THERAPEUTIC HYPOTHERMIA IN MANAGEMENT OF HIE

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INTRODUCTION

- Perinatal asphyxia is a major cause of neonatal and under-5 mortality particularly in developing countries.
- All newborns who are at or near term with moderate-severe HIE should be treated with therapeutic hypothermia within 6 hours of birth.
- Passive cooling is safe and effective with close temperature monitoring and management.
- Careful management of ventilation, oxygenation, perfusion, metabolic and fluid balance are critical to optimize outcome.

NATIONAL NEONATAL PERINATAL DATABASE

Perinatal asphyxia accounts for

- 9.4% of total under-5 child mortality worldwide.
- 45.1% of total still births.

DEFINITIONS OF PERINATAL ASPHYXIA

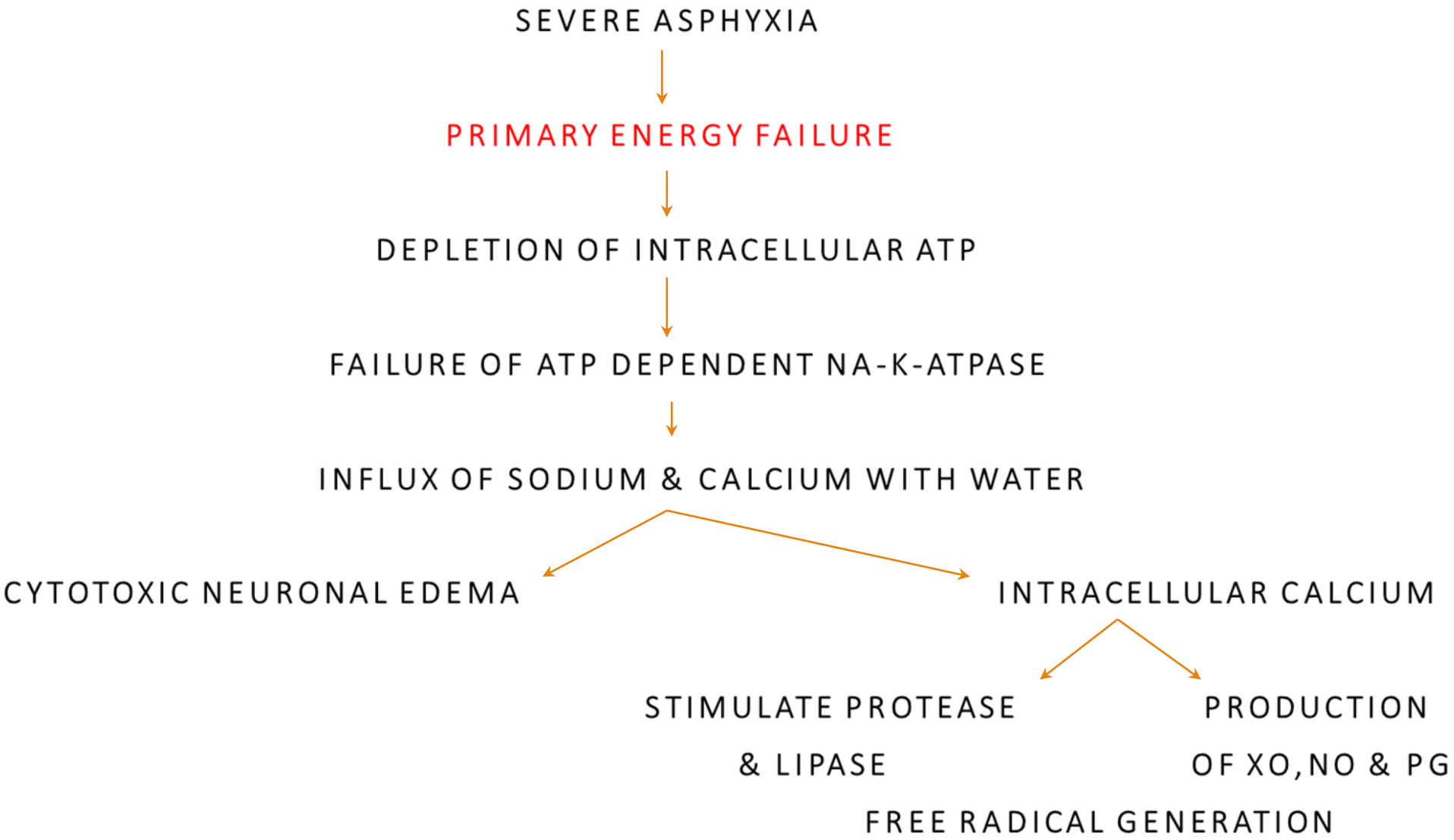
- **NNPD NETWORK**
- Moderate PA: slow/gasping breathing or an Apgar score of 4 to 6 at 1 min.
- Severe PA: No breathing or an Apgar score of 0-3 at 1 min of age.

- **AMERICAN ACADEMY OF PEDIATRICS & AMERICAN COLLEGE OF OBSTETRICS & GYNECOLOGY**

Presence of all of following criteria-

- pH <7.0 in umblical cord blood.
- Persistent low Apgar scores less than 3 for more than 5 minutes.
- Signs of neonatal neurologic dysfunction.
- Evidence of multi organ involvement

PATHOPHYSIOLOGY OF HIE



LATENT PHASE/ THERAPEUTIC WINDOW (6HRS)

↓

SECONDARY ENERGY FAILURE

↓

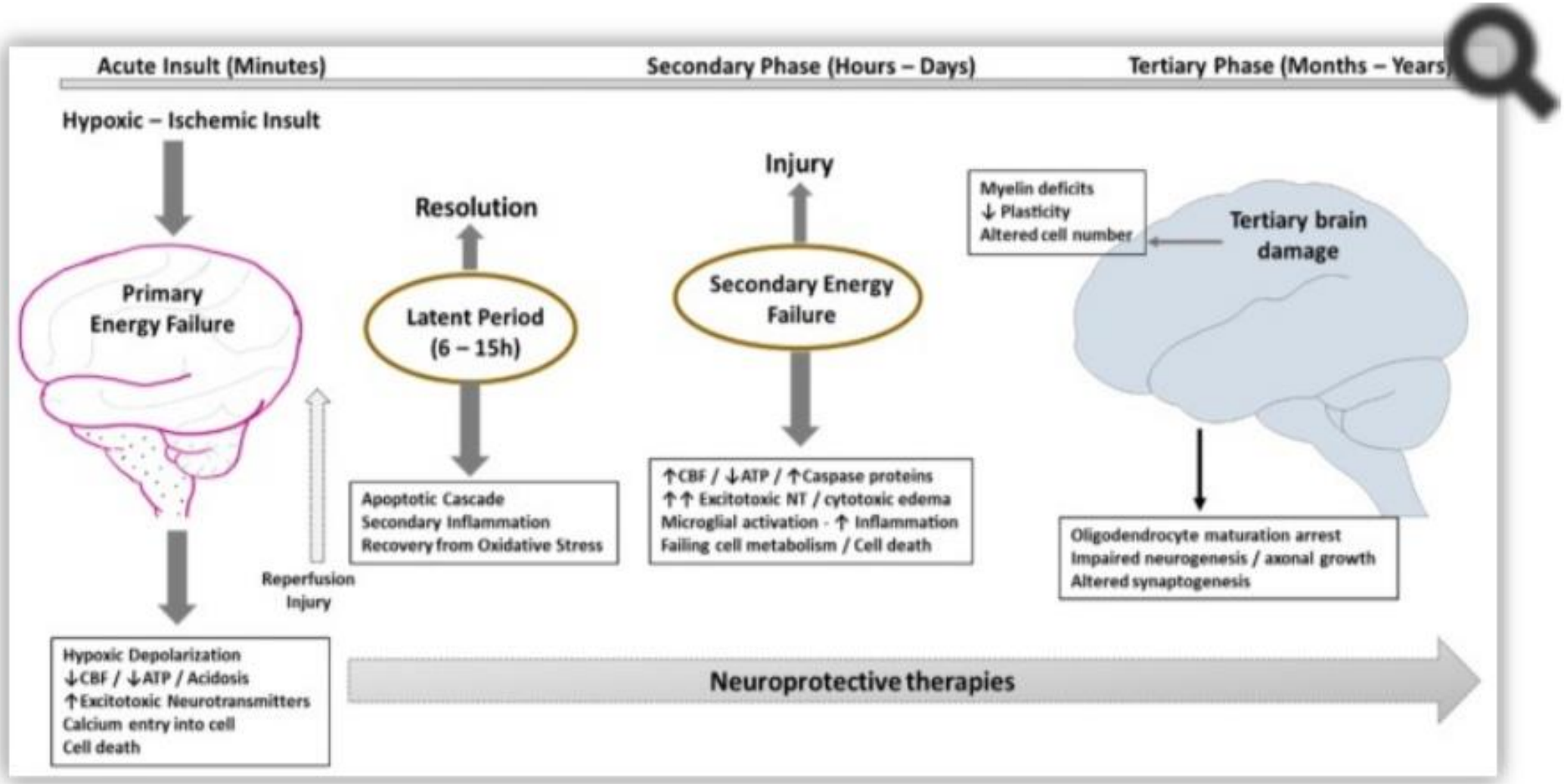
OXYGEN FREE RADICALS

↓

NEURONAL INJURY IN AREA ADJACENT TO INFARCTION (PENUMBRA)

↓

NEURONAL NECROSIS /APOPTOSIS DURING NEXT 24-48 HRS


Acute Insult (Minutes)
Secondary Phase (Hours – Days)
Tertiary Phase (Months – Years)
Hypoxic – Ischemic Insult
Primary Energy Failure
Hypoxic Depolarization
↓CBF / ↓ATP / Acidosis
↑Excitotoxic Neurotransmitters
Calcium entry into cell
Cell death
Reperfusion Injury
Resolution
Latent Period (6 – 15h)
Apoptotic Cascade
Secondary Inflammation
Recovery from Oxidative Stress
Injury
Secondary Energy Failure
↑CBF / ↓ATP / ↑Caspase proteins
↑↑ Excitotoxic NT / cytotoxic edema
Microglial activation - ↑ Inflammation
Failing cell metabolism / Cell death
Myelin deficits
↓ Plasticity
Altered cell number
Tertiary brain damage
Oligodendrocyte maturation arrest
Impaired neurogenesis / axonal growth
Altered synaptogenesis
Neuroprotective therapies

MULTI	ORGAN DYSFUNCTION IN PERINATAL ASPHYXIA
CNS	Hypoxic ischemic encephalopathy, intracranial hemorrhage, seizures, long term neurological sequelae
CARDIAC	Myocardial dysfunction, valvular dysfunction, rhythm abnormalities, congestive cardiac failure
RENAL	Hematuria, acute tubular necrosis, renal vein thrombosis
PULMONARY	Meconium aspiration, hyaline membrane disease, transient tachypnea, PPHN, pulmonary hemorrhage, pneumonia
GI TRACT	Necrotising enterocolitis, GI bleeding , paralytic ileus, hepatic dysfunction
HEMATOLOGICAL	Thrombocytopenia, coagulation abnormalities
METABOLIC	Acidosis, hypoglycemia, hypocalcemia, hyponatremia.

CLINICAL DIAGNOSIS

- Prolonged (>1 hour) antenatal acidosis.
- Fetal HR<60 beats/min.
- Apgar score <3 mins for >10 mins.
- Need for positive pressure ventilation for >1min or first cry delayed by >5 mins.
- Seizures within 12-24 hours of birth.

- Burst suppression or suppressed background pattern on EEG.

Level of consciousness	Stage 1 (mild) Hyperalert	Stage 2 (moderate) Lethargic/obtunded	Stage 3 (severe) Stuporous
Neuromuscular control			
Muscular tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch	Overactive	Overactive	Decreased/absent
Segmental myoclonus	Present	Present	Absent
Complex reflexes			
Suck	Weak	Weak/absent	Absent
Moro	Strong	Weak	Absent
Oculovestibular	Normal	Overactive	Weak/absent
Tonic neck	Slight	Strong	Absent
Autonomic function			
Pupils	Mydriasis	Miosis	Variable
Heart rate	Tachycardia	Bradycardia	Variable
Bronchial/salivary secretions	Sparse	Profuse	Variable
Gastrointestinal motility	Normal/decreased	Increased/diarrhea	Variable
Seizures	None	Common/focal or multifocal	Uncommon
EEG	Normal/decreased	Early low voltage continuous delta and theta, later periodic, seizues focal 1–1.5 Hz spike-wave	Early periodic pattern with isopotential phases, later isopotential
Duration	<24 h	2–14 days	Hours–weeks

EEG, electroencephalogram.

EMERGING MODALITIES FOR DIAGNOSIS

- **BIOMARKERS**
- S100B
- NSE (NEURON SPECIFIC ENOLASE)
- GFAP (GLIAL FIBRILLARY ACIDIC PROTEIN)
- UCH-L1 (UBIQUITIN CARBOXYL TERMINAL HYDROLASE L1)

- **INFLAMMATORY MARKERS**
- plasma levels of IL-6, IL-8 and

  Vascular endothelia growth factors.

- **METABOLOMIC ANALYSIS AND METABOLITES**
- Elevated levels of arachidonic acid, butanoic acid, citric acid,

  fumaric acid, lactate, malate, propanoic acid and succinic acid.

- **IMAGING**

- **Diffusion weighted MRI can detect abnormalities within 24 to 48 hours after birth.**
- **An altered signal at the level of posterior limb of internal capsule & abnormalities of the thalami & basal ganglia are strong predictors of poor neurodevelopmental outcome.**

- **EEG**

- It is used to both detect and monitor seizure activity and also to define abnormal background patterns such as discontinuous, burst suppression, low voltage or iso-electric patterns.

- In a recent meta-analysis of 29 studies describing 13 prognostic tests in 1306 term neonates with HIE, a-EEG in the first 6 hours showed maximum sensitivity & specificity (93% and 90% respectively)

MANAGEMENT OF A NEONATE WITH PERINATAL ASPHYXIA

- **MAINTAIN NORMAL TEMPERATURE**
- After drying , place the baby under radiant warmer
- Avoid hyperthermia
- **MAINTAIN NORMAL OXYGENATION AND VENTILATION**
- Target spO2 : 90-95%
- Maintain paO2 : 60-90 mm Hg
- Maintain pCO2 : 35-45 mm Hg
- **MAINTAIN NORMAL TISSUE PERFUSION**
- Donot restrict fluids routinely because it may predispose to hypoperfusion
- Restrict only if there is hyponatremia (Na <120 mEq/l) secondary to SIADH or renal failure.

- **MAINTAIN NORAML HEMATOCRIT & METABOLIC MILIEU**
- Maintain blood glucose levels between 75-100mg/dl
- Maintain hematocrit between 45-55%
- Maintain pH above 7.3
- In case of severe asphyxia provide calcium in a maintenance dose of 4 ml/kg/day of 10% calcium gluconate for 1-2 days.

- **TREAT SEIZURES.**

THERAPEUTIC HYPOTHERMIA

ELIGIBILITY CRITERIA

- Post menstrual age (PMA >36 weeks,BW >2,ooog)
- Evidence of fetal distress as evidenced by

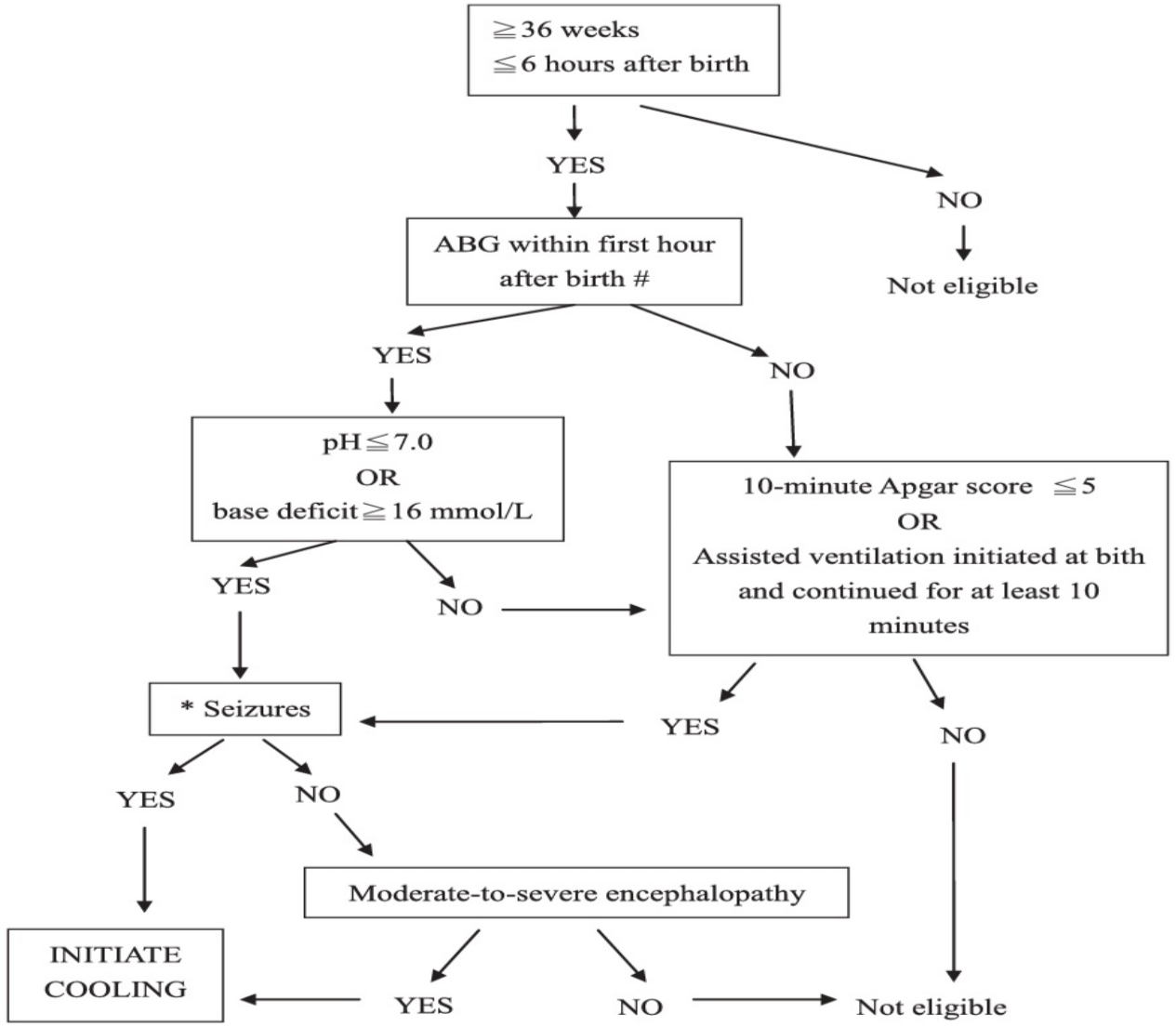
i. History of acute perinatal event

ii. pH <7 or base deficit >16mmol/L in cord gas

iii. 10 minute Apgar score of <5

iv. Assisted ventilation initiated at birth and continued for atleast 10 mins.

- Evidence of moderate to severe neonatal encephalopathy.



#: Umbilical cord or any arterial or venous blood sample.

*: Seizures indicate that patient has moderate encephalopathy.

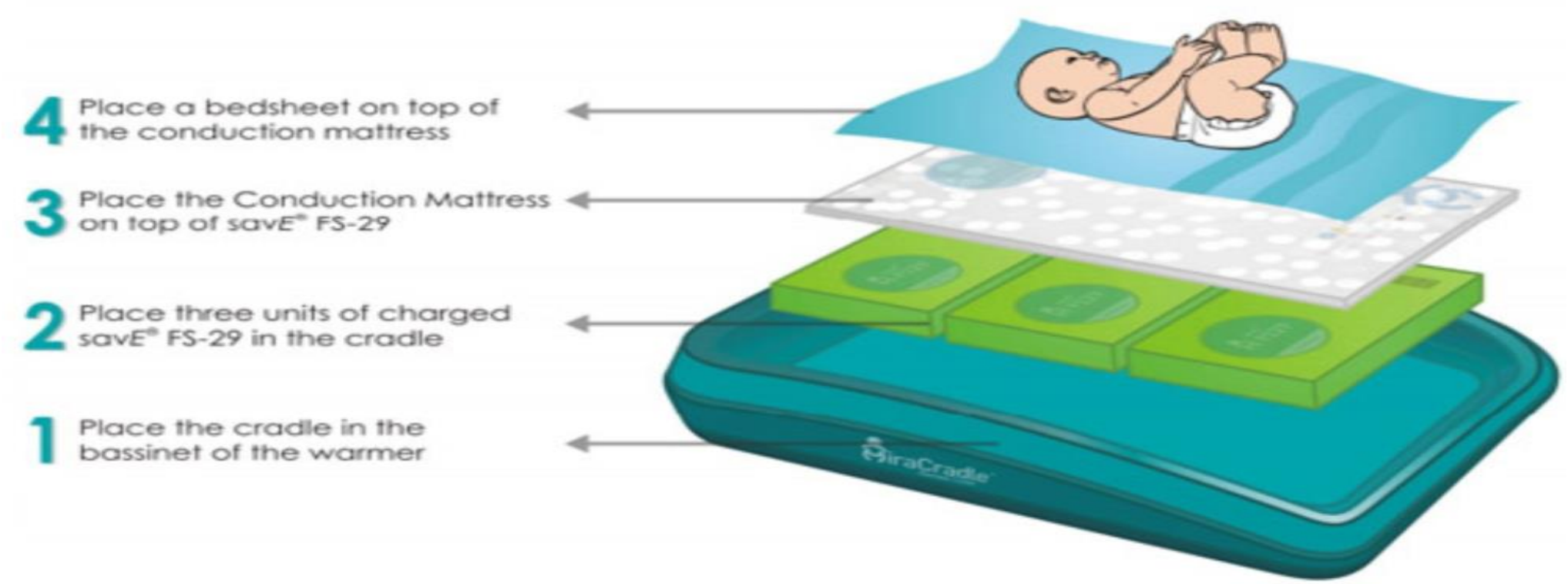
EXCLUSION CRITERIA

- Presence of lethal chromosomal anomaly (eg. Trisomy 13 or 18)
- Presence of severe congenital anomalies
  (eg. Complex cyanotic congenital heart disease, major CNS anomaly)
- Symptomatic systemic congenital viral infection (eg.hepatosplenomegaly, microcephaly)
- Symptomatic systemic congenital bacterial infection (eg. Meningitis, DIC)
- Significant bleeding diathesis.
- Major intracranial hemorrhage.

METHODS AND EQUIPMENTS

- Whole body cooling (WBC) or selective head cooling (SHC) can be used to induce TH.
- There is no significant difference in adverse events, 12 month neuromotor development or mortality rates between the two groups.
- Fully servo-controlled devices are suggested for WBC.
- Cool-cap system is used for SHC.

MIRACRADLE

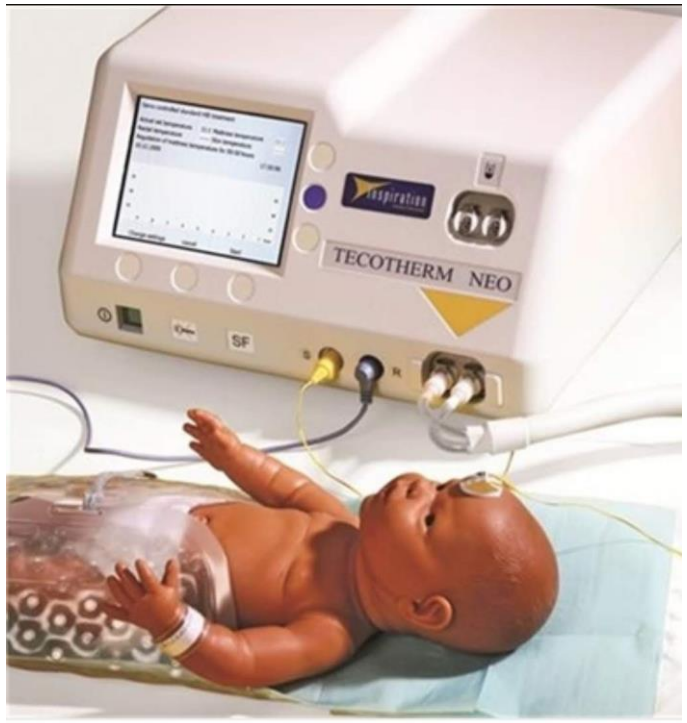

4 Place a bedsheet on top of the conduction mattress
3 Place the Conduction Mattress on top of savE® FS-29
2 Place three units of charged savE® FS-29 in the cradle
1 Place the cradle in the bassinet of the warmer
MiraCradle

CRITICOOL

The Cool Cap Study

By parental permission, Dr Durand, Oakland

TECOTHERM



TEMPERATURE MAINTENANCE AND REWARMING

- The target core temperature goal during cooling is 33.5 c

  (33-34c)
- Acceptable duration is 72 hrs.
- Rewarming should be performed slowly and the core temperature rise should not be more than 0.5 c/h.

- Rebound seizures have been noted during rewarming phase.

SAFETY MONITORING

- **TEMPERATURE**
- Core temperature should be monitored every 15 minutes until 1 hour after goal temperature of 33.5 c, & then hourly.

RESPIRATORY SYSTEM

- During TH, the metabolic rate reduce by 5-8%, when body temperature drops by 1 c, & the production of CO2 is decreased as well.
- Low Pco2 leads to altered auto regulation of cerebral blood flow & reduced cerebral perfusion.
- Severe hyperoxemia(Po2 > 200 mmHg) & severe hypocapnia (Pco2< 20 mmHg) during the first 2 hours of life is associated with adverse outcomes.
- ABG & S. lactate should be monitored at baseline & then at 4, 8, 12, 24, 48 & 72 hours of treatment and as clinically indicated.

- **CARDIOVASCULAR SYSTEM**

- **There is no difference in the incidence of hypotension between TH infants & normothermic (NT)infants with same severity of asphyxia.**
- **Mean arterial blood pressure should be maintained within 40-60 mmHg.**
- **If there is hypotension, then cautious correction of hypovolemia because unnecessary excess fluid may exacerbate cerebral edema**

- **In patients with reduced myocardial contractility , dobutamine is indicated**

FLUID, ELECTROLYTES AND NUTRITION

- NPO when passive cooling starts, until rewarmed to normal temperature. Glucose, S. electrolytes, BUN/Cr and AST/ALT should be done at baseline and then at 24, 48 & 72 hours of treatment.
- Some centers provide trophic feeds of about 10ml/kg/day if no contraindication.
- Parenteral nutrition- protein(3-3.5 g/kg/day) & lipids(3g/kg/day).

- To avoid cerebral edema, goal Na at high end of normal range.
- PT, APTT, INR & Platelet count should be measured daily and as clinically indicated.

- **MONITORING AND MANAGEMENT OF SEIZURES**

- Seizures are common within the first 1-2 days of life, monitoring seizure activity is important using aEEG or continuous video EEG.
- Phenobarbitone remains the first line of treatment.

CLINICAL TRIALS

- **METHOD OF COOLING. DURATIONS & DEPTH OF COOLING**

- Unde the NICHD RCT, 208 term infants with moderate or severe encephalopathy were randomly assigned to whole body cooling to an esophageal temperature of 33.5° for 72 hours or usual care. Primary outcome was death or disability at 18 months. Death or disability occurred in 62% cases of usual care and 44% of hypothermia group.

- The TOBY enrolled 325 infants and assigned them to whole body hypothermia to a rectal temperature of 33° - 34°C for 72 hours or usual care. Death or disability occurred in 53% cases under usual care and 45% in hypothermia care.

- The European Network RCT enrolled 129 infants. In the hypothermia group, rectal temperature of 33°-34°C was maintained. All infants received Morphine(0.1mg/g) infusions. Death or severe disability occurred in 51% of hypothermia group and 83% of normothermia group.

- Infant Cooling Evaluation (ICE) trial enrolled 221 infants. Whole body cooling was initiated at the referral hospital after clinical diagnosis of encephalopathy. Primary outcome was death or disability at 24 months. Mild encephalopathy was noted in 15% hypothermia and 23% control infants. The primary outcome occurred in 51% hypothermia and 66% control infants.

- In summary, eligibility criteria for application of cooling should include severe acidosis and the presence of moderate or severe encephalopathy.

- The depth of temperature should be 33°-34°C and the duration of cooling should be 72 hours followed by rewarming at 0.5°C per hour.

CONTROVERSIES IN ADMINISTERING THERAPEUTIC HYPOTHERMIA

- **HYPOTHERMIA OF GREATER DURATION OR DEPTH**
- Neither cooling for 120 hours nor cooling to a temperature of 32c offered additional benefit & instead showed a trend to worse outcome, with the trial being stopped early.

- **LATE INITIATION OF HYPOTHERMIA**
- There are data showing improved outcome if TH is started at <3 -4 hrs after birth but it is unclear if there is a benefit at >6 hours after birth.
- Some centers consider cooling at 6-12 hrs if other criterias are met.

- **GESTATIONAL AGE 34-36 WEEKS**
- It is unclear what is the lowest gestational age for which TH remains both effective & safe.
- Some centers consider cooling at 34-36 weeks if other criterias are met, the newborns are of normal weight & a US is performed early to rule out intraventricular hemorrhage.

- **UNDERLYING MEDICAL CONDITIONS**

- There is also controversy about providing hypothermia to newborns with underlying surgical or genetic conditions.

- **MILD HIE**
- Although there are some objective entry criteria such as the pH, base excess or voltage by aEEG, other criteria are subjective such as determination of fetal distress or the severity of encephalopathy by clinical exam.

EMERGING MODALITIES

- **OXYGEN FREE RADICAL INHIBITORS & SCAVENGERS**
- Drugs that inhibit the formation of oxygen free radicals or block entry of calcium ions decrease the severity of HIE.
- Eg-
- Indomethacin
- N-acetyl cysteine
- Melatonin
- Allopurinol.

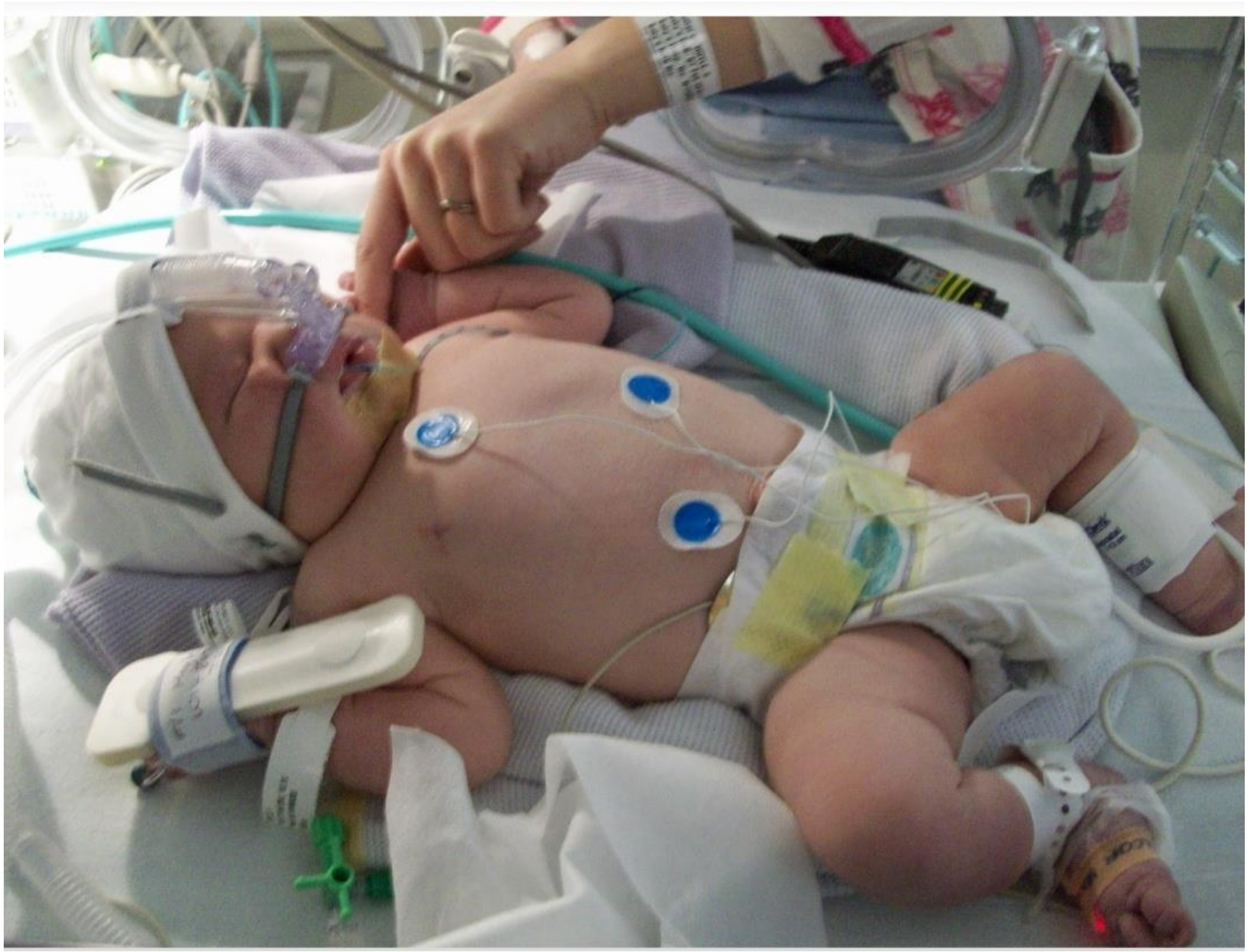
- **CALCIUM CHANNEL INHIBITORS**
- Calcium being an intracellular second messenger is a regulator of cellular metabolism.
- Eg-
- Flunarizine
- Nimodipine.

- **ERYTHROPOIETIN**
- its neuroprotective mechanism include direct neurotropic effect , decreased susceptibility to glutamate toxicity, release of antiapoptotic factors, reduced inflammation and anti oxidant effects.
- High (5000U/kg) and multiple doses of recombinant human Epo provide significant neuroprotection.

- **EXCITATORY AMINO ACID ANTAGONISTS**
- Glutamate has been implicated in the pathogenesis of HIE.
- Agents which block glutamate or NMDA receptors include-
- Baclofen
- Phencyclidine
- Dextromethorphan
- Ketamine
- MK-801.

- **PREVENTION OF EXCESS NITRIC OXIDE FORMATION**
- NO is a free-radical gas.
- Administration of nitroarginine 15 hours prior to cerebral hypoxia-ischemia cause prolonged inhibition of NO synthesis & reduction in extent of brain injury.

- **STEM CELL TRANSPLANTATION**
- It may repair the damaged neurons in the brain.
- Several types of stem cells have been used in rodent models like neuronal, mesenchymal & hematopoietic stem cells.




THANK YOU
WELLS FARGO
JDRF 2005
We're on Track For a Cure