conflicting data exist regarding the effectiveness of MgSO4 as a neuroprotective agent
- Prenatal administration is associated with reducedincidence of cerebral palsy at 3 years and improvedneurodevelopmental outcomes
- When MgSO4 was administered postnatally to term infants with HIE, there was no improvement in their EEG

Allopurinol

- Allopurinol is an antioxidant that inhibits formation of the free radicals that play such a significant role in the cellular damage associated with HIE
- when term infants with HIE received allopurinol within 3 hours after birth, there was less free radical formation

Stem Cells

- Stem cell transplantation may minimize the effect of HIE by replacing damaged cells, promoting cell regeneration, inhibiting inflammation, and releasing trophic factors that heal and improve cell survival
- Efficacy of stem cell transplantation, however, appears dependent on timing of implantation, and this therapeutic window is presently unknown