

# Hypoxic-Ischemic Encephalopathy

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Feb 2012

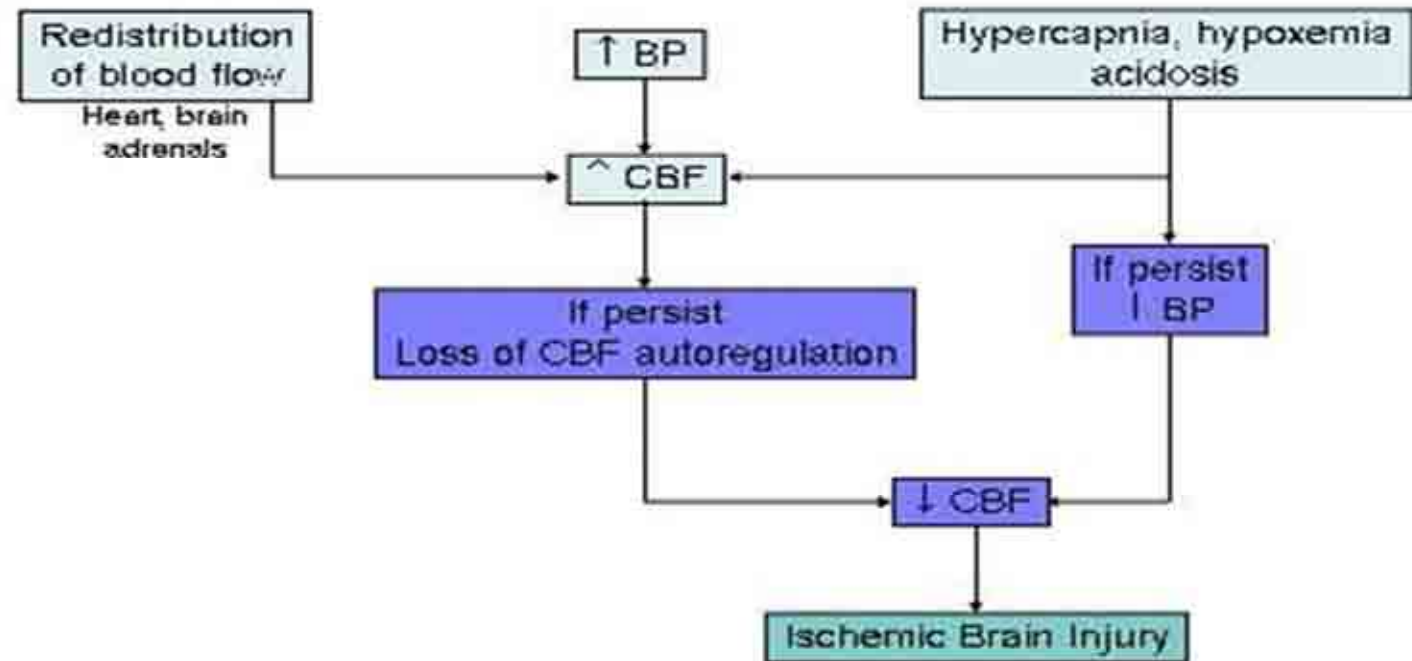
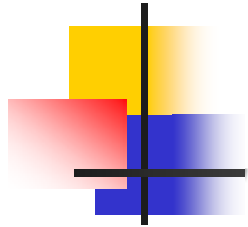


# Background

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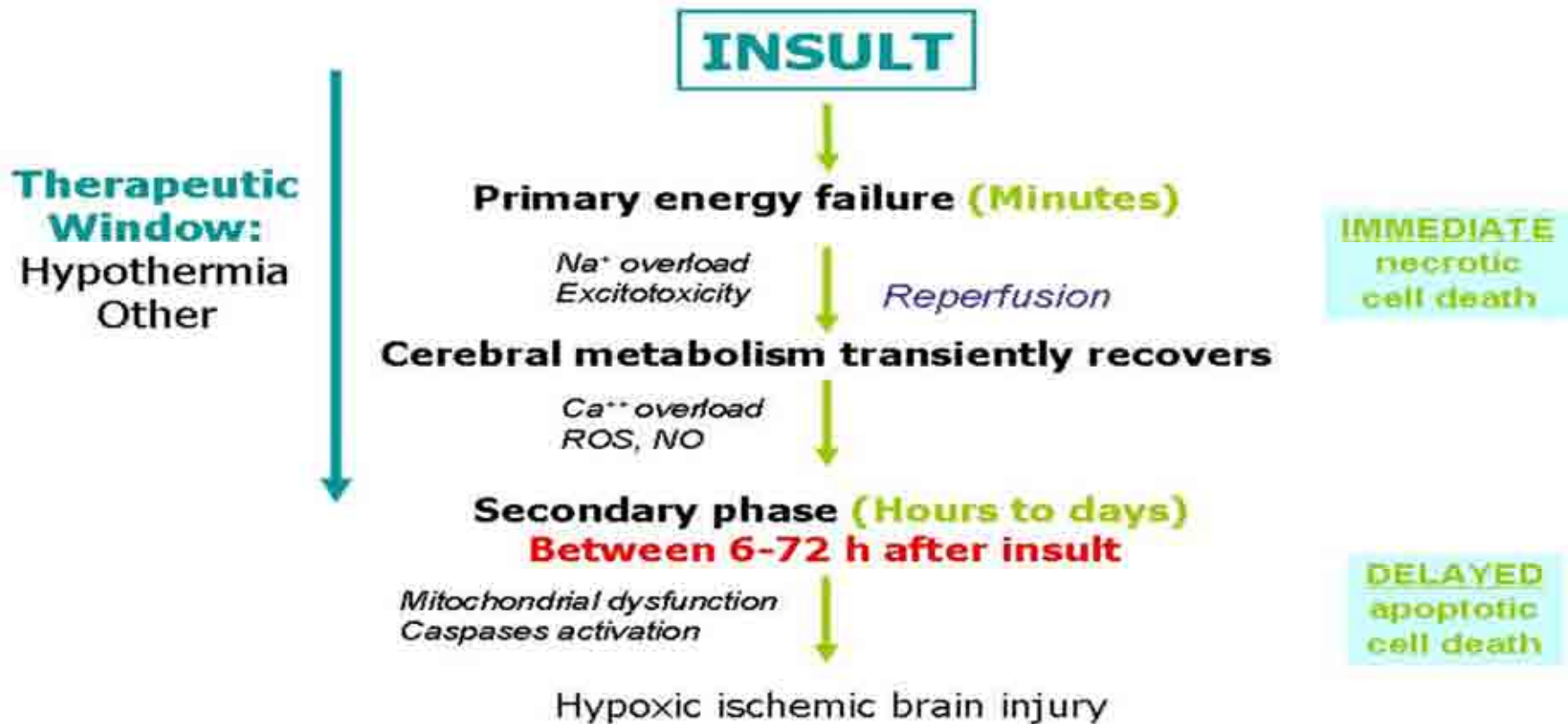
- HIE remains a serious condition that causes significant mortality and long-term morbidity.

# Physiology / Pathology



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

# Patho-physiology (cont.)



**Interventions NEED TO BE WITHIN 6 hrs of insult**

# Frequency



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- HIE is the most important reason why term babies die in South Africa

# Mortality/Morbidity



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- Grade 3 HIE
  - 80% DIED
  - 20% SEVERE DISABILITIES

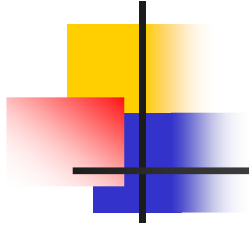
Data: Pretoria Academic Hospital 2004



# Guidelines for the diagnosis of HIE.

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- Profound metabolic or mixed acidemia (pH <7) in an umbilical artery blood sample.
- Persistence of an Apgar score of 0-3 for longer than 5 minutes
- Neonatal neurologic sequelae (eg, seizures, coma, hypotonia)
- Multiple organ involvement (eg, kidney, lungs, liver, heart, intestines)
  
- However, infants may have experienced asphyxia or brain hypoxia remote from the time of delivery and may have exhibited the signs and symptoms of hypoxic encephalopathy prior to the time of birth and, therefore, may not meet all of the criteria set forth by the AAP and ACOG at birth.



Clinical manifestations and course vary depending on hypoxic-ischemic encephalopathy severity.





# Mild hypoxic-ischemic encephalopathy

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- Muscle tone - slightly increased
- Deep tendon reflexes - brisk
- Behavioral abnormalities-
  - poor feeding
  - Irritability
  - excessive crying
  - sleepiness.
- By 3-4 days of life, the CNS examination become normal.



# Moderately severe hypoxic-ischemic encephalopathy

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- Lethargic, hypotonia and diminished deep tendon reflexes.
- Primitive reflexes sluggish or absent
  - Moro, grasping sucking reflexes
- Periods of apnea.
- Seizures within the first 24 hours of life.
- Full recovery within 1-2 weeks is possible and is associated with a better long-term outcome.
  
- An initial period of well-being or mild hypoxic-ischemic encephalopathy may be followed by sudden deterioration, suggesting ongoing brain cell dysfunction, injury, and death; during this period, seizure intensity might increase.



# Severe hypoxic-ischemic encephalopathy

- Stupor or coma. No response to any physical stimulus.
- Breathing irregular, (gaspings) and the infant often requires ventilatory support
- Generalized hypotonia and depressed deep tendon reflexes
- Neonatal reflexes (eg, sucking, swallowing, grasping, Moro) are absent.
- Disturbances of ocular motion, such as a skewed deviation of the eyes, nystagmus, bobbing, and loss of "doll's eye"
- Pupils dilated, fixed, or poorly reactive to light.



# Severe hypoxic-ischemic encephalopathy (cont.)

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- Seizures - early frequency may increase during the 24-48 hours after onset.
- As the injury progresses, seizures subside and the EEG becomes isoelectric or shows a burst suppression pattern.
- Fontanelle bulge- increasing cerebral edema.
- Irregularities of heart rate and blood pressure (BP)



# Infants who survive

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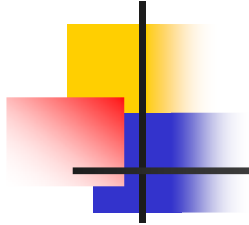
- The level of alertness improves by days 4-5 of life
- Hypotonia and feeding difficulties persist, requiring tube feeding for weeks to months.
- Severe CP



# Multi-organ dysfunction

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- Heart (43-78%):
- Lungs (71-86%):
- Renal (46-72%):.
- Liver (80-85%):
- GI dysfunction:
- Hematologic (32-54%):
- Severely depressed respiratory and cardiac functions and signs of brainstem compression suggest a life-threatening rupture of the vein of Galen (ie, great cerebral vein) with a hematoma in the posterior cranial fossa.



# SARNAT CLASSIFICATION or SHANKARAN

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# CAUSES HIE

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- South Africa –
  - high incidence of intra-partum asphyxia





# Diagnosis

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- No specific test can always confirm or exclude a diagnosis of hypoxic-ischemic encephalopathy (HIE) because the diagnosis is made based on the history and physical and neurological examinations.
- 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.



# WORK-UP

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- **Serum electrolytes**

- Acute tubular necrosis.
- Polyuria

- **Renal function studies:**

- Serum creatinine levels, and urea.

- **Coagulation system evaluation:**

- prothrombin time, partial thromboplastin time, and fibrinogen levels.

- **ABG:**

- acid-base status hyperoxia and hypoxia as well as hypercapnia and hypocapnia.

- **Cardiac and liver enzymes:**

- degree of hypoxic-ischemic injury



# Imaging studies

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- MRI is the imaging modality of choice for the diagnosis and follow-up of infants diagnosed with moderate-to-severe hypoxic-ischemic encephalopathy.

Not regularly available NICU / SBAH

# Imaging Studies



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- **Cranial ultrasonography:**
  - Findings in hypoxic-ischemic encephalopathy may be imprecise.
  - It can reveal intracerebral or intraventricular hemorrhage.
  - Cerebral edema may be evident in the form of decreased ventricular size or indistinct sulci and gyral patterns.
  - Gross structural abnormalities

# Amplitude-integrated electroencephalography (aEEG)



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- **Single-channel a-EEG**

- Discontinuous tracing
- Burst suppression pattern
- Continuous low voltage
- Inactive pattern with no detectable cortical activity
- Seizures, abrupt rise in both the lower and upper margins

# Standard EEG



## ■ Generalized depression varying degrees of superimposed seizures

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- Burst suppression and iso-electric EEG patterns are particularly ominous.
- Note that large doses of anticonvulsant therapy may alter the EEG findings.
- Serial EEGs to assess seizure control and evolution of background abnormalities.
- Repeat EEGs obtained just prior to discharge can be helpful in establishing prognosis.
- Improvement in the EEG findings over the first week, in conjunction with improvement in the clinical condition, may help predict a better long-term outcome.

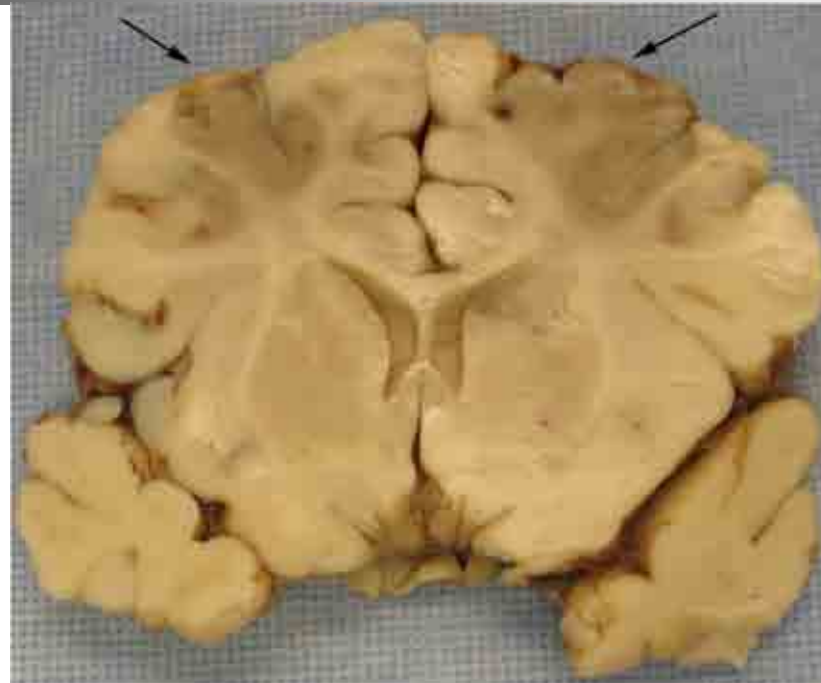


# Special sensory evaluation:

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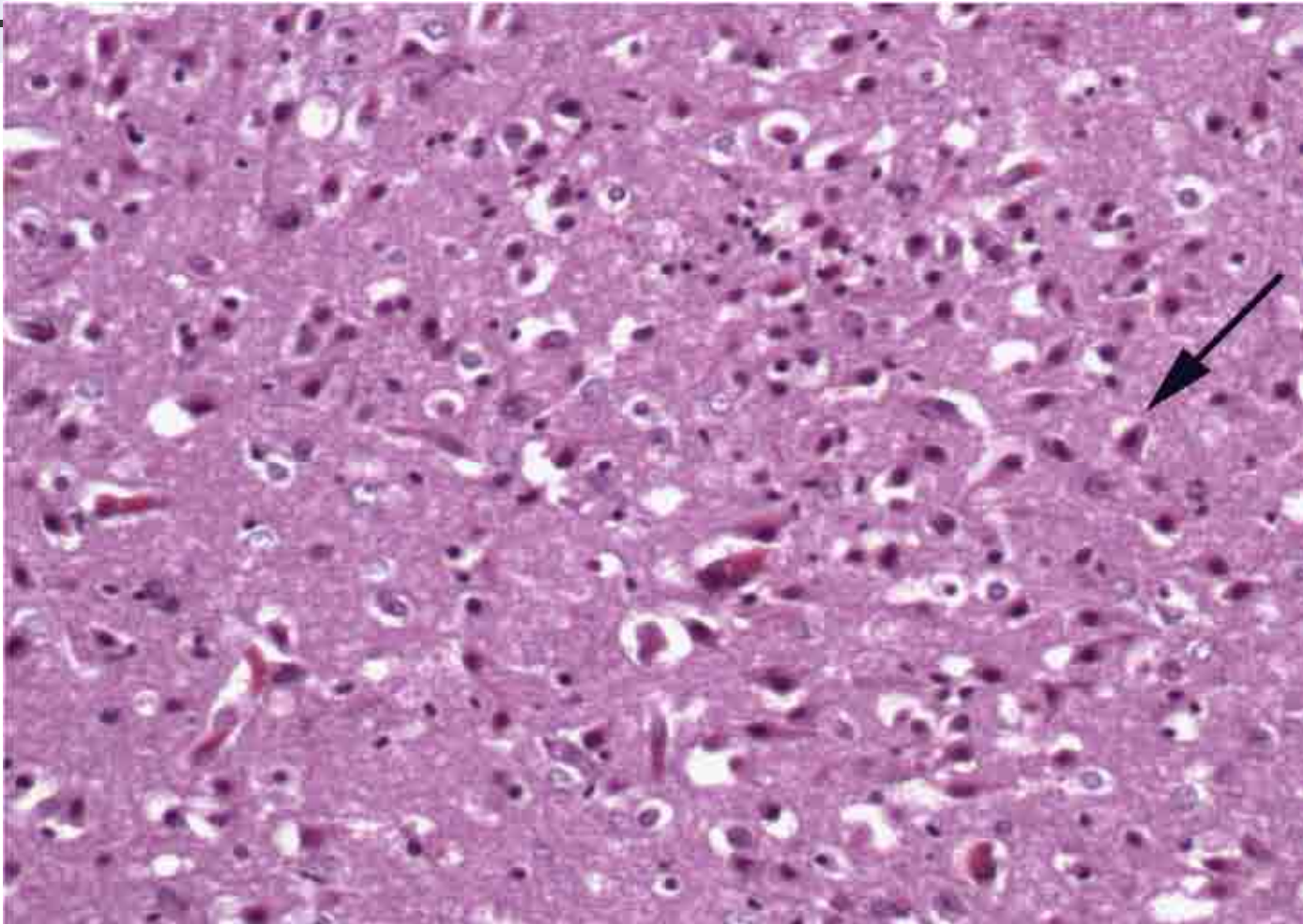
- Hearing test
  - increased incidence of deafness
- Retinal and ophthalmic examination
  - for developmental abnormalities of the brain.

# Bilateral acute infarctions of the frontal lobe



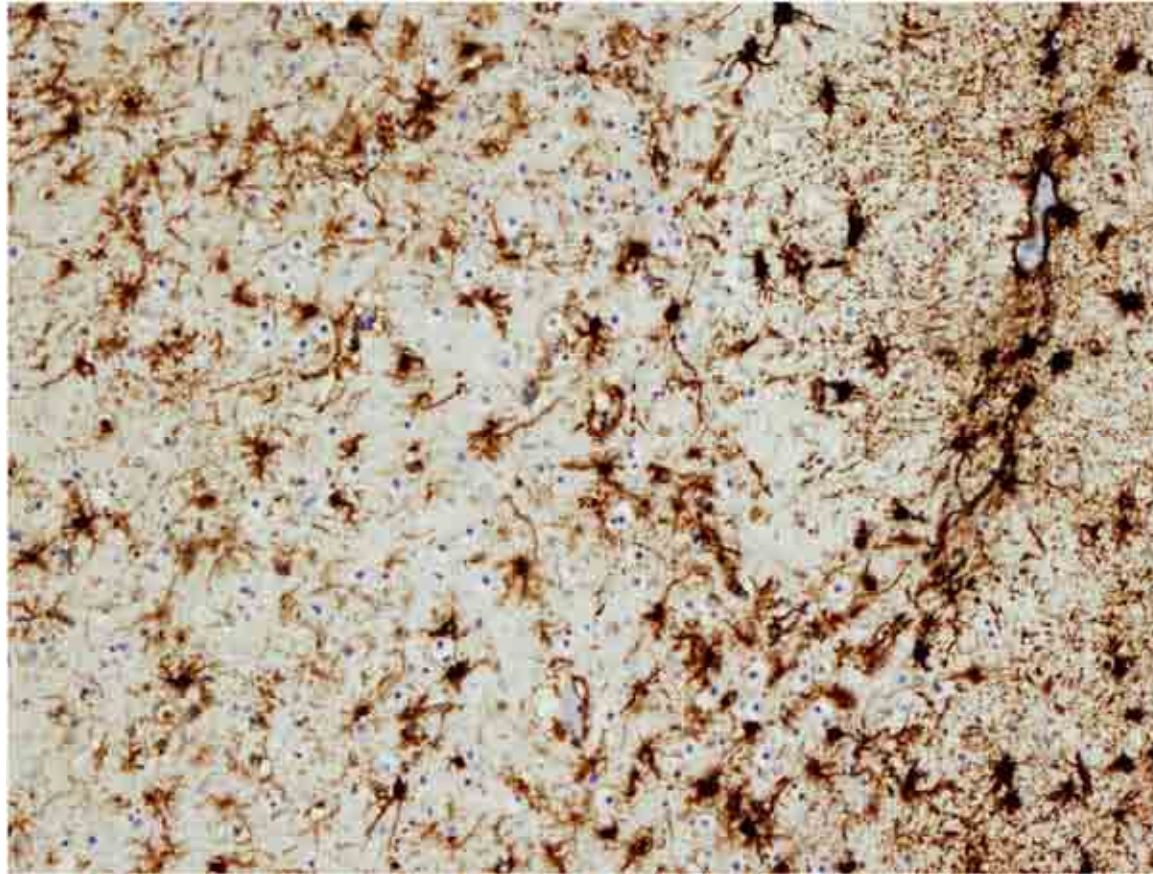


# Severe acute hypoxic-ischemic neuronal change



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# Gliosis secondary to the hypoxic-ischemic event



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# Treatment: Medical Care



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- **PREVENTION**

- Obstetric and Neonatal resuscitation

- **Supportive care**

- Maintain adequate ventilation
- Maintain the blood gases and acid-base status in the physiological ranges

- **Maintain adequate perfusion.**

- Maintain the mean blood pressure (BP) above 35-40 mm Hg (for term infants). Dopamine or dobutamine can be used to maintain adequate cardiac output.

# Treatment: Medical Care



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- **Maintain adequate metabolic status.**
  - Fluid and glucose homeostasis
  - Because of the concern for acute tubular necrosis (ATN) insensible water loss (40-60 mL/kg/d in term infant).
- **Avoid hyperthermia.**

# Treatment of seizures



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- **S**eizures should be treated early and be well controlled because even asymptomatic seizures (ie, seen only on EEG) may continue to injure the brain.
- Seizures should be treated with phenobarbital or lorazepam; phenytoin may be added if either of these medications fails to control the seizures.

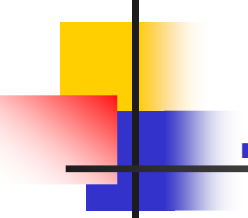
# Hypothermia treatment



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- Extensive experimental data suggest that mild hypothermia (3-4°C below the baseline temperature) applied within a few hours (no later than 6 h) of hypoxia-ischemia injury is neuro-protective.
- Therapeutic hypothermia is now the standard of care in neonates with moderate-to-severe hypoxic-ischemic encephalopathy.

# Hypothermia treatment

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- **Near-term infants born at 36 weeks' gestation or less with birth weight of 1800-2000 g or less, 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 (In the study by Shankaran et al, this needed to be in conjunction with either evidence of acute perinatal event or need for assisted ventilation for at least 10 min.<sup>13</sup> )**
    - **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**
    - **Clinically determined (at least 2)**
      - **Lethargy, stupor, or coma**
      - **Abnormal tone or posture**
      - **Abnormal reflexes (suck, grasp, Moro, gag, stretch reflexes)**
      - **Decrease or absent spontaneous activity**
      - **Autonomic dysfunction (including bradycardia, abnormal pupils, apneas)**
      - **Clinical evidence of seizures**
    - **Moderately or severely abnormal aEEG background or seizures**

# Hypothermia studies

Study	Enrollment criteria	Method	Duration of cooling	N	Time of Follow-up	Results
Gluckman et al (2005)	< 6h pH<7.0, BE≥16 Apgar≤5 @ 10' Encephalopathy by aEEG	Head cooling	72h 34-35°C Rectal	110 (H) 108 (N)	18 mth	No effect in most severe aEEG Death or severe disability: 66% (N) vs 48% (H) *; NNT= 6 Severe neuromotor disability: 28% (N) vs. 12% (H) * MDI: 77 (N) vs. 85 (H) * PDI: 85 (N) vs. 90 (H) *
Eicher et al (2005)	< 6h pH<7.0, BE≥14 Apgar≤5 @ 10' Clinical enceph	Whole body cooling	48h 33-33.5°C Rectal	32 (H) 33 (N)	12 mth	Death or mod/severe disability: 84% (N) vs. 52% (H) * PDI <70: 64% (N) vs 24% (H) * Mortality: 42% (N) vs 31% (H)
Shankaran et al (2005)	< 6h pH<7.0, BE>16 Clinical enceph	Whole body cooling	72h 33-33.5°C Esophageal	102 (H) 106 (N)	18 mth	Death or mod/severe disability: 62%(N) vs. 45%(H) ** NNT=6 Mortality: 36% (N) vs. 24%(H)

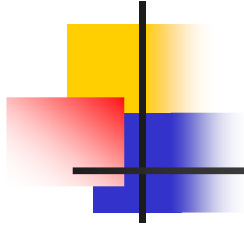
H= hypothermia group, N= normothermia group

\* p<0.05 vs. N; \*\* p<0.01 vs. N



# Neuro-protective strategies

Strategies	Interventions
↓ cerebral metabolic rate	Hypothermia
Block NMDA receptor channel	Magnesium
↓ glutamate release	Adenosine Adenosine agonists Adenosine uptake inhibitors
Inhibit voltage-sensitive Ca <sup>++</sup> 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- $\alpha$ , steroids)
Attenuate apoptosis pathway	Caspase inhibitors

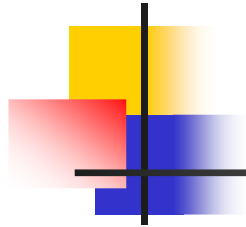


## **Surgical Care**

Posterior cranial fossa hematoma- surgical drainage

## **Diet**

Trophic feeding with expressed breast milk about 5 mL every 3-4 hours if bowel sounds audible. Individualize increments in feeding volume and composition



## **Anticonvulsants**

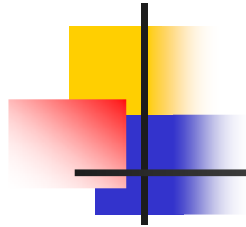
These agents are used to control seizures.

### **Phenobarbital**

Clinical or EEG seizures - continued on the basis of both EEG findings and clinical status.

Weaned and stopped during the first month of life if no further convulsions.

EEG and clinical status should guide decision.



## **Follow-up**

**Physical therapy and developmental evaluation are needed before discharge.**

### **Further Outpatient Care**

**Severely disabled children may need to be monitored in multi-disciplinary clinics and by a developmental neurologist.**



# Experimental treatment.

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- None has shown consistent efficacy in infants.
  - Alloperinol
  - High dosis Phenobarb



## Prognosis

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Accurate prediction of the severity of long-term complications is difficult, although the following pointers may be used:

Lack of spontaneous respiratory effort within 20-30 minutes of birth almost always associated with death.

The presence of seizures is an ominous sign. The risk of poor neurological outcome is distinctly greater in such infants,

Abnormal clinical neurological findings persisting beyond the first 7-10 days of life usually indicate poor prognosis. Among these, abnormalities of muscle tone and posture (hypotonia, rigidity, weakness) should be carefully noted.



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## **Prognosis ( cont.)**

An EEG done at about 7 days that has normal background activity is a good prognostic sign.

Persistent feeding difficulties, which generally are due to abnormal tone of the muscles of sucking and swallowing, also suggest significant CNS damage.

Poor head growth during the postnatal period and the first year of life is a sensitive finding predicting higher frequency of neurologic deficits.



# Medico-legal pitfalls

~~Birth asphyxia, birth injury, and perinatal asphyxia are terms often used incorrectly to describe hypoxic-ischemic encephalopathy (HIE).~~

It is recommend using hypoxic-ischemic encephalopathy because this term accurately describes the clinical condition, encephalopathy from asphyxia, without implying the time of brain injury.

Counseling the parents with realistic explanations about their infant's clinical status and prognosis is always recommended.

Always document and sign the counseling session.





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