Cooling in a low-resource environment: lost in translation

Paolo Montaldo^a, Shreela S. Pauliah^a, Peter J. Lally^a, Linus Olson^b, Sudhin Thayyil^{a,*}

^a*Centre for Perinatal Neuroscience, Imperial College London, Hammersmith Hospital, London, UK*

^b*Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden*

*Corresponding author. Address: Centre for Perinatal Neuroscience, Level 5, Hammersmith House, Department of Paediatrics, Imperial College London and Imperial College Healthcare NHS Trust, Du Cane Road, London W12 0HS, UK. Tel.: +44 203 313 8515.

E-mail address: s.thayyil@imperial.ac.uk (S. Thayyil).

SUMMARY

Although cooling therapy has been the standard of care for neonatal encephalopathy (NE) in high-income countries for more than half a decade, it is still not widely used in low- and middle-income countries (LMIC), which bear 99% of the encephalopathy burden; neither is it listed as a priority research area. Here we explore the major roadblocks that prevent the use of cooling in LMIC, including differences in population comorbidities, suboptimal intensive care, and the lack of affordable servo-controlled cooling devices. The emerging data from LMIC suggest that the incidence of coexisting perinatal infections in NE is no different to that in high-income countries, and that cooling can be effectively provided without tertiary intensive care and ventilatory support; however, the data on safety and efficacy of cooling are limited. Without adequately powered clinical trials, the creeping and uncertain introduction of cooling therapy in LMIC will be plagued by residual safety concerns, and any therapeutic benefit will be even more difficult to translate into widespread clinical use.

Keywords:

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1. Introduction

Perinatal asphyxia associated with moderate to severe neonatal encephalopathy (NE) occurs at an approximate rate of 1–2 per 1000 live births in high-income countries [1] and 10–20 per 1000 live births in low- and middle-income countries (LMIC) [2]. Following moderate or severe encephalopathy, ~25–60% of the affected infants die and more than half of the survivors sustain

significant brain injury and lifelong disability in LMIC [3]. Of the one million annual neonatal deaths caused by perinatal asphyxia, 99% occur in LMIC [4].

Therapeutic hypothermia has become the standard of care for NE in high-income countries following two decades of rigorous experimental and clinical research. This began with the demonstration of secondary energy failure and its amelioration with therapeutic hypothermia in animal models, followed by clinical trials, meta-analyses, registries, and finally its inclusion in national and international guidelines [5]. Therapeutic hypothermia reduces mortality after NE [typical relative risk (RR): 0.75; 95% confidence interval (CI): 0.64–0.88] and neurodisability in survivors at 18 months (typical RR: 0.77; 95% CI: 0.63–0.94) [6] and at school age (typical RR: 0.59; 95% CI: 0.37–0.94) [7,8]. Almost all eligible babies receive therapeutic hypothermia in the UK at present (~800 per year), and this is estimated to have saved the National Health Service a total of £125m since 2009 [9].

Given the simplicity of the intervention and the global disease burden, therapeutic hypothermia may have a considerable impact on the health and economies in LMIC. Unfortunately, in these settings the uptake of therapeutic hypothermia has been poor. Here we examine the various factors which have prevented the use of this highly effective therapy in settings which shoulder the greatest burden.

2. Issues related to healthcare infrastructure

2.1. Home deliveries and the lack of transport systems

In the ‘standard model’ of perinatal services practised in high-income countries, critically ill newborns are rapidly transported to resource-intensive tertiary neonatal units for therapeutic hypothermia – this is not readily applicable to the LMIC. In fact, such models are neither feasible nor desirable in LMIC, where simpler, affordable, and cost-effective interventions in primary and secondary care may be more effective in reducing neonatal mortality. In low-income countries in regions such as Sub-Saharan Africa, some communities have no access by road; communication systems are weak; many cannot afford private transport [10]; and many deliveries happen at home or in poorly equipped facilities [11]. Even in institutional deliveries, delayed maternity admissions (often in prolonged or obstructed labor due to the lack of effective transport systems) may mean that the time window for initiation of therapeutic hypothermia is already lost by the time of delivery.

On the other hand, with rapidly improving standards of healthcare in urban settings and referral facilities available in transitional economies such as China, India, and Brazil, a large number of deliveries occur in hospitals, or infants may be admitted within the window period for initiation of rescue hypothermic neuroprotection. In fact, in the last two to three decades, the

number of neonatal intensive care units and special care neonatal units in transitional countries such as India and China has increased exponentially [12,13]. Approximately 75% of deliveries in India now occur in hospitals, though this varies from 50% in North India to 95% in South India [14,15]. Although accurate morbidity statistics are lacking, at least one million babies are likely to suffer from encephalopathy in India every year, and up to half of these deliveries may occur in a hospital setting. If therapeutic hypothermia were available to even a small proportion of these hospitals, it may provide substantial health benefits.

2.2. The use of therapeutic hypothermia outside optimal tertiary neonatal intensive care

Interventions that are safe and highly effective within well-resourced tertiary intensive care units may not be so elsewhere. For example, the use of fluid bolus in septic shock is a routine clinical practice in well-resourced pediatric intensive care units with facilities for cardiorespiratory support and invasive monitoring of vital signs. However, in Sub-Saharan African hospitals without these facilities, the intervention was associated with increased mortality [16].

It is unclear how much intensive care support is required for the safe administration of therapeutic hypothermia. The earliest therapeutic hypothermia trials in high-income countries were conducted only in tertiary neonatal units with facilities for optimal cardiorespiratory support and neurological monitoring, and the vast majority of the babies were kept ventilated and sedated during therapy. As experience with therapeutic hypothermia has increased, it is now offered by many secondary care units in the UK; and indeed many babies (especially with moderate encephalopathy) are not ventilated, or are extubated soon after initial resuscitation while undergoing therapeutic hypothermia. Most infants undergoing therapeutic hypothermia receive sedation in the UK; however, such routine sedation was not used in the NICHD cooling trial [17] and is not part of routine clinical practice in the NICHD Neonatal Research Network (NRN) in the USA (personal communication: Prof. Seetha Shankaran). In addition, studies have now shown that therapeutic hypothermia improves respiratory, renal, and other metabolic parameters in encephalopathic babies [18,19]. Thus, there is no reason to believe that therapeutic hypothermia may be ineffective without ventilatory support (although caution will need to be exercised in babies with persistent pulmonary hypertension from meconium aspiration). On the contrary, it is possible that the infants with moderate encephalopathy not requiring ventilatory support might be those who benefit most from therapeutic hypothermia in LMIC, and may achieve normal outcomes. Finally, many encephalopathic babies have a low core body temperature during first 24 h after birth [20], although this might be more apparent in babies born in low-resource settings, where radiant warmers are not routinely used [21]. It is unclear whether this hypothermia would have any neuroprotective effect, or whether rewarming these babies would cause more harm or benefit [22].

Unfortunately, the use of therapeutic hypothermia in low-resource settings has received bad publicity after a pilot study in Sub-Saharan Africa showed five-fold higher mortality in cooled babies, albeit statistically non-significant (RR: 5.0; 95% CI: 0.7–37) [21]. It remains unclear whether this was related to a lack of basic neonatal care facilities and medical/nursing expertise in this setting (for example adequate neonatal resuscitation and routine monitoring of basic physiology); inadequate cooling devices (water bottles); lack of sedation [23]; or due to the recruitment of more severely encephalopathic infants in the cooled arm. Nevertheless, therapeutic hypothermia has now disappeared from the priority list of global health researchers, with infection being highlighted as a potential cause for the increased mortality with therapeutic hypothermia [24], despite little evidence to support this. This situation is not dissimilar to the 1960s, when therapeutic hypothermia received negative publicity after a clinical trial showed an increased mortality of hypothermic preterm infants [25]. Therapeutic hypothermia then disappeared from the clinic for several decades before it was rigorously re-evaluated in high-income countries. A repeat of this history would be unfortunate, and may deprive babies in LMIC from the benefits of one of the most important and simple interventions in medicine.

3. Concerns about perinatal infection

Fetal inflammation and infection has been shown to increase brain vulnerability to hypoxia–ischemia via stimulation of immune and inflammatory responses, chemotaxis, toll-like receptors and cell death [26]. Emerging experimental data also suggest that hypothermia may not be neuroprotective after bacterial lipopolysaccharide-sensitized NE brain injury as compared to hypothermia without bacterial lipopolysaccharide [27]. Hence, therapeutic hypothermia in the presence of infection might even be deleterious as hypothermia may impair innate immune function, including neutrophil migration and function [28].

In a prospective study, Tann et al. [29] reported that the prevalence of neonatal bacteremia with a pathogenic organism among encephalopathic infants was 3.5% by blood culture alone, 6.9% by polymerase chain reaction (PCR) alone, and 8.9% by blood culture and PCR in combination. A similar incidence of coexistent bloodstream-positive infection and encephalopathy has been reported from India [30,31]. This is similar to that reported from high-income countries: 8.1% in the ICE trial [32], 6% in NICHD [17], 17% in the TOBY registry [33]. Therefore, coexistent perinatal infection is unlikely to have a role in influencing the treatment efficacy of therapeutic hypothermia for the vast majority of babies in LMIC.

4. Concerns about established brain injury

Cerebral magnetic resonance imaging (MRI) in high-income countries has shown that cerebral injury is acute and acquired perinatally, and is not established (antenatal injury) at the time

of birth; hence it is amenable to therapeutic hypothermia [34]. Emerging evidence from LMIC suggests similar perinatal origins of brain injury. Tann et al. [35] reported that 80% of the early cranial ultrasound (USG) scans were normal in encephalopathic babies admitted to a Sub-Saharan African neonatal unit, and none of them had evidence of established brain injury. Although the utility of USG in term encephalopathic infants is limited [36], these findings are similar to the cerebral MRI reported by Lally et al. from a South Indian cohort ($n = 54$), in which none of the encephalopathic babies had evidence of established brain injury. However, unlike in high-income countries, the predominant injury was in the white matter, rather than in the deep gray matter nuclei. Reduced white matter fractional anisotropy was associated with adverse neurological outcomes at three-and-a-half years in this population (Figs 1, 2). Thus, it is possible that the brain injury in LMIC encephalopathic babies may be ameliorated with therapeutic hypothermia.

5. Health and economic impact of cooling

Neurodisability related to NE is a lifelong condition placing substantial burden on individuals, their families, and wider society. Therapeutic hypothermia reduces long-term neurodisability after neonatal encephalopathy; hence, in high-income countries where this intervention is applied widely, it has important health and economic benefits. Azzopardi et al. showed that, with respect to the current lifetime costs for each child with cerebral palsy (about £750,000) [37] and the economic benefit of additional healthy lives (about £800,000) [38], the total benefit to the UK economy as a result of the implementation of therapeutic hypothermia is likely to be in excess of £125 million so far, despite the high cost of cooling devices [9].

As the burden of NE is far higher in LMIC [2,39], the health and economic benefit of therapeutic hypothermia may be substantially higher in these settings, if it can be delivered via the existing infrastructure using inexpensive cooling devices. Nevertheless, health economic evaluation in LMIC is challenging due to the lack of accurate data on cost estimates of neonatal encephalopathy and neurodisability, and because expenses are borne by individual families rather than by healthcare systems.

6. Ethical aspects of cooling therapy

To some, controlled trials of hypothermia in LMIC are already entering an ethical gray area. For example, the World Medical Association Declaration of Helsinki specifically indicates that comparisons with no treatment or placebo are only appropriate where there is no current proven intervention [40]. Others argue that it can be neither acceptable nor safe to extrapolate the evidence from high-income country therapeutic hypothermia trials performed under optimal intensive care settings to LMIC, where the population comorbidities and neonatal care are very different. Furthermore, maintaining normothermia is one of the founding pillars of newborn survival in LMIC

due to the strong epidemiological association of hypothermia and neonatal mortality. Very strong evidence is required before this conventional wisdom is challenged in LMIC.

Although there have been past concerns that therapeutic hypothermia might convert death into disability for those babies with severe encephalopathy (an extremely undesirable situation, particularly in LMIC), the data from therapeutic hypothermia trials have not supported this hypothesis [6]. Therapeutic hypothermia not only reduces mortality, but also decreases neurodisability in survivors [6]. Furthermore, most of the babies recruited to LMIC therapeutic hypothermia trials appear to have moderate rather than severe encephalopathy (Table 1); these babies are more likely to benefit from therapeutic hypothermia [6].

Another argument might be that resources should be invested to improve poor antenatal care, thus preventing neonatal encephalopathy rather than treating it. On the other hand, given the large number of infants affected by neonatal encephalopathy, it is unreasonable not to explore therapeutic hypothermia for these babies – a simple and potential highly effective neuroprotectant therapy.

7. Cooling equipment

The equipment used to provide therapeutic hypothermia in developed countries is prohibitively expensive and unsuitable for wide use in LMIC. Instead, several low-technology devices have been used for cooling therapy in LMIC (Fig. 3). A brief summary is given below.

7.1. Passive cooling

Several studies have reported use of passive cooling (i.e keeping baby naked without the use of radiant warmer) for induction of cooling and during transport. Although this facilitates early induction of cooling, significant overcooling ($<32^{\circ}\text{C}$) has been reported in up to one-third of the infants [41,42]. It is unlikely that the target temperatures can be maintained by passive cooling alone.

7.2. Water and ice

Effective whole-body cooling has been reported using water bottles and gloves [43] filled with water. Selective head cooling using ice may result in marked temperature fluctuations, and effective whole-body cooling has been achieved using ice and frozen gel packs in some studies. Although therapeutic hypothermia with ice showed improved outcomes in high-income tertiary neonatal units with 1:1 nursing care [44], the vast majority of neonatal units in LMIC do not have such nursing and monitoring resources. In our experience, cooling using ice may result in wide temperature fluctuations without close nursing monitoring.

7.2.1. Laminar flow device

Perez et al. [45] have reported effective whole-body cooling in 23 babies with encephalopathy admitted to a Brazilian neonatal unit using a laminar flow device (Neonatflow). Hypothermia could be induced within 90 min in all babies.

7.2.2. Cooling using fans

A servo-controlled cooling fan developed by Horn et al. [46] appears to be an effective low-cost cooling device, and a feasibility study on 10 babies using this device has been reported. Five of these babies had shivering at higher fan speeds.

7.2.3. Clay pot cooling

Kim et al. have developed an interesting cooling device using two clay pots, sand, and a urea-based powder. When water is added to the mixture of powder and sand, the powder dissolves and leaks through the outer clay pot. Hypothermia is achieved by evaporative cooling, and has been shown to be effective in a newborn piglet model [47].

7.3. Phase change materials

Phase change materials (PCM) that can be used for medicine are normally made of salt hydride, fatty acid, and esters of paraffin and melt (or sets) at a set temperature [48]. One useful composition is based on Glauber salt, modified by varying the amount of sodium chloride and additional components to achieve desired phase change properties. The ability of PCM to maintain a steady temperature by storing or releasing a large amount of thermal energy provides a natural feedback loop. Outside the phase-change temperature range, these materials act like any other substance. Effective hypothermia was induced and maintained using phase-changing material with a set temperature of 32°C in encephalopathic babies in south India (approximate cost US\$200); however, this was effective only when the ambient temperature was <28°C and additional nursing input was required to maintain the target temperature, limiting wider use in tropical countries as a cooling device [49].

7.4. Affordable servo-controlled cooling devices

The emerging data suggest that therapeutic hypothermia is effective only within a narrow range of 33–34°C, and elective cooling to 32°C for three or five days may worsen outcomes [50], hence the importance of tight temperature control during cooling therapy should not be underestimated. It is unlikely that manual cooling devices are able to achieve such tight temperature control without additional nursing resources that may offset the cost benefit of an inexpensive cooling method. Hence, another alternative is simplified and affordable versions of existing high-income country servo-controlled cooling devices modified for LMIC conditions. Tecotherm-HELIX is one such servo-controlled cooling device developed for exclusive use in LMIC (estimated to cost US\$1000). It works by single-switch operation to achieve a set temperature of

33.5°C, re-circulating water through a re-usable cooling mattress. It can also work on battery and have no ongoing cost. Feasibility studies using this device in south India show effective cooling times [51] similar to the expensive high-income country cooling devices, with minimal additional nursing input and ongoing costs [52].

8. Low- and middle-income country cooling trials

Although a number of pilot therapeutic hypothermia studies have been reported from LMIC, none of these studies was adequately powered to examine clinically important outcomes (Table 1). The largest of these was from China, which unfortunately was of poor quality. Zhou et al. [53] reported 18-month outcome data on 256 babies randomized to selective head cooling or usual care. Infants at risk of sepsis were excluded, and there were post-randomization exclusions. A homemade head-cooling device was used, but details were unclear as there was no documented trade name on this equipment. It is likely that the investigators cooled the body via the head, and that this may be whole-body cooling rather than selective head cooling, which requires heating of the body to obtain a head-to-body gradient. Twenty four percent were lost to follow-up. Although the authors claimed that selective cooling improved outcomes, the validity of this claim is questionable [53].

More worrying is the very low mortality rate (<5%) reported in some therapeutic hypothermia studies from India on infants who were reported to have moderate or severe encephalopathy [32,54]. Although the exact reasons are unclear, this is likely to be due to lack of a standardized neurological examination to define encephalopathy, thus potentially including babies without encephalopathy based on low Apgar scores alone. Such a practice may expose babies with a very low risk of adverse outcome to the adverse effects of unnecessary therapeutic hypothermia.

A recent meta-analysis of therapeutic hypothermia in LMIC has shown that the pooled data from seven randomised controlled trials [21,31,49,53,55–57], including a total of 567 infants, showed a reduction in neonatal mortality, although this was not statistically significant (RR: 0.74; 95% CI: 0.44–1.25) [58]. This observation has been confirmed in another systematic review by Galvao et al. [59], which showed that studies in lower income economies did not have statistical power to detect significant effects of hypothermia after stratification by country income. Interestingly, this meta-regression failed to show that countries' gross domestic product per capita (an indirect measure of healthcare resources) affects the efficacy of hypothermia [59].

Unfortunately, the poor quality of the trials in both of these systematic reviews [21,31,49,53,55–57], including the lack of comprehensive follow-up of trial subjects, currently provides no evidence for either safety or efficacy in the use of hypothermia as a neuroprotectant for neonatal encephalopathy in LMIC.

Another challenge is assessing long-term neurodevelopmental outcome after encephalopathy due to a lack of robust standardized tools for the local population, particularly with regard to language assessments and high attrition rates. There have been concerns about the artificial lowering of scores yielded by tools typically applied in developed countries (e.g. Bayley III and Griffiths) when used in LMIC. However, in our experience this has not been an issue, and the Bayley III scores on healthy south Indian children were similar to the UK scores. Unfortunately, these tools are prohibitively expensive for routine use in LMIC at present.

9. The way forward

Although there are differences in population comorbidities and in the underlying brain injury after neonatal encephalopathy, the therapeutic benefits of hypothermia when used within the existing healthcare infrastructure in LMIC (i.e. without optimal tertiary intensive care and respiratory support) cannot be excluded. Indeed, the health and economic benefit of therapeutic hypothermia may be far higher in LMIC than in high-income countries, considering the disease burden. However, adequate powered clinical trials are required to ensure that cooling is indeed safe and effective in LMIC neonatal units, before routine clinical use can be recommended. One such large multi-country cooling trial in LMIC (HELIX trial: Hypothermia for Encephalopathy in Low and Middle-Income Countries) is currently in progress (<http://clinicaltrials.gov/show/NCT01760629>).

Without such trials, therapeutic hypothermia will creep into use in LMIC, but wider adoption will be constantly sabotaged by residual safety concerns; thus, one of the greatest discoveries in neonatal medicine may be lost in translation. Policy changes and incorporation of therapeutic hypothermia into the World Health Organization guidelines are unlikely to occur without robust evidence of its safety and efficacy. Meanwhile, it would be prudent for enthusiastic clinicians offering therapeutic hypothermia in LMIC to adhere to the therapeutic hypothermia guidelines and inclusion criteria established in high-income countries.

Practice points

- Although cooling is a highly effective therapy for neonatal encephalopathy in high-income countries, its safety and efficacy in LMIC is unclear.
- Clinicians offering cooling therapy in LMIC should adhere to the established protocols from high-income countries, and offer this only to infants with moderate or severe encephalopathy as assessed using a structured neurological examination.
- Inexpensive manual cooling methods such as ice and gel packs require close nursing monitoring to maintain core temperature within the target range, limiting wider use in LMIC.

Research directions

- Investigations of the nature and origins of brain injury after neonatal encephalopathy, its interaction with perinatal infections, the implications for long-term neurological outcomes, and its impact on the health and economic burden in LMIC.
- Clinical trials to establish the safety and efficacy of cooling therapy in LMIC.
- Development of affordable servo-controlled cooling devices suitable for use in LMIC.

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Table 1

Published studies on cooling after neonatal encephalopathy in low- and middle-income countries

Country	Study	<i>N</i>	Type of study	Cooling device	WBC/SHC	Grade of HIE Mild/moderate/severe	Neonatal mortality (%)
Africa	Horn et al. [60]	4 H	Case series	Insulated ice caps	SHC	Not mentioned	Not reported
	Robertson et al. [21]	36 21 H, 15 S	RCT	Water bottles	WBC	9/20/7	33.3 H, 6.6 S
	Horn et al. [46]	10 H	Case series	Servo-controlled fans	SHC	0/6/4	10 H
	Horn et al. [61]	5 H	Case series	Frozen gel packs	SHC	1/2/2	Not reported
	Horn et al. [62]	14 H	Case series	Frozen gel packs	SHC	14 moderate to severe	21.4 H
	Biselele et al. [63]	50 H	Prospective cohort study	Not cooled	NA	16/20/8	28 H
India	Bhatt et al. [57]	35 20 H, 15 S	RCT	Not described	WBC	Severe birth asphyxia (5 m Apgar <3)	15 H, 33.3 S
	Rajhans et al. [64]	5 H	Case series	Blanketrol II	WBC	All moderate to severe	Not reported
	Thomas et al. [54]	20 H	Case series	Frozen gel packs	WBC	0/16/4	5 H
	Bharadwaj et al. [31]	124 62 H, 62 S	RCT	Frozen gel packs	WBC	0/109/15	4.8 H, 9.7 S

	Thayyil et al. [49]	33 17 H, 16 S	RCT	Phase changing material	WBC	18/11/4	23.5 H	12.5 S
	Joy et al. [65]	116 58 H, 58 S	RCT	Frozen gel packs	WBC	0/100/16	1.7 H	6.9 S
	Gane et al. [66]	120 60 H, 60 S	RCT	Frozen gel packs	WBC	0/89/31	8 H	16 S
China	Lin et al. [56]	62 32 H, 30 S	RCT	Water cooling caps	SHC	14/31/17	6 H	7 S
	Li et al. [67]	93 46 H, 47 S	RCT	Not described	WBC	Moderate to severe	18.4 H	47.7 S
	Zhou et al. [53]	256 138 H, 118 S	RCT	Water cooling caps	SHC	39/82/73	20 H	29 S
Turkey	Akisu et al. [55]	21 11 H, 10 S	RCT	Water cooling caps	SHC	0/12/6	0 H	20 S
Malaysia	See et al. [68]	17 H	Case series	Ambient temperature	WBC	0/15/2	12 H	

n, no. of cases in the non-cooling arm; WBC, whole-body cooling; SHC selective head cooling; HIE, hypoxic–ischemic encephalopathy; RCT, randomized controlled trial; H, hypothermic arm; S, standard care arm.

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Fig. 1. Axial T1 (lower left and centre)- and T2-weighted (top left and centre) magnetic resonance images acquired during the first week after birth in an infant with mild neonatal encephalopathy in south India. Extensive white matter injury (white arrows and blue arrowheads), and a small intraventricular bleed (red arrow) are seen. Hemiplegic cerebral palsy was noted on neurodevelopmental assessment at 3.5 years of age. Reproduced with permission from Lally et al. [30].

Fig. 2. Tract-based spatial statistics of whole-brain fractional anisotropy and long-term neurological outcomes after neonatal encephalopathy in south India. Axial (upper right) and coronal (lower right) sections of the cohort white matter skeleton (green) show significant reductions in fractional anisotropy (red–yellow) in children who had adverse neurological outcome ($n = 4$) after neonatal encephalopathy at 3.5 years of age, when compared with those who had favorable outcome ($N = 21$). Reproduced with permission from Lally et al. [30].

Fig. 3. Manual low-technology cooling devices. (i) Water bottle (bottle filled with tap water at 25°C and laid sideways under the infant in the cot). (ii) Phase change material mattress (PCM, melting point 32°C). Principles of heat exchange (A); structure of the mattress (B), a baby receiving cooling by PCM at Government Medical College, Kozhikode, India (C); and passive re-warming (D). (iii) Cooling using frozen gel packs at Christian Medical College, Vellore, India (photograph courtesy of Niranjana Thomas). (iv) Clay pot cooling device. Temperature changes are based on heat transfer, water diffusion, and air flow of the surrounding system. As water evaporates, heat is drawn from the inner clay pot.