Learning Objectives
1. Discuss the significance, pathophysiology, and management of neonatal hypoxic ischemic encephalopathy.
2. Review the pharmacokinetic properties of epoetin alfa and its potential neuroprotective role for hypoxic ischemic encephalopathy.
3. Analyze evidence for use of epoetin alfa for neuroprotection in hypoxic ischemic encephalopathy and apply to a patient.
Hypoxic Ischemic Encephalopathy (HIE)

I. Background
   A. Neurologic injury during the intrapartum period due to impaired oxygen delivery to the brain\(^1\)
   B. Incidence:\(^1,2\)
      i. One to four cases per 1000 live births in high income countries
      ii. 26 cases per 1000 live births in low income countries
   C. Contributed to 22% of deaths in first month of life in 2013\(^1\)
   D. Accounts for an estimated one million deaths annually\(^3\)
   E. Complications:\(^1\)
      i. Mortality (28%)
      ii. Cognitive impairment (24%)
      iii. Cerebral palsy (CP) (22%)
      iv. Epilepsy (19%)
   F. Combined death or moderate/severe disability: 48%\(^1\)

II. Pathophysiology
   A. Impaired oxygen delivery to brain tissue\(^3\)
      i. Due to reduced oxygen carrying capacity, reduced cerebral blood flow (volume loss, impaired circulation)
      ii. Lack of oxygen for up to 18-25 minutes causes moderate to severe brain injury in animal models
   B. Injury occurs in phases:
      i. Acute insult (minutes)\(^1,3-6\)
         a. Primary energy failure due to oxygen deprivation
            • Shift from oxidative phosphorylation to anaerobic metabolism
            • Accumulation of lactate
            • Depletion of ATP
            • Intracellular accumulation of sodium, calcium, and water
         b. Cell death
      ii. Latent and secondary phases (hours to days)\(^1,3-6\)
         a. Mitochondrial failure
         b. Seizures
         c. Excitotoxicity
         d. Generation of free radicals
         e. Injury from inflammatory mediators
         f. Further oxidative stress
      iii. Tertiary phase (days to months)\(^3,5,6\)
         a. Late cell death
         b. Remodeling
         c. Astroglisis
Figure 1. Pathophysiology of HIE

III. Clinical Presentation
   A. Varies according to severity
   B. Depressed level of consciousness
   C. Abnormality of muscle tone
   D. Suppressed neonatal reflexes
   E. Low Apgar scores
   F. Metabolic acidosis
   G. Multiorgan dysfunction

IV. Diagnosis
   A. No specific test → based on presence of neurologic dysfunction in form of neonatal encephalopathy
   B. Three criteria:
      i. Neurologic dysfunction
      ii. Metabolic acidosis
      iii. Low Apgar scores
   C. Neuroimaging
      i. Assessed at four to five days of life (DOL)
      ii. Evidence of acute injury on brain MRI or MR Spectroscopy consistent with hypoxia-ischemia
   D. Classification of severity: Modified Sarnat Scoring System
      i. Encephalopathy defined as at least three of six criteria present
      ii. Severity determined by column with the most symptoms
      iii. If equal distribution, base on level of consciousness
Table 1. Modified Sarnat Scoring System

<table>
<thead>
<tr>
<th>Category</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of consciousness</td>
<td>Hyperalert or irritable</td>
<td>Lethargic or poorly-responsive</td>
<td>Minimal or no responsiveness</td>
</tr>
<tr>
<td>Spontaneous activity</td>
<td>Slightly decreased</td>
<td>Decreased</td>
<td>Absent</td>
</tr>
<tr>
<td>Posture</td>
<td>Mild distal flexion</td>
<td>Distal flexion, complete extension</td>
<td>Decerebrate</td>
</tr>
<tr>
<td>Tone</td>
<td>Hypertonic</td>
<td>Hypotonic</td>
<td>Flaccid</td>
</tr>
<tr>
<td>Primitive reflexes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suck</td>
<td>N/A</td>
<td>Weak or bite</td>
<td>Absent</td>
</tr>
<tr>
<td>Moro</td>
<td>Low threshold to elicit</td>
<td>Weak or incomplete</td>
<td>Absent</td>
</tr>
<tr>
<td>Autonomic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pupils</td>
<td>N/A</td>
<td>Constricted</td>
<td>Dilated and/or fixed, sluggishly reactive, asymmetric</td>
</tr>
<tr>
<td>Respiration</td>
<td>N/A</td>
<td>Periodic breathing</td>
<td>Intubated/ventilated</td>
</tr>
</tbody>
</table>

V. Treatment: Therapeutic hypothermia
   A. Standard of care in high income countries\(^1\)
   B. Maintain body temperature of 32-35 °C for 72 hours\(^1,4,6\)
   C. Provides modest benefits for moderate HIE when initiated within 6 hours of birth\(^8\)
   D. Targets early mechanisms of injury\(^9\)
      i. ↓ cerebral metabolism
      ii. ↓ ATP depletion
      iii. ↓ excitotoxic neurotransmitter accumulation
      iv. ↓ free radical release
   E. For each 1 °C ↓ in temperature, cerebral metabolic rate ↓ by 6-7%\(^10\)
   F. Head cooling\(^11,12\)
      i. Cap placed on infant’s head
      ii. Cold water circulates through cap
   G. Whole body cooling\(^11,12\)
      i. Cooling blanket placed on infant
      ii. Cold water circulates through blanket

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Epoetin Alfa

I. Mechanism\(^13,14\)
   A. Glycoprotein that regulates production of red blood cells
   B. Stimulates division and differentiation of erythroid progenitor cells in bone marrow
   C. Same activity as biological erythropoietin
II. Biological erythropoietin$^{13,15}$
   A. Fetus: 100% produced in liver
   B. At birth production is transferred to kidney
   C. Adults: ~90% produced in kidney, ~10% produced in liver

III. Proposed mechanism in HIE$^{1,3,15-17}$
   A. Animal models demonstrate reduced infarct volume and improved neurologic recovery with use of epoetin alfa
   B. Epoetin alfa receptors widely expressed throughout CNS
      i. Progenitor cells, astrocytes, oligodendrocytes, microglia
   C. Reduces apoptotic cell death
   D. Antioxidant and anti-inflammatory properties
   E. Stimulates growth factors
      i. Neurogenesis
      ii. Angiogenesis
      iii. Oligodendrogenesis
      iv. Long-term repair

IV. Distribution$^{15,17}$
   A. Rapidly distributed throughout plasma
   B. Concentrates in liver, kidneys, and bone marrow
   C. Blood brain barrier (BBB) penetration
      i. Large molecule size (37 kilodaltons)
      ii. Crosses BBB via passive diffusion
      iii. Only 1-2% of circulating erythropoietin crosses BBB
   D. Target plasma concentrations
      i. Neuroprotection in animals with$^{18}$
         a. Maximum concentration (Cmax) 6,000-10,000 units/L
         b. Area under the curve (AUC) 117,000-140,000 units*hrs/L

V. Contraindications$^{13,14}$
   A. Serious allergic reactions to epoetin alfa products or any component of the formulation
   B. Uncontrolled hypertension (HTN)
   C. Multi-dose vials contain benzyl alcohol → contraindicated in neonates, infants, pregnant women, breastfeeding women

VI. Select warnings and adverse effects$^{13,14}$
   A. Black Box Warning: erythropoiesis-stimulating agents increased risk of serious cardiovascular events, myocardial infarction, stroke, venous thromboembolism, vascular access thrombosis, and mortality in clinical studies when administered to target hemoglobin levels > 11 g/dL
   B. Cutaneous reactions: erythema multiforme and Stevens-Johnson Syndrome/toxic epidermal necrolysis
   C. Hypersensitivity
   D. Possible increased risk retinopathy of prematurity demonstrated when used for anemia of prematurity$^{14,15}$
      i. Not concern for term infants
   E. HTN
   F. Polycythemia
Clinical Question and Overview of Literature

Clinical Question: Can epoetin alfa be used for neuroprotection in neonates with HIE?

Figure 2. Overview of Literature\textsuperscript{15,16,19}

First study in human neonates: evaluates use of epoetin alfa for HIE without TH

Phase I trial: evaluates dose and safety of epoetin alfa in infants with HIE receiving concurrent TH

Phase II trial: evaluates impact of epoetin alfa on neurodevelopmental outcomes in infants with HIE receiving concurrent TH

Review of Literature

Table 2. Erythropoietin Improved Neurologic Outcomes in Newborns with Hypoxic Ischemic Encephalopathy (Zhu C, et al, 2009)\textsuperscript{16}

<table>
<thead>
<tr>
<th>Study Design and Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
</tr>
</tbody>
</table>
| **Methods** | • First study examining use of epoetin alfa for neonatal HIE in humans
• 2 center, 2-phase, prospective randomized trial
• Infants randomized to epoetin alfa or conventional care within 48 hours of birth
• Dose increased in 2\textsuperscript{nd} phase
  o Positive safety data
  o Speculation that higher dose would be more efficacious |
| **Patient Population** | **Inclusion:**
  • > 37 weeks GA
  • Weight > 2500 g
  • Clinical evidence of perinatal HIE (Sarnat Scoring System)
  • Apgar scores ≤ 5 at 5 min or continued need for resuscitation at 10 min after birth

**Exclusion:**
  • Major congenital abnormalities
  • Postnatal age > 48 hours
  • Head trauma or skull fracture causing ICH
  • Body temperature < 34 °C (93.2 °F)
  • Financial problems of parents
  • Lack of permanent address |
Phase 1: Epoetin alfa 300 units/kg subcut x1 dose, then IV every 48 hours for 2 weeks vs conventional care

Phase 2: Epoetin alfa 500 units/kg subcut x1 dose, then IV every 48 hours for 2 weeks vs conventional care

Primary Outcomes
- Death or disability at 18 months of age
  - Criteria for moderate/severe disability: CP, severe hearing loss, blindness, GMFCS 3-5, or MDI < 70

Secondary Outcomes
- Death or disability stratified by severity of HIE and gender
- Thompson Neurologic Assessment at DOL 1, 3, and 7
- MDI score at 18 months of age
- Presence of CP at 18 months of age

Statistical Analysis
- 65 patients needed for each group for 80% power
- Randomization stratified by severity of HIE
- Outcome differences analyzed with Fischer’s exact tests, 2-sided p-values
- P < 0.05 considered significant

Results

Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control (N=82)</th>
<th>Epo 300 units/kg (N=47)</th>
<th>Epo 500 units/kg (N=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA, mean ± SD, wks</td>
<td>39.6 ± 1.6</td>
<td>39.6 ± 1.4</td>
<td>40.0 ± 1.4</td>
</tr>
<tr>
<td>Birth weight, mean ± SD, g</td>
<td>3274 ± 478</td>
<td>3310 ± 450</td>
<td>3362 ± 472</td>
</tr>
<tr>
<td>Female/male</td>
<td>24/58</td>
<td>9/38</td>
<td>8/21</td>
</tr>
<tr>
<td>5-min Agar, mean ± SD</td>
<td>6.8 ± 1.5</td>
<td>6.9 ± 1.6</td>
<td>5.0 ± 3.0</td>
</tr>
<tr>
<td>Age at 1st dose, median, (range), hours</td>
<td>24 (2-48)</td>
<td>20 (1-48)</td>
<td>24 (1-48)</td>
</tr>
<tr>
<td>Sarnat grade, n</td>
<td>Moderate</td>
<td>61 (74%)</td>
<td>27 (57%)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>21 (26%)</td>
<td>20 (43%)</td>
</tr>
</tbody>
</table>

Primary Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n/N (%)</th>
<th>Relative Risk</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epo (N=73)</td>
<td>Control (N=80)</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>3/73 (4.1)</td>
<td>4/80 (5.0)</td>
<td>0.89 (0.37-2.13)</td>
</tr>
<tr>
<td>Disability</td>
<td>15/70 (21.4)</td>
<td>31/76 (40.8)</td>
<td>0.59 (0.38-0.93)</td>
</tr>
</tbody>
</table>
### Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Epo (N=73)</th>
<th>Control (N=80)</th>
<th>Relative Risk (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or Disability</td>
<td>18/73 (24.6)</td>
<td>35/80 (43.8)</td>
<td>0.62 (0.41-0.94)</td>
<td>0.017</td>
</tr>
<tr>
<td>Moderate HIE</td>
<td>3/47 (6.4)</td>
<td>19/59 (32.2)</td>
<td>0.26 (0.09-0.76)</td>
<td>0.001</td>
</tr>
<tr>
<td>Severe HIE</td>
<td>15/26 (57.7)</td>
<td>16/21 (76.2)</td>
<td>0.70 (0.43-1.15)</td>
<td>0.227</td>
</tr>
<tr>
<td>Male</td>
<td>17/57 (29.8)</td>
<td>25/55 (45.5)</td>
<td>0.71 (0.47-1.08)</td>
<td>0.118</td>
</tr>
<tr>
<td>Female</td>
<td>1/16</td>
<td>10/25 (40.0)</td>
<td>0.18 (0.03-1.22)</td>
<td>0.29</td>
</tr>
<tr>
<td>MDI &lt; 70</td>
<td>7/70 (10.0)</td>
<td>17/76 (22.4)</td>
<td>0.56 (0.30-1.08)</td>
<td>0.048</td>
</tr>
<tr>
<td>Moderate HIE</td>
<td>2/47 (4.3)</td>
<td>9/57 (15.8)</td>
<td>0.38 (0.11-1.34)</td>
<td>0.106</td>
</tr>
<tr>
<td>Severe HIE</td>
<td>5/23 (21.7)</td>
<td>8/19 (42.1)</td>
<td>0.62 (0.29-1.30)</td>
<td>0.193</td>
</tr>
<tr>
<td>CP</td>
<td>5/70 (6.8)</td>
<td>14/76 (18.4)</td>
<td>0.51 (0.23-1.11)</td>
<td>0.051</td>
</tr>
<tr>
<td>Moderate HIE</td>
<td>1/47 (2.1)</td>
<td>8/57 (14.0)</td>
<td>0.23 (0.04-1.47)</td>
<td>0.039</td>
</tr>
<tr>
<td>Severe HIE</td>
<td>4/23 (17.4)</td>
<td>6/19 (31.6)</td>
<td>0.67 (0.30-1.52)</td>
<td>0.468</td>
</tr>
</tbody>
</table>

**Thompson Neurologic Assessment Scores (Mean ± SD)**

<table>
<thead>
<tr>
<th>Control (N=82)</th>
<th>Epo 300 units/kg (N=47)</th>
<th>Epo 500 units/kg (N=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 day</td>
<td>10.4 ± 2.4</td>
<td>9.7 ± 3.1</td>
</tr>
<tr>
<td>3 days</td>
<td>8.7 ± 3.4</td>
<td>7.1 ± 3.3</td>
</tr>
<tr>
<td>7 days</td>
<td>3.8 ± 2.7</td>
<td>2.4 ± 2.1*</td>
</tr>
</tbody>
</table>

*a P < 0.05

### Conclusions

**Strengths**
- First study to evaluate use of epoetin alfa for HIE in human subjects
- Time window of 48 hours
- Investigators performing outcome assessments were blinded

**Limitations**
- Use of lower epoetin alfa doses may have limited potential benefits
- No TH limits extrapolation to United States population

**Authors’ Conclusions**
Epoetin alfa 300-500 units/kg every other day for 2 weeks was safe and resulted in improved neurologic outcomes at 18 months of age

**Reviewer’s Conclusion**
- Low-dose epoetin alfa improved neurodevelopmental outcomes without TH, especially in moderate HIE
- Benefit was seen with time to first dose < 48 hours offers potential extended treatment window
- Limited applicability to USA where TH within 6 hours is standard of care


<table>
<thead>
<tr>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
</tr>
</tbody>
</table>
| **Methods** | • Multicenter, open-label, prospective, dose escalation, phase 1 trial  
• Infants received one of four doses of erythropoietin alfa IV every 48 hrs (first dose within 24 hrs of birth) |
| **Patient Population** | Inclusion:  
• Patients with HIE undergoing TH  
• ≥ 36 wks GA  
• Under 23.5 hrs of age at time of consent  
• Altered level of consciousness with at least one of: lethargy, stupor, coma, abnormal reflexes, absent/weak suck, clinical seizures  
• Perinatal depression with at least 1 of the following:  
  o 10 min Apgar score ≤ 5  
  o Need for resuscitation at 10 min  
• Cord or arterial blood pH < 7.00 or base deficit ≥ 12 within 60 min of birth  
Exclusion:  
• Severe EEG abnormalities  
• Birth weight < 1800 g  
• Congenital anomaly  
• Genetic syndrome  
• Metabolic disorder  
• Infection  
• Head circumference < 2 SD  
• Infant judged likely to die due to severity of illness  
• Hct > 60%  
• No indwelling line |
| **Intervention** | Epoetin alfa x 6 doses: within 24 hrs of birth then at 48 hr intervals  
Escalated to subsequent dose after data and safety monitoring board approval  
Doses: 250 units/kg (N=3), 500 units/kg (N=6), 1000 units/kg (N=7), 2500 units/kg (N=8) |
| **Primary Outcomes** | • PK properties: dose to produce plasma Cmax and AUC comparable to those demonstrating benefit in animal models  
  • Safety  
    o Major venous thrombosis  
    o Polycythemia (Hct > 60% or Hct ↑ ≥ 15% not due to RBC transfusion)  
    o HTN (SBP > 95 mmHg if 0-7 days old, SBP > 100 mmHg if 8-14 days, SBP > 105 mmHg if over 2 wks)  
    o Intraparenchymal hemorrhage or grade III/IV IVH  
    o Unexpected death  
• HIE comorbidity rates  
  o Compared with rates from CoolCap® trial |
| **Secondary Outcomes** | Neurodevelopmental follow up in 2014 (Rogers EE, et al, 2014)  
• Brain MRI  
• Moderate to severe neurodevelopmental disability, defined by:  
  o Presence of CP with GMFCS III-V  
  o Cognitive impairment based on Bayley Scales II and III |
| **Statistical Analysis** | 1-way ANOVA for between-subject measurements  
Repeated measures ANOVA for comparison of consecutive peaks within individual subjects.  
Paired t test for consecutive trough differences |
Results

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>12 (50)</td>
</tr>
<tr>
<td>5 min Apgar</td>
<td></td>
</tr>
<tr>
<td>0-3</td>
<td>14 (58)</td>
</tr>
<tr>
<td>4-6</td>
<td>7 (29)</td>
</tr>
<tr>
<td>7-10</td>
<td>4 (20)</td>
</tr>
<tr>
<td>10 min Apgar</td>
<td></td>
</tr>
<tr>
<td>0-3</td>
<td>5 (25)</td>
</tr>
<tr>
<td>4-6</td>
<td>11 (55)</td>
</tr>
<tr>
<td>7-10</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Resuscitation &gt; 10 min</td>
<td>21 (88)</td>
</tr>
<tr>
<td>Whole body cooling</td>
<td>21 (88)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight, kg</td>
<td>3.3 (0.6)</td>
</tr>
<tr>
<td>GA, wks</td>
<td>39 (1.8)</td>
</tr>
<tr>
<td>Head circumference, cm</td>
<td>34.4 (1.8)</td>
</tr>
</tbody>
</table>

PK:
- Non-linear kinetics
- Increasing dose of epoetin alfa by 2x, 4x, and 10x yielded AUC increased by 2.7x, 7.1x, and 17.8x
- Peak and trough concentrations remained stable
- Steady state achieved after 48 hrs
- Reduced rate of epoetin alfa elimination compared with pre-term infants (may be due to hypothermia and/or hypoxia-ischemia)
- 1000 units/kg produced Cmax and AUC levels most comparable with neuroprotective levels reported in animal models

PK parameters according to dose:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>250 U/kg</th>
<th>500 U/kg</th>
<th>1000 U/kg</th>
<th>2500 U/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (IU/h/L)</td>
<td>18 426 ± 8976</td>
<td>50 306 ± 7426</td>
<td>131 054 ± 17 083</td>
<td>328 002 ± 61 945</td>
</tr>
<tr>
<td>Cmax (U/L)</td>
<td>3156 ± 1615</td>
<td>7046 ± 814</td>
<td>13 780 ± 2874</td>
<td>33 316 ± 7377</td>
</tr>
<tr>
<td>Cl (mL/h per kg)</td>
<td>15.8 ± 6.3</td>
<td>10.1 ± 1.5</td>
<td>7.7 ± 0.9</td>
<td>7.9 ± 1.5</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>7.6 ± 6.9</td>
<td>7.2 ± 1.9</td>
<td>15.0 ± 4.5</td>
<td>18.7 ± 4.7</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>8.7 ± 6.6</td>
<td>9.6 ± 1.7</td>
<td>19.1 ± 5.2</td>
<td>23.0 ± 5.4</td>
</tr>
<tr>
<td>Vss (mL/kg)</td>
<td>133 ± 119</td>
<td>95 ± 18</td>
<td>146 ± 38</td>
<td>178 ± 48</td>
</tr>
<tr>
<td>Varea (mL/kg)</td>
<td>170 ± 178</td>
<td>104 ± 25</td>
<td>166 ± 48</td>
<td>209 ± 60</td>
</tr>
</tbody>
</table>

Cl, clearance; t1/2, terminal half-life; Vss, steady-state volume of distribution; Varea, volume of distribution using the area method.

a P < .0001 (ANOVA).
b P < .001 (Tukey HSD, compared with 250 U/kg).
c P < .001 (ANOVA).
d P < .05 (Tukey HSD, compared with 250 U/kg).
e P < .01 (Tukey HSD, compared with 250 U/kg).
**Safety:**
- Serious adverse events: none reported
- Comorbidity rates compared with cooled controls from CoolCap® Trial\(^2\)

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Epo + TH (N=24) n (%)</th>
<th>TH Only (N=112) n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intubated for RD</td>
<td>23 (96)</td>
<td>94 (84)</td>
<td>0.13</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>18 (75)</td>
<td>71 (63)</td>
<td>0.28</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>12 (50)</td>
<td>73 (65)</td>
<td>0.16</td>
</tr>
<tr>
<td>AST or ALT elevation</td>
<td>11 (46)</td>
<td>42 (38)</td>
<td>0.45</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11 (46)</td>
<td>36 (32)</td>
<td>0.20</td>
</tr>
<tr>
<td>Hypotension</td>
<td>10 (42)</td>
<td>62 (55)</td>
<td>0.22</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>9 (38)</td>
<td>49 (44)</td>
<td>0.57</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>9 (38)</td>
<td>49 (44)</td>
<td>0.57</td>
</tr>
<tr>
<td>DIC</td>
<td>2 (8)</td>
<td>21 (19)</td>
<td>0.37</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>1 (4)</td>
<td>14 (13)</td>
<td>0.47</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>N/A</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>N/A</td>
</tr>
<tr>
<td>Direct hyperbilirubinemia</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>N/A</td>
</tr>
<tr>
<td>Sepsis or bacteremia</td>
<td>0 (0)</td>
<td>3 (3)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Primary Outcome**

**Secondary Outcomes**
- Brain MRI at median 6 days (range 4-13 days):\(^8\)
  - Moderate to severe brain injury present in 8 infants (33%)
- Moderate to severe neurodevelopmental disability (follow up with 22 infants at 6 months):\(^8\)
  - Moderate to severe motor/cognitive disability: 1 (4.5%)
  - Mild neurodevelopmental abnormality: 6 (27%)

**Conclusions**

**Strengths**
- Comprehensive PK evaluation
- Established appropriate dose based on available neuroprotection data in animals

**Limitations**
- Unknown whether optimal levels for neuroprotection in humans are the same as animals
- Small patient population (N=24)
- Lack of neurologic outcomes data

**Authors’ Conclusions**
- Epoetin alfa 1000 units/kg per dose in conjunction with TH is well tolerated and produces plasma concentrations that have demonstrated benefit in animals
- Rates of adverse outcomes were no different than in patients receiving TH alone.

**Reviewer’s Conclusions**
- Established dose of epoetin alfa 1000 units/kg to produce plasma concentrations that are consistent with neuroprotection.
- Small, phase I trial not designed to extensively evaluate neurological outcomes.
- Promising safety data but small population limits utility of this information.

Table 4. High-Dose Erythropoietin and Hypothermia for Hypoxic-Ischemic Encephalopathy: A Phase II Trial (Wu YW, et al, 2016)\textsuperscript{19}

<table>
<thead>
<tr>
<th>Study Design and Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
</tr>
</tbody>
</table>
| **Methods**              | • Phase II multi-center, double-blind, placebo-controlled, randomized trial  
                           • Infants with moderate to severe HIE undergoing TH received either epoetin alfa or placebo for 5 doses |
| **Patient Population**   | **Inclusion:**  
                           • ≥ 36 wks GA  
                           • Whole-body hypothermia or selective head cooling initiated by 6 hrs of age  
                           • Perinatal depression with at least 1 of the following:  
                             o 10 min Apgar score < 5  
                             o Need for chest compressions or endotracheal/mask ventilation at 10 min  
                             o pH < 7.00 or base deficit ≥ 15 in cord or arterial blood within 60 min of birth  
                           • Moderate/severe encephalopathy per Sarnat criteria at 1-6 hrs of age  
                           **Exclusion:**  
                           • Age at time of consent > 23.5 hrs  
                           • Congenital anomaly  
                           • Suspected genetic syndrome  
                           • Birth weight < 1800 g  
                           • Head circumference < 2 SDs below mean  
                           • No indwelling line  
                           • Considering withdrawal of care because of moribund condition  
                           • Unlikely to obtain follow-up at 12 months of age |
| **Intervention**         | Epoetin alfa 1000 units/kg IV or placebo on days 1, 2, 3, 5, and 7 (5 doses total) |
| **Primary Outcome**      | Neurodevelopment at 12 months of age assessed by:  
                           • Alberta Infant Motor Scale (AIMS)  
                             o Moderate to severe impairment score < 5\textsuperscript{th} percentile for age  
                           • Warner Initial Developmental Evaluation (WIDEA)  
                             o Moderate to severe impairment score < 2 SDs below the mean |
| **Secondary Outcomes**   | • Infant development at 6 months of age measured by WIDEA score  
                           • Safety  
                           • Severity of brain injury on MRI |
| **Statistical Analysis** | • Intention to treat analysis  
                           • Categorical variables: Chi-squared test or Fischer’s exact test when count ≤ 5  
                           • Baseline continuous variables: two-sided t test  
                           • Global brain injury score: Wilcoxon rank sum test  
                           • Performed by independent statistician |
### Results

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Epo (N=24) n (%)</th>
<th>Placebo (N=26) n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>14 (58)</td>
<td>10 (39)</td>
<td>0.26</td>
</tr>
<tr>
<td>Severe Modified Sarnat Score</td>
<td>5 (21)</td>
<td>4 (15)</td>
<td>0.72</td>
</tr>
<tr>
<td>Large for GA</td>
<td>6 (25)</td>
<td>1 (4)</td>
<td>0.04</td>
</tr>
<tr>
<td>Resuscitation &gt; 10 min</td>
<td>21 (88)</td>
<td>21 (81)</td>
<td>0.70</td>
</tr>
<tr>
<td>5 min Apgar</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-3</td>
<td>11 (48)</td>
<td>14 (56)</td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>10 (43)</td>
<td>10 (40)</td>
<td></td>
</tr>
<tr>
<td>7-10</td>
<td>2 (9)</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>10 min Apgar</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-3</td>
<td>5 (24)</td>
<td>7 (28)</td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>13 (62)</td>
<td>11 (44)</td>
<td></td>
</tr>
<tr>
<td>7-10</td>
<td>3 (14)</td>
<td>7 (28)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age, yrs</td>
<td>29.4 (7.2)</td>
<td>29.7 (6.6)</td>
<td>0.87</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>3556 (618)</td>
<td>3243 (512)</td>
<td>0.06</td>
</tr>
<tr>
<td>GA, wks</td>
<td>38.7 (1.9)</td>
<td>38.7 (1.6)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

#### Primary Outcomes

- 41 (82%) of subjects survived (Epo: 2 deaths, Placebo: 5 deaths)
- 1 Epo and 1 placebo lost to follow up

**Neurodevelopmental (12 months of age):**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Epo (n=21)</th>
<th>Placebo (n=20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WIDEA Age at testing, months</td>
<td>12.7 (0.9)</td>
<td>12.6 (0.9)</td>
<td>0.71</td>
</tr>
<tr>
<td>Total score</td>
<td>122 (14)</td>
<td>110 (31)</td>
<td>0.15</td>
</tr>
<tr>
<td>Self-care</td>
<td>36.7 (5.1)</td>
<td>33.8 (7.7)</td>
<td>0.18</td>
</tr>
<tr>
<td>Mobility</td>
<td>28.6 (3.8)</td>
<td>23.8 (8.9)</td>
<td>0.048</td>
</tr>
<tr>
<td>Communication</td>
<td>28.2 (5.1)</td>
<td>25.5 (8.8)</td>
<td>0.33</td>
</tr>
<tr>
<td>Social</td>
<td>28.8 (6.4)</td>
<td>26.9 (8.9)</td>
<td>0.57</td>
</tr>
<tr>
<td>AIMS</td>
<td>55.5 (5.2)</td>
<td>42.8 (19.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>Moderate to severe NDI*, n (%)</td>
<td>2 (8)</td>
<td>5 (19)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

* *Moderate to severe NDI defined as AIMS < 5th percentile for age or WIDEA < 2 SDs below mean*

#### Secondary Outcomes

**Neurodevelopmental (6 months of age):**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Epo (n=21)</th>
<th>Placebo (n=21)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WIDEA Age at testing, months</td>
<td>6.3 (0.6)</td>
<td>6.1 (0.4)</td>
<td>0.34</td>
</tr>
<tr>
<td>Total score</td>
<td>75.3 (9.1)</td>
<td>68.8 (10.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>Self-care</td>
<td>28.1 (4.2)</td>
<td>26.1 (4.7)</td>
<td>0.20</td>
</tr>
<tr>
<td>Mobility</td>
<td>14.1 (2.7)</td>
<td>12.4 (2.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>Communication</td>
<td>16.4 (3.2)</td>
<td>15.3 (2.8)</td>
<td>0.20</td>
</tr>
<tr>
<td>Social</td>
<td>16.7 (4.5)</td>
<td>14.9 (3.2)</td>
<td>0.09</td>
</tr>
<tr>
<td>Secondary Outcomes</td>
<td>Neuroimaging: Moderate to severe injury on MRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------</td>
<td>-----------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Epoetin alfa: 1 (4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Placebo: 5 (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• P &lt; 0.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Safety:**
- No adverse events were attributed to Epo

<table>
<thead>
<tr>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strengths</strong></td>
</tr>
<tr>
<td>• Adjusted analysis for birth weight did not affect results</td>
</tr>
<tr>
<td>• Evaluators received training to maximize consistency across sites</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Reported outcomes not characterized according to severity of HIE</td>
</tr>
<tr>
<td>• Small sample size</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author’s Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple doses of epoetin alfa 1000 units/kg in infants undergoing TH for HIE may result in less MRI brain injury and improved short-term motor outcomes.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reviewer’s Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Epoetin alfa 1000 units/kg on days 1, 2, 3, 5, and 7 resulted in less brain injury on MRI, and demonstrated improvement in neurological outcomes at 6 and 12 months</td>
</tr>
<tr>
<td>• No adverse events occurred that were attributed to epoetin alfa</td>
</tr>
</tbody>
</table>


**Figure 3. NEATO Trial Design**

---

**Secondary Outcomes**

<table>
<thead>
<tr>
<th>Neuroimaging: Moderate to severe injury on MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Epoetin alfa: 1 (4%)</td>
</tr>
<tr>
<td>• Placebo: 5 (20%)</td>
</tr>
<tr>
<td>• P &lt; 0.05</td>
</tr>
</tbody>
</table>

**Safety:**
- No adverse events were attributed to Epo
**Literature Summary**

**Figure 4. Summary of Literature**

<table>
<thead>
<tr>
<th>Study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhu C, et al, 2009.</td>
<td>Epoetin alfa 300-500 units/kg every 48 hrs without TH improved neurologic outcomes at 18 months of age, especially with moderate severity HIE</td>
</tr>
<tr>
<td>Wu WY, et al, 2012.</td>
<td>Epoetin alfa 1000 units/kg/dose in conjunction with TH was well tolerated and produced plasma concentrations that are consistent with neuroprotection</td>
</tr>
<tr>
<td>Wu WY, et al, 2016.</td>
<td>Epoetin alfa 1000 units/kg was safe and demonstrated improvement in MRI brain injury and neurologic outcomes</td>
</tr>
</tbody>
</table>

**Future Directions**

**Table 5. High-Dose Erythropoietin for Asphyxia and Encephalopathy (HEAL): A Randomized Controlled Trial – Background, Aims, and Study Protocol (Juul S, et al, 2018)**

<table>
<thead>
<tr>
<th>Objective</th>
<th>To evaluate whether high-dose epoetin alfa reduces the combined outcome of death or neurodevelopmental disability when given in conjunction with TH to newborns with moderate/severe HIE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Phase III multi-center, double-blind, randomized, placebo-controlled trial</td>
</tr>
</tbody>
</table>

**Study Design and Methods**

**Patient Population**

- ≥ 36 weeks GA
- Active or passive whole-body cooling started prior to 6 hrs of age
- Perinatal depression with at least 1 of the following:
  - 10 minute Apgar score < 5
  - Need for resuscitation at 10 min
  - pH < 7.00 or base deficit ≥ 15 mmol/L in a cord (arterial or venous) gas or an infant gas (arterial or venous) obtained at < 60 min of age
- Moderate or severe encephalopathy per Sarnat criteria between 1-6 hours of age

**Exclusion:**

- Study drug unlikely to be administered within 26 hrs of birth
- Infant has living twin (or higher order multiple) who is also being cooled
- Birth weight < 1800 g
- Genetic or congenital condition that affects neurodevelopment or requires multiple surgeries
- Head circumference < 2 SDs below mean
- No indwelling line
- Considering withdrawal of care because of moribund condition
- Unlikely to obtain follow-up at 12 months of age
Intervention | Epoetin alfa 1000 units/kg IV or placebo on days 1, 2, 3, 4, and 7 (5 doses total)
--- | ---
Primary Outcome | Death or mild/moderate/severe neurodevelopmental impairment at 24 months of age
Secondary Outcomes | • Presence of CP  
• WIDEA score, administered at 12, 18, and 24 months of age  
• Severity of motor impairment  
• Epilepsy  
• Behavioral abnormalities  
• Safety


Figure 5. HEAL Study Protocol

Conclusion and Recommendations

I. Use of epoetin alfa for HIE  
   A. Improved neurologic outcomes with and without concurrent TH  
      i. Significant benefit especially in moderate HIE  
   B. No significant risk of adverse effects has been demonstrated  
   C. Even with TH, neurologic consequences of HIE can be devastating  
   D. Minimal risk vs large potential benefit with epoetin alfa therapy

II. Recommendation: Epoetin alfa should be considered for moderate or severe HIE  
   A. GA > 36 weeks  
   B. With or without TH  
   C. Initiate within 24 hours

III. HEAL trial\(^1\) may provide further guidance in the future
Appendix: Scoring Tools

I. Apgar Score

A. Standardized method of rapid assessment of clinical status of newborn
B. Reported at 1 minute and 5 minutes of life for all infants
   i. If score < 7, continued every 5 minutes until 20 minutes of life
C. Interpretation of scores:
   i. 7-10: Normal
   ii. 0-6: Abnormal
D. Low Apgar score may be first indicator of encephalopathy
E. Cannot be used alone to diagnose HIE

Table 6. Apgar Score

<table>
<thead>
<tr>
<th>Sign</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color</td>
<td>Blue or pale</td>
<td>Acrocyanotic</td>
<td>Completely pink</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Absent</td>
<td>&lt; 100 bpm</td>
<td>&gt; 100 bpm</td>
</tr>
<tr>
<td>Reflex irritability</td>
<td>No response</td>
<td>Grimace</td>
<td>Cry or active withdrawal</td>
</tr>
<tr>
<td>Muscle tone</td>
<td>Limp</td>
<td>Some flexion</td>
<td>Active motion</td>
</tr>
<tr>
<td>Respiration</td>
<td>Absent</td>
<td>Weak cry, hypoventilation</td>
<td>Good, crying</td>
</tr>
</tbody>
</table>

II. Thompson Score

A. Clinical tool used to assess severity of HIE
B. Assigned points according to clinical status in 9 categories
C. Higher score = higher severity (maximum 22 points)
D. Scoring:
   i. 1-10: Mild
   ii. 11-14: Moderate
   iii. 15-22: Severe
E. Score > 10 after 7 days predicts worse outcomes

Table 7. The Thompson HIE Score

<table>
<thead>
<tr>
<th>LOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>Tone</td>
</tr>
<tr>
<td>LOC</td>
</tr>
<tr>
<td>Fits</td>
</tr>
<tr>
<td>Posture</td>
</tr>
<tr>
<td>Moro</td>
</tr>
<tr>
<td>Grasp</td>
</tr>
<tr>
<td>Suck</td>
</tr>
<tr>
<td>Respiration</td>
</tr>
<tr>
<td>Fontanelle</td>
</tr>
</tbody>
</table>

LOC: level of consciousness

III. Bayley II Mental Development Index (MDI)

A. Assesses cognition through sensory-perception, knowledge, memory, problem solving, and early language
B. Cognitive delay if score < 70
IV. Gross Motor Function Classification System (GMFCS)\textsuperscript{24}
   A. Categorizes motor function of children with CP into 5 different levels
   B. Classification level increase indicates increase in mobility limitations
   C. For children < 2 years:
      i. Level 1: no impairment, walking between 18 months and 2 years of age without assistance
      ii. Level 5: unable to sit, requires assistance to roll

V. Alberta Infant Motor Scale (AIMS)\textsuperscript{19,25}
   A. Screening tool for identifying delayed motor development from birth to 18 months of age
   B. Consists of 58 scored items measuring quality of movements in four positions
      i. Prone
      ii. Supine
      iii. Sitting
      iv. Standing
   C. Sum of the scores = total raw score
   D. Total raw score converted to percentile rank for comparison with age norms

VI. Warner Initial Developmental Evaluation (WIDEA)\textsuperscript{19}
   A. 43-item parental questionnaire
   B. Assesses 4 domains of infant development:
      i. Self-care
      ii. Mobility
      iii. Communication
      iv. Social cognition
   C. Maximum score: 200
References