February 21, 2007

Re: Redefinition of Hypoxic Ischemic Encephalopathy (HIE) by the US Food and Drug Administration (FDA) and by the National Institutes of Health (NIH)

When an infant suffers HIE, there are three populations of central nervous system neurons affected. The first set simply dies. The second set is the survivors that will pull through. There is a third set that is compromised and are on the border of surviving or not.

This third set is under attack by released neurochemicals, free radicals, electrolytes, local edema, and may have internal genetic programs triggered leading to apoptosis (genetically programmed cell death). Over the past several years it has been shown that cooling the HIE infant, by body cooling or by head cooling, can help this population of neurons survive, producing better survival rates and improved neurologic outcomes.

FDA approved protocol for the definition of moderate to severe HIE

Recently the FDA has approved the use of the Olympic Cool-Cap to treat term infants with moderate to severe HIE, within the first six hours of life.

In so doing, the FDA gave approval to the proposed definition of moderate to severe HIE, which is considerably different from that found in The American College of Obstetricians and Gynecologists publication Neonatal Encephalopathy and Cerebral Palsy (2003). This definition of moderate to severe HIE is similar to the one used in a nation-wide study of body cooling organized by the NIH, the results of which were published in the New England Journal of Medicine 2005; 353:1574-84 (October 13, 2005 issue).

In the FDA-approved protocol, clinical evidence of moderate to severe HIE is defined by meeting criteria A, B and C.

A. The infant must be greater than 36 weeks gestational age, and have **at least one** of the following:

- Apgar score less than or equal to 5 at 10 minutes after birth.
- Continued need for resuscitation, including endotracheal or mask ventilation, at 10 minutes after birth.
- Acidosis defined as either umbilical cord pH or any arterial pH within 60 minutes of birth less than 7.00.
- Base deficit great than or equal to 16 mmol/L in umbilical cord blood sample or any blood sample within 60 minutes of birth (i.e., arterial or venous blood).

B. Infant with moderate to severe encephalopathy consisting of altered state of consciousness (as shown by lethargy, stupor or coma) and **at least one** of the following:

- Hypotonia.
- Abnormal reflexes, including oculomotor or pupillary abnormalities.
- Absent or weak suck.
- Clinical seizures.

C. The infant either has seizures **or** moderately/severely abnormal amplitude-integrated electroencephalogram/cerebral function monitor (aEEG/CFM) results.

Further details can be found in the approval letter dated December 20, 2006, and other related documents, which are on the FDA website: www.FDA.gov.

It should be noted that the emphasis is to identify newborns with moderate to severe HIE so that head cooling could be started within the first six hours of life. There was no attempt to define criteria that would be applicable to the definition of HIE after 6 hours of age, or to define mild HIE.

Although not specifically mentioned in the approval letter, implicitly and clinically the newborn must not have another medical or neurologic disease that may mimic the appearance of HIE. That is, other medical and neurologic diseases must be excluded.

NIH protocol definition of moderate to severe HIE

The definition of moderate or severe HIE used in the NIH study (New England Journal of Medicine 2005; 353:1574-84; authored by the National Institute of Child Health and Human Development Neonatal Research Network, a branch of the NIH) differs in that aEEG information was not used in patient selection.

In the eligibility criteria, the cord pH (**or any** blood gas sample in the first hour of life) is to have a pH of 7.0 or less, **or** a base deficit of 16.0 or more.

However, in cases where the pH was between 7.01 and 7.15, **or** a base deficit was between 10 and 15.9, if additional clinical criteria were met, the infants were enrolled in the study. The two necessary additional criteria were simply:

1. Acute perinatal event (late or variable decelerations, cord prolapse, cord rupture, uterine rupture, maternal trauma, hemorrhage or cardiorespiratory arrest) **and one** of the following:

- a 10 minute Apgar score of 5 or less;
- assisted ventilation initiated at birth and continued for at least 10 minutes.

2. Seizures, **or** evidence of moderate or severe encephalopathy.

The precise definition of the NIH protocol for moderate or severe encephalopathy differs somewhat from the FDA-approved criteria listed above.

Encephalopathy was defined as the presence of one or more signs in at least three of the following six categories (see Table): level of consciousness, spontaneous activity, posture, tone, primitive reflexes (such or Moro), and autonomic nervous system (pupils, heart rate, or respiration).

Table. Criteria for Defining Moderate and Severe Encephalopathy

Category	**Moderate Encephalopathy**	**Severe Encephalopathy**
Level of consciousness	Lethargic	Stupor or coma
Spontaneous activity	Decreased activity	No activity
Posture	Distal flexion, complete extension	Decerebrate
Tone	Hypotonia (focal or general)	Flaccid
Primitive reflexes		
Suck	Weak	Absent
Moro	Incomplete	Absent
Autonomic system		
Pupils	Constricted	Deviated, dilated or nonreactive to light
Heart rate	Bradycardia	Variable
Respiration	Periodic breathing	Apnea

As with the FDA-approved criteria, these NIH criteria were intended only for full term infants within the first six hours of life. There was no attempt to define criteria that would be applicable to the definition of HIE after 6 hours of age, or to define mild HIE.

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