

October 8, 2009

Re: European definition of Perinatal Asphyxial Encephalopathy
(Hypoxic Ischemic Encephalopathy, HIE)

In February 2007, I summarized two new definitions of neonatal HIE, one of which was developed by the National Institute of Child Health and Human Development (NICHD, a division of the National Institutes of Health, NIH), and the other developed by the manufacturers of the Cool-Cap, head cooling device which was approved by the Food and Drug Administration (FDA).

In the October 1, 2009 issue of the New England Journal of Medicine, the Total Body Hypothermia for Neonatal Encephalopathy Trial (TOBY) group published their results. The study was organized in the United Kingdom, and involved 36 neonatal intensive care units across the UK and Europe.

The study enrolled a total of 325 infants with HIE, half of whom were treated with 72 hours of body cooling. The body cooling resulted in no change in the combined rate of death and severe disability.

In the survivors, cooling resulted in statistically significantly better neurologic outcomes at 18 months of age. In the cooled group, the incidence of cerebral palsy was reduced from 41% to 28%. Mental development index score greater than 85 rose from 55% in the control group to 70% in the cooled group.

In conducting enrollment of infants, this European group used a definition of HIE, which is almost identical to the FDA-approved criteria mentioned above. Further details concerning these criteria can be found in the approval letter dated December 22, 2006, and related documents, where are on the FDA website: www.FDA.gov.

Enrolment was limited to infants 36 weeks of gestational age, or older, and who were less than 6 hours of age.

Exclusionary conditions included any need for possible surgery, and any dysmorphic findings which may suggest the presence of brain dysgenesis.

Given the above basic enrolment criteria, the definition of HIE was:

REQUIREMENT 1

Either A or B must be met

A at 10 minutes of age, Apgar score is 5 or less **OR** there is the continued need for resuscitation

B within 60 minutes of age, acidosis is present, defined by blood pH <7.00 **OR** base deficit \geq 16 mmol per liter (blood sample being umbilical, arterial or capillary)

REQUIREMENT 2

Moderate to severe encephalopathy (evidenced by lethargy, stupor or coma)

REQUIREMENT 3

At least one of the following is present:

A Hypotonia

B Abnormal reflexes (including oculomotor or pupillary)

C Absent or weak suck

D Clinical seizures

REQUIREMENT 4

On amplitude-integrated electroencephalography, abnormal background activity for a minimum of 30 minutes **OR** seizures

These criteria are basically the same as the FDA-approved criteria. Thus, these criteria have become the international standard for the diagnosis of HIE within the first six hours of life.

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TOBY Study Group, Moderate Hypothermia to Treat Perinatal Asphyxial Encephalopathy, New England Journal of Medicine, 361: 1349-1358, 2009