



## EDITORIAL

# Therapeutic hypothermia for hypoxic–ischemic encephalopathy: challenges during transfer and global perspectives ☆,☆☆



## Hipotermia terapêutica para encefalopatia hipóxico-isquêmica: desafios durante a transferência e perspectivas globais

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Perinatal asphyxia resulting in hypoxic–ischemic encephalopathy (HIE) occurs in 1–2/1000 live births in high income countries, and 10–20/1000 in low- and middle-income countries (LMICs).<sup>1</sup> Worldwide, HIE affects around 2.7 million newborn infants, of whom 690,000 die.<sup>2</sup> Over half of survivors go on to develop cerebral palsy, epilepsy, and other forms of lifelong neurological disability. The adoption of therapeutic hypothermia (TH) in high-income countries has been one of the most significant advances in neonatal care over the past 20 years, and follows rigorous basic science and clinical research.<sup>3</sup> The meta-analysis of the clinical trials showed a remarkable consistency toward the benefit of TH in both mortality and neurodisability.<sup>4</sup> It may surprise, however, given the global burden of HIE and relative simplicity of the treatment, that TH has not been universally adopted outside high income countries. The reasons for this are complex and multifactorial.

The idea of cooling an infant following perinatal asphyxia is not new. A quick survey of the literature will bring up the

work of James Miller from New Orleans and Bjorn Westin from Stockholm, who in the 1950s described the use of hypothermia in infants with ‘asphyxia neonatorum’.<sup>5</sup> Their original study, on 10 infants who had failed to respond to conventional resuscitation and were subsequently placed in a cold-water bath and cooled to between 23 °C and 30 °C, showed remarkable outcomes: at follow up at 10 years, nine infants had survived with normal neurology.<sup>6</sup> However, the importance of keeping all newborn infants warm overshadowed development in this field, until the work of Reynolds et al. in the 1980s, who, using the recently developed technique of magnetic resonance spectroscopy (MRS), showed a latency in cell death following perinatal asphyxia, which could be ameliorated by mild hypothermia.<sup>7,8</sup> Research in this field gained traction and moved from experimental models to large, randomized clinical trials.

One of the reasons that cooling may be so effective in newborns, where it appears to lack efficacy in older children and adults following cardiac arrest, could be that hypothermia is a physiological response in the newborn, which has evolved precisely to prevent potential brain injury

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following hypoxia–ischemia at birth. Born naked, wet, and devoid of fur, with a large head, the newborn infant will lose heat rapidly without intervention. Around the same period that Miller and Westin published their work on cooling infants, Burnard & Cross published a study showing that infants with asphyxia get colder and take longer to establish normothermia.<sup>9</sup> Indeed, the fact that babies get cold after birth forms the basis of the 'World Health Organization warm chain,' as outside the controlled setting of neonatal intensive care, the morbidity and mortality associated with hypothermia is significant and preventable.<sup>10</sup> Whether natural hypothermia following perinatal asphyxia is a physiological or pathophysiological phenomenon is difficult to prove; however, in the era of TH, it does highlight the importance of good thermal control of infants with HIE, particularly during transfer.

Most infants who suffer perinatal asphyxia are born outside tertiary-level units who have the necessary equipment and expertise not only to cool infants for 72 h, but also to provide the neurophysiological, radiological, and other services necessary for diagnostic and prognostic purposes. However, both experimental and clinical evidence suggests that the sooner cooling is initiated, the more efficacious the therapy.<sup>11,12</sup> It is now standard practice in most delivery settings to begin cooling as soon as possible after birth, and maintain this until arrival at the cooling center. A number of studies have been published, including this latest one from Carreras et al., describing cooling during transfer.<sup>13</sup> The majority of the publications describe passive cooling. In the study by Carreras et al., it is interesting to note that the majority of infants were transferred without the need for external heating sources; however, 22% of infants were not at target temperature at arrival at the cooling center and 16% were below target temperature. Interestingly, the risk of overcooling was associated with severity of HIE and acidosis at birth, confirming the findings of Burnard & Cross almost 60 years ago.

Only two studies have been published comparing active vs. passive cooling on transport. One, by Chaudhary et al. for the Acute Neonatal Transfer Service, based in the East of England, UK, was a retrospective observational study comparing 64 passively cooled infants and 70 infants cooled using a servo-controlled cooling mattress.<sup>14</sup> In the passively cooled group 27% of infants did not reach the target temperature, and 34% of infants were overcooled (more than double in the study of Carreras et al.). In the active cooling group, all infants were at target temperature on arrival at the cooling center; perhaps more significantly, the stabilization time was significantly reduced, perhaps reflecting the reduced need for thermal management by the transfer team, facilitating the transfer process. The second study by Akula et al., from a consortium in California, was a randomized controlled trial of mode of cooling on transfer; 49 infants were transferred with passive cooling, whereas 51 infants were actively cooled using a servo-controlled system.<sup>15</sup> The actively controlled group achieved better thermal control than the passive group, although in this study stabilization time was not improved. The limited evidence available would therefore suggest that there are advantages to active cooling on transfer; however, in the study by Akula et al., operational errors occurred in nine newborns receiving active cooling and centers with higher

enrolment had fewer device usage errors; this highlights that with any equipment, there is both a learning curve and critical usage activity required. Perhaps the most important message from all the studies published to date is the importance of core (rectal) temperature monitoring, especially to prevent overcooling.

The decision as to who to cool is, at first sight, relatively straightforward. All the clinical trials used a combination of (A) evidence of fetal compromise (reduced pH, high lactate, low Apgar score, prolonged resuscitation, etc.) and (B) evidence of on-going encephalopathy and/or seizures, with some trials including an abnormal amplitude integrated electroencephalography (aEEG) recording, with all infants being enrolled before 6 h of age. In clinical practice, with the desire to start cooling as early as possible, criterion A can be identified relatively easily; however, criterion (b) is an evolving picture, which can be harder to objectively assess in the first hour of life. Similarly, application of the aEEG during the initial stabilization phase may not be appropriate; moreover, access to both equipment and expertise to read the aEEG may not be available, particularly in more remote delivery settings. The practice described by Carreras et al. is to transfer all infants with encephalopathy and then formally assess them at the cooling center, before commencing active cooling. This ensures that there is consistency in assessment of the infants, and delayed presentation of infants with moderate-to-severe HIE, who were initially thought to be mild, is prevented. However, this approach may not be applicable in all settings, as it is both resource intensive for the transfer team and cooling centers, and also takes babies away from their mothers – sometimes to considerable distances – when not always necessary. The importance of early and regular neurological assessment in such infants cannot be underestimated. Horn et al. have shown that early clinical signs in neonates with HIE can predict abnormal aEEG at 6 h of life.<sup>16</sup> With improved telemedicine facilities, it is also possible to link aEEG recordings to regional centers for assessment. How to manage the infant who meets criteria A but where criteria B is unclear or evolving remains controversial; it may be that specific guidelines should be drawn up, depending on the local resources available.

There is no doubt that TH has had a major impact in the survival and neurological outcome of many infants in high-income countries. The impact in low- and middle-income countries, where most of these infants are born, is less clear. A number of small studies have been undertaken in LMICs; none have been adequately powered to examine clinically important outcomes.<sup>17</sup> A recent meta-analysis of therapeutic hypothermia in LMICs has shown a reduction in neonatal mortality based upon seven RCT's enrolling a total of 567 infants, although the reduction was not statistically significant.<sup>18</sup> However, the data is difficult to interpret due to inconsistent inclusion and exclusion criteria, as well as poor follow up. The studies are heavily biased toward India, with only one RCT in Africa and none in Central and South America. There is an urgent need to develop better evidence base for different resource settings across the globe, not only for the efficacy of cooling in specific populations, but also regarding the best way of stabilizing and transferring such infants to specialist centers. Clearly, establishing TH early is important and maintaining it during transfer is feasible, but as first described in 1958, careful core temperature

monitoring is essential to prevent overcooling, particularly in infants with severe HIE.

## Conflicts of interest

The author declares no conflicts of interest.

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