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### Therapeutic Temperature Management in Critically Ill Patients

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**Therapeutic temperature management is an increasingly important therapeutic intervention in critical care, particularly in patients with neurological injuries. This applies both to induced therapeutic hypothermia and fever management. It has been conclusively demonstrated that patients with any type of neurological injury who develop either infectious or non-infectious fever have a significantly increased risk of adverse outcome. In addition, patients who develop fever also incur stays of increased length in the ICU and hospital, and higher costs of care. Therapeutic hypothermia has been shown to improve outcomes in patients with post-hypoxic brain injury, particularly newborn babies with neonatal asphyxia and patients with out-of-hospital cardiac arrest. Recent literature suggests that therapeutic cooling is cost-effective in these categories of patients.**

#### Increasing Temperature Worsens Injury

Elevations in temperature can stimulate destructive processes that occur after tissue injury; this applies in particular to ischaemiareperfusion injury and brain oedema. Conversely, decreases in temperature can inhibit these processes. Numerous animal studies, in particular in neurologic injury models, have found that increasing temperature worsens injury, while reducing core temperature mitigates such injury. This observation was made in regards to different animal models across various types of injury. This in turn, led to numerous clinical studies addressing the possible effect of temperature on neurological outcomes. Although not every issue has been resolved, a number of important findings have been made.

#### Controlled Normothermia

Fever is a strong independent predictor of adverse neurological outcome and mortality in ischaemic stroke, traumatic brain injury, postanoxic injury, subarachnoid haemorrhage, and intracranial haemorrhage. This has been consistently demonstrated in more than 20 large observational studies, and persists on multivariate analysis (Azzimondi et al. 1995; Castillo et al. 1998; Hajat et al. 2000; Kammersgaard et al. 2002; Polderman 2008; Reith et al. 1996; Schwarz et al. 2000). Fever can be detrimental even when it is mild, even if it is of short duration, and even when it occurs long after the initial injury, although the effects become more pronounced if hyperthermia coincides with an episode of ischaemia, suggesting that ischaemic brain cells are more susceptible to the harmful effects of fever (Castillo et al. 1998).

The link is extremely powerful; for example, fever developing within 24 hours after onset of ischaemic stroke has been independently linked to larger infarct volumes with an odds ratio of more than three (Castillo et al. 1998), and in another study has been associated with a more than threefold risk of adverse outcome in patients with acute ischaemic stroke. Others have reported that each 1°C increase of admission body temperature independently predicted a 30 percent relative increase in risk of longterm mortality (Azzimondi et al. 1995). Several studies have demonstrated that fever is a strong predictor of adverse outcome for both in-hospital and out of hospital cardiac arrest (Suffoletto et al. 2009; Zeiner et al. 2001). With regards to cost-effectiveness, a large study by Diringier and co-workers demonstrated that elevated body temperature was associated not only with increased mortality and morbidity, but also with higher costs and increased length of stay both in the ICU (average of 3.2 additional days) and in the hospital (4.3 additional days) (Diringier et al. 2004). Although it remains to be conclusively determined whether treatment of fever can improve outcome and decrease length of stay, this would appear to be an excellent target in attempting to decrease length of stay. The costs of temperature management will depend on the type of device that is used, but would in no case exceed a total of 1,000 Euros when using the most expensive equipment for a short period of time; in most cases the costs would be substantially lower. Thus, if length of stay could be reduced even by a single day the intervention would already be highly cost-effective.

#### Therapeutic Hypothermia

The positive effects of therapeutic hypothermia have been most convincingly demonstrated in two categories of patients with global post-ischaemic brain injury.

The first category, with the strongest evidence for the efficacy of therapeutic cooling, is in newborn babies with neonatal asphyxia. Five multi-centred randomised controlled trials and a number of additional studies have demonstrated that neurological outcome in these babies can be improved by therapeutic cooling (Azzopardi et al. 2009; Eicher et al. 2005; Gluckman et al. 2005; Shankaran et al. 2005; Zhou et al. 2010). A recent meta-analysis concluded that the number needed to treat (NNT) for the combined endpoint of increased survival with normal neurological

function was eight, with a 95 percent confidence interval (CI) of five to 17 (Edwards et al. 2010). In addition, in survivors there were significant reductions in the incidence of severe disability ( $P = 0.006$ ) and cerebral palsy ( $P = 0.004$ ), as well as other indicators of permanent brain injury (Edwards et al. 2010). A recent analysis of costs concluded that therapeutic cooling led to a cost increase of around 5,000 Euros, with a 95 percent CI from minus 3,400 Euros to 17,000 Euros.

The incremental cost per deficit-free life year gained was 26,920 Euros (Regier et al. 2010). This is well within traditional limits for cost-effectiveness per QALY. In addition, substantial parts of the costs may be offset by the decrease in later costs for caring for patients with permanent neurological injuries.

The second category is in patients with cardiac arrest with post-anoxic encephalopathy. Two randomised trials and more than twenty non-randomised studies have shown the benefits of therapeutic cooling in adult patients who remained comatose after a witnessed cardiac arrest with an initial rhythm of ventricular fibrillation (VF) or ventricular tachycardia (VT) (Bernard et al. 2002; Polderman 2008; The Hypothermia after Cardiac Arrest Study Group, 2002). Both the European Resuscitation Council (ERC) and American Heart Association (AHA) now recommend using hypothermia in survivors of witnessed cardiac arrest, regardless of the initial rhythm (level 1 recommendation for VT VF, level 2b for asystole/PEA) (Peberdy et al. 2010). A recent study from Europe found that mortality is decreased by 20 percent with this treatment (van der Wal et al. 2011). The NNT is six, according to a meta-analysis (Holzer et al. 2005). The average rate of good outcome in patients with OHCA and initial rhythm of VT/VF treated with therapeutic cooling in all randomised and non-randomised studies is around 50 percent, giving a one in two survival rate.

In a recent analysis of cost-effectiveness in the United States it was concluded that postarrest patients treated with therapeutic hypothermia gained an average of 0.66 quality-adjusted life years compared with conventional care, at an incremental cost of 31,254 USD, yielding an incremental cost-effectiveness ratio of 47,168 USD per quality-adjusted life year, well below the general norm for the price per QALY in the US of around 100,000 USD (Merchant et al. 2009). This number would likely be more favourable in Europe, where outcome rates for cardiac arrest tend to be better, where implementation of therapeutic cooling is more widespread, and where costs of healthcare are significantly lower compared to the United States. In addition, if cooling is initiated in a post-cardiac arrest patient the same cooling device/disposables (either surface cooling pads or cooling catheters) can be used subsequently to control fever, making the overall intervention more cost-effective.

#### **Hypothermia & Intracranial Pressure Reduction**

Hypothermia can also be used to decrease intracranial pressure (ICP) in patients with traumatic brain injury or ischaemic stroke, to mitigate myocardial injury following myocardial infarction, to reduce the inflammatory response in ARDS, and in numerous other situations (Polderman 2008). These need to be further studied to assess the effect of cooling and no firm conclusions regarding efficacy or cost effectiveness can be made at this time.

However, it seems clear that therapeutic temperature management, including fever control and therapeutic hypothermia, will play an important role in critical care medicine in years to come, mainly but not exclusively in patients with neurologic injuries.

The prices of the currently available cooling devices range from around 10,000 to 40,000 Euros. The price of disposables ranges from 120 to 1,000 Euros per patient. There is a considerable variation in efficacy, which can be summarised from a combination of properties including speed of cooling, ability to maintain target temperature within a narrow range, ability to achieve slow and controlled re-warming, and low incidence of side effects (Polderman 2009; Polderman and Herold 2009). Another factor that should be taken into account is the effect on nursing and physician workload. Maintaining hypothermia or normothermia using an automated cooling device has a significantly lower workload compared to non-automated devices and/or non-device cooling with ice packs (Polderman 2009; Polderman and Callaghan 2006; Polderman and Herold 2009).

Another consideration in this regard is the difference between low-volume and high-volume ICUs. Obviously, write-off costs for a cooling device will be much lower in high-volume units and units that use the devices more frequently, in different categories of patients. Thus the per-patient costs will vary considerably, and will be determined by the factors listed above. However, regardless of the setting and precise indication adopted by individual units, it seems clear that therapeutic temperature management will be a highly cost-effective treatment, comparing favourably with many routine interventions in critical care.

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