

# A multicentre audit of temperature patterns after traumatic brain injury

Manoj K Saxena, Colman Taylor, Naomi Hammond, Paul Young, Jayanthi Mysore, Laurent Billot, Ashleigh Myburgh and John Myburgh

During acute illness, an elevation of body temperature commonly occurs and is part of a complex biological response to injury. In this context, elevated body temperature may be a marker of illness severity, a protective host response to illness, and/or a potential target for therapeutic intervention. The febrile response may be adaptive in patients with infection,<sup>1</sup> but its role after acute traumatic brain injury (TBI) is uncertain.<sup>2</sup>

We found three types of evidence for avoiding fever (defined as a core temperature of  $>37^{\circ}\text{C}$ ) after TBI. First, reports of animal models of TBI show beneficial effects of induced normothermia ( $36.5^{\circ}\text{C}^{3-5}$  or  $37^{\circ}\text{C}^{4,5}$ ) compared with induced hyperthermia ( $39^{\circ}\text{C}^{3-5}$  or  $39.5^{\circ}\text{C}^{6,7}$ ); the effects were seen in indices of inflammation,<sup>3,6</sup> histopathological findings<sup>4,5</sup> and neurobehavioural assessment.<sup>8</sup> Second, observational clinical studies<sup>9</sup> suggest that elevated body temperature after TBI may be associated with adverse long-term clinical outcomes.<sup>10-12</sup> Third, clinical studies of temperature manipulation (evaluating the effects of induced normothermia and hypothermia) report a reduction in intracranial pressure (ICP)<sup>13-16</sup> associated with the interventions.<sup>7</sup> There are no randomised clinical trials evaluating the effect of normothermia on patient-centred outcomes,<sup>2</sup> and clinical guidelines do not make a recommendation for normothermia or provide a definition for it.<sup>17,18</sup>

We undertook an audit to describe usual clinical care in the intensive care units of designated trauma hospitals in two Australian states. This was part of a research program on the feasibility and study design of a clinical trial investigating the effect of normothermia on patient-centred outcomes for critically ill patients with TBI. As there was no agreed clinical definition of normothermia, we used a definition based on animal models of TBI and hypothesised that temperature would be maintained below  $37^{\circ}\text{C}^{3-5}$  in clinical practice. We planned to carry out a secondary analysis using a temperature threshold of  $38^{\circ}\text{C}$ , based on the association of temperatures above this threshold with adverse outcomes that had been reported in previous observational studies.<sup>10-12</sup>

## Methods

Our audit was a retrospective, multicentre cohort study conducted in the ICUs of eight of the 10 major trauma

## ABSTRACT

**Background:** Elevation of body temperature is common after traumatic brain injury (TBI). Suppressing fever may be beneficial.

**Hypothesis:** In clinical practice, temperature is maintained  $\leq 37^{\circ}\text{C}$ .

**Participants, setting and methods:** A retrospective, multicentre, cohort study of patients with an intensive care unit admission diagnosis of TBI over a 6-month period.

**Main outcome measures:** The mean proportion of time per day that temperature  $\geq 37^{\circ}\text{C}$  or  $\geq 38^{\circ}\text{C}$  (to correct for unequal measurements between patients, imputation was used between consecutive temperature measurements and a linear relationship was assumed); and the proportion of patients on each day with a peak temperature  $\geq 37^{\circ}\text{C}$ .

**Results:** 217 patients with TBI were admitted to eight ICUs. The mean Acute Physiology and Chronic Health Evaluation II score of the cohort was 15.7 (SD, 7.7) and intracranial pressure monitoring was done in 29% of patients. The mean proportion of time on each day that temperature was  $\geq 37^{\circ}\text{C}$  varied between 56% (SE, 2.6%) on Day 1 and 89% (SE, 3.7%) on Day 14. The mean proportion of time per day that temperature was  $>38^{\circ}\text{C}$  was between a minimum of 11% (SE, 1.5%) on Day 1 and a maximum of 25% (SE, 4.4%) Day 11. The proportion of patients for whom daily peak temperature was  $>37^{\circ}\text{C}$  ranged between a minimum of 73.2% (153/209) on Day 1 and a maximum of 97.4% (26/33) on Day 13.

**Conclusion:** In patients with TBI, a substantial proportion of time is spent with a temperature  $\geq 37^{\circ}\text{C}$ . Prospective validation of these data are required.

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centres in two states (New South Wales and Queensland) in Australia. Six of the ICUs were general medical–surgical ICUs (which admitted neurosurgical patients) and two ICUs admitted patients with TBI to dedicated neurosurgical ICUs. Between 1 January 2008 and 30 June 2008, we reviewed the ICU admissions records and identified patients with an ICU admission diagnosis that included TBI (this definition for TBI

**Table 1. Demographic characteristics for 217 patients with traumatic brain injury**

Characteristic	Mean (SD)	Median (IQR)
Age, years	38.9 (19.6)	35 (22–52)
Men, <i>n/N</i> (%)	163/217 (75%)	–
Mechanism of injury, <i>n/N</i> (%)		
Vehicular	105/209 (50%)	–
Non-vehicular	104/209 (50%)	–
APACHE II score	15.7 (7.7)	15 (10–20)
MV at ICU admission, <i>n/N</i> (%)	171/210 (81%)	–
Duration of MV, days	6.3 (6.6)	4 (1.9–10)
ICP monitoring during ICU stay, <i>n/N</i> (%)	60/208 (29%)	–
Duration of ICP monitoring, days	5.9 (3.9)	5 (3–8)
ICU length of stay, days	9.0 (11.1)	5 (2–11)

IQR = interquartile range. APACHE = Acute Physiology and Chronic Health Evaluation. MV = mechanical ventilation. ICU = intensive care unit. ICP = intracranial pressure.

was felt to be appropriate for this exploratory audit, given the retrospective study design). We collected demographic information and data on temperature management during the first 14 days of ICU admission. Demographic data included age, sex, Acute Physiology and Chronic Health Evaluation (APACHE) II score<sup>19</sup> (calculated using physiological data from the first 24 hours of ICU admission), mechanism of injury, duration of mechanical ventilation and ICU length of stay.<sup>20,21</sup> Data related to temperature management included measured temperature (including location of the temperature

measurement) as recorded during standard clinical care. Core temperature measurement was defined as temperature measured from the oesophagus, nasopharynx, oropharynx, bladder, rectum or an intravascular location. Non-core temperature measurement was defined as temperature measured with tympanic, axillary, groin or oral methods.

We also recorded the following data: pharmacological agents used (eg, paracetamol, non-steroidal anti-inflammatory drugs [NSAIDs] and cyclooxygenase-2 [COX-2] inhibitors) and their total daily doses and administration routes; and physical interventions used (eg, fans, ice packs, cooling blankets, vests and wraps, intravascular cooling catheters, internal cavity lavage, and the use of extracorporeal circuits).

Ethics and research governance approvals were obtained at all sites and included a waiver of the need for informed consent. Data were extracted from hospital medical records and ICU observation charts onto paper case report forms (CRFs) by the principal investigator or research coordinator at each site (see Appendix 1). Data from the paper CRFs were then entered into a database at The George Institute for Global Health and statistical analysis was performed using SAS, version 9.2 (SAS Institute).

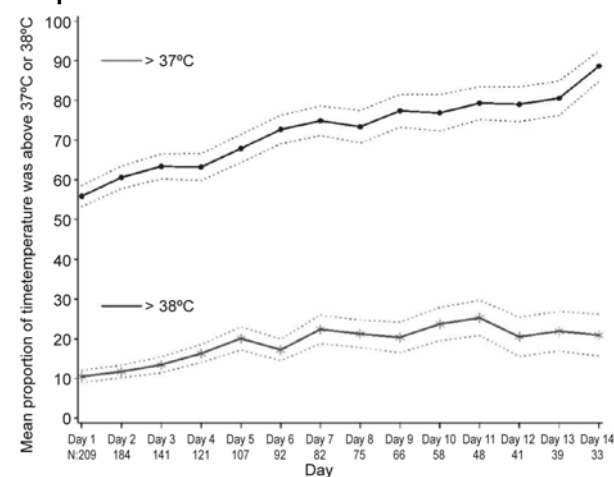
Differences between means were compared using the student *t* test for normally distributed data, and using the Wilcoxon signed-rank test for non-normally distributed data. Differences in proportions were compared using  $\chi^2$  tests. Tests of trends over time were conducted using linear mixed models.

Our principal objective was to determine the mean proportion of time per day that patient temperature was  $\geq 37^\circ\text{C}$ . Our secondary objectives were to determine the mean proportion of time per day that patient temperature was  $\geq 38^\circ\text{C}$ , the proportion of patients on each day with their highest temperature exceeding  $37^\circ\text{C}$  and  $38^\circ\text{C}$ , the distribution of all temperature measurements (in  $1^\circ\text{C}$  bands from  $31^\circ\text{C}$  to  $41^\circ\text{C}$ ) and the use of interventions to modify temperature.

To correct for unequal numbers of temperature measurements between patients, we used interpolation, with the assumption of linearity, between consecutive temperature measurements. This statistical method converts a discrete number of measurements for an individual patient on a specific day into a continuous temperature curve for that day and corrects for unequal measurements between patients. Non-core temperatures were adjusted by the addition of  $0.3^\circ\text{C}$ .<sup>22</sup>

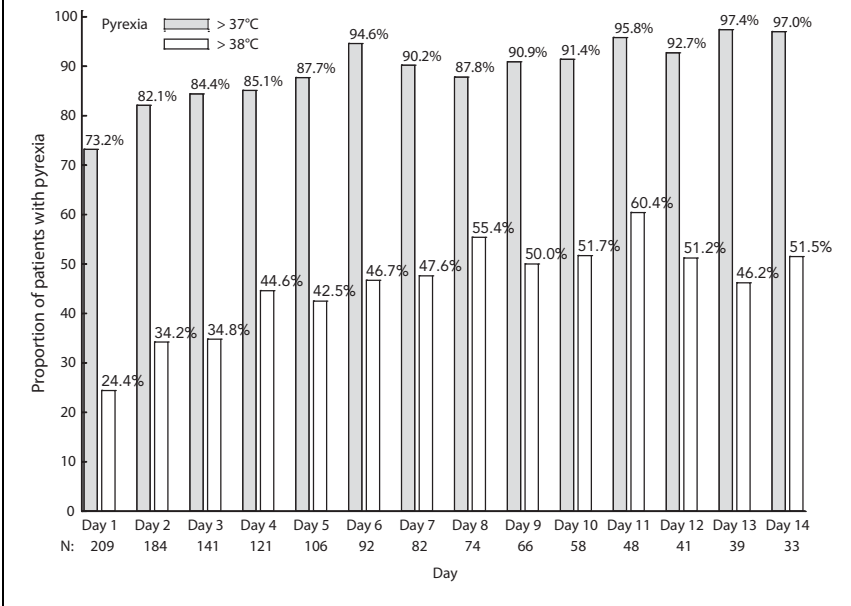
## Results

During the 6-month study period, 217 patients were identified from the two dedicated neurosurgical ICUs and

**Figure 1. Mean proportion of time on each day that temperature exceeded  $37^\circ\text{C}$  and  $38^\circ\text{C}$ \***

\* Dotted lines are SEs.

**Figure 2. Proportion of patients on each day with peak temperature above 37°C or 38°C**



The mean age of the cohort was 38.9 years (SD, 19.6 years). Seventy-five per cent of the patients were men (163/217) and 50% of patients acquired their TBI from vehicular trauma (105/209) (Table 1). The mean APACHE II score was 15.7 (SD, 7.7) and 81% of the cohort (171/210) received invasive mechanical ventilation. ICP was monitored in 29% of patients (60/208) for a mean duration of 5.9 days (SD, 3.9 days). The mean length of ICU stay for the cohort was 9 days (SD, 11).

**Method of temperature measurement**

There was a total of 14977 temperature measurements from 217 patients. Classification of measurement technique was available for 140/217 patients. Non-core temperature measurement was more commonly used than core temperature measurement (83% v 17% of total patient-days;  $P < 0.001$ ).

the six mixed medical–surgical ICUs. The median number of beds per participating ICU was 18 (range, 8–25). All of the sites had a protocol that provided a framework for the management of patients with TBI, allowing for clinician discretion based on individual patient characteristics. One site specified in the protocol how temperature should be managed and another site had a separate protocol for temperature management; both of these sites specified that interventions should be considered if temperature exceeded 37.5°C.

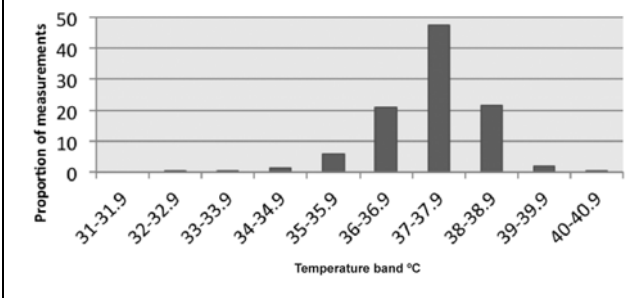
The median number of TBI patients admitted at each site during the 6-month study period was 23 (range, 4–51). The median number of patients at each site who underwent ICP monitoring during the 6-month study period was eight (range, 2–15).

**Longitudinal variation of temperature**

The mean proportion of time per day that temperature exceeded 37°C varied between a minimum of 56% (SE, 2.6%) on Day 1 and a maximum of 89% (SE, 3.7%) on Day 14 (Figure 1). A test of linear trend showed an average increase of 2.6% per day in the proportion of time per day that temperature exceeded 37°C from Day 1 to Day 14 ( $P < 0.001$ ). The proportion of patients for whom daily peak temperature exceeded 37°C ranged between a minimum of 73% (153/209) on Day 1 and a maximum of 97% (26/33) on Day 13 (Figure 2).

The mean proportion of time per day that temperature exceeded 38°C ranged between a minimum of 11% (SE, 1.5%) on Day 1 and a maximum of 25% (SE, 4.4%) on Day 11. The proportion of patients for whom daily peak temperature exceeded 38°C ranged between a minimum of 24% (51/209) on Day 1 and a maximum of 60% (29/48) on Day 13 (Figure 2).

**Figure 3. Distribution of all temperature measurements during intensive care unit admission**



**Distribution of temperature measurements**

For all patients, the proportion of measurements  $\geq 37^\circ\text{C}$  was 71%, with 47% of all temperature measurements between 37°C and 38°C, and 21% of measurements between 38°C and 39°C (Figure 3). Twenty-one per cent of measurements were between 36°C and 37°C.

**Use of interventions to modify temperature**

In the entire cohort, paracetamol was administered on a mean of 54.5% of total patient-days (SE, 39.3%) and the

mean daily dose varied between 739 mg (95% CI, 582–895 mg) on Day 1, to 1489 mg (95% CI, 1164–1813 mg) on Day 6. NSAIDs were used in 4/217 patients (range, 0–3 patient-days), steroids were used in 6/217 patients (range, 0–11 patient-days) and no patient received COX-2 inhibitors. Physical cooling was administered on a mean of 19.4% of patient-days (SE, 34.2% patient-days).

## DISCUSSION

### Statement of principal findings

We have shown that critically ill patients with TBI have a temperature that exceeds 37°C for a substantial proportion (>50%) of each day. Paracetamol was used on most patient-days, but at less than half the maximum dose. NSAIDs were rarely used (used for 2% of patients), COX-2 inhibitors were not used, and physical cooling was used overall for 20% of patient-days.

### Comparison with previous studies

Our results for observed temperature in clinical practice are consistent with the observations from a point prevalence study<sup>23</sup> and other cohort studies<sup>10,14,24,25</sup> that suggest temperature elevation above the 37°C is common after TBI. The point prevalence study of a mixed cohort of 106 critically ill patients with acute brain injury, during a 24-hour study period, reported that the proportion of temperature measurements above 37°C, 37.5°C and 38°C were 62%, 43% and 22%, respectively.<sup>23</sup> A single-centre, retrospective cohort study of patients with TBI reported that 68% of patients ( $n = 846$ ) had a rectal temperature of >37°C,<sup>11</sup> and a multicentre, retrospective cohort study reported that 13% of patients ( $n = 7145$ ) had an axillary temperature >38°C,<sup>12</sup> during the first 3 days of their ICU admission.

The use of interventions to modify temperature in our study is comparable with point prevalence data and other retrospective studies<sup>10,14,26</sup> for the use of paracetamol and physical cooling. However, the low use of NSAIDs in Australia and New Zealand contrasts with use in other jurisdictions.<sup>14,27</sup>

### Clinical implications and significance

Our study suggests that paracetamol is infrequently used at the maximum daily licensed dose and that NSAIDs and COX-2 inhibitors are rarely used in Australia and New Zealand for TBI. This may be due to the weak evidence for normothermia improving patient outcomes, uncertainty about the efficacy of these interventions in reducing body temperature, or because of concerns about toxicity.<sup>28,29</sup> Increasing the dose of paracetamol administered may be a simple method by which temperature may be modified. Data from patients with stroke suggest that paracetamol

6 g/day safely reduces temperature by a mean of 0.26°C (95% CI, 0.18–0.31°C) compared with placebo.<sup>30,31</sup> The additional uses of NSAIDs or COX-2 inhibitors are further ways in which control of temperature may be achieved. There are observational<sup>32–34</sup> and Phase 2 interventional studies<sup>35,36</sup> supporting the further evaluation of these agents.

Physical cooling was used on 19% of patient-days, with 15%–25% of patients receiving physical cooling on each day. These levels of use may be due to clinical uncertainty about efficacy, concerns about potential complications associated with the use of the prolonged sedation needed to facilitate physical cooling, resource or equipment limitations, or other issues, such as the need for neurological evaluation being given clinical priority over temperature control.

### Strengths and limitations

The strengths of our study are that it provides data from eight of the 10 major trauma centres in New South Wales and Queensland over a 6-month period, providing detailed information (>14 000 temperature measurements) on the longitudinal variation of temperature over time in the acute phase of TBI. Additionally, the demographic characteristics of our patient population are consistent with those reported in an Australia and New Zealand epidemiological study of patients with TBI,<sup>37</sup> which suggests that the cohort may be representative of general Australian practice.

The limitations of our study include first that our definition of TBI was based on information recorded from the ICU admission book, rather than the triad of appropriate mechanism, Glasgow Coma Scale abnormality, and computed tomography findings consistent with TBI. However, this definition was pragmatic, based on the retrospective study design and the unfunded nature of this study, and will be further explored in a prospective study. Second, our retrospective study design affects the ability to accurately capture information on the use of physical cooling, although this information is usually recorded in the medical notes or daily ICU chart. Third, the submaximal use of interventions that modify temperature in the overall cohort may be related to the illness severity of the cohort studied.

### Future studies

A prospective observational study is warranted to externally validate the findings of our audit.

### Conclusion

In patients with TBI of mixed illness severity, a substantial proportion of time each day (>50%) is spent with a temperature  $\geq 37^\circ\text{C}$ . Further observational data from pro-

spective studies are required to validate our preliminary observations, particularly regarding the use of physical cooling. Understanding usual practice may inform the feasibility and design of subsequent Phase 2 and Phase 3 randomised controlled trials, which are needed to ascertain whether maintaining a normal temperature in patients with TBI improves clinical patient outcomes.

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## Competing interests

None declared.

## Author details

**Manoj K Saxena**, Intensive Care Physician,<sup>1</sup> Research Fellow (PhD Candidate),<sup>2</sup> and Conjoint Lecturer<sup>3</sup>

**Colman Taylor**, Senior Research Fellow<sup>2</sup>

**Naomi Hammond**, Research Fellow<sup>2</sup>

**Paul Young**, Intensive Care Specialist,<sup>4</sup> and Intensive Care Research Program Director<sup>5</sup>

**Jayanthi Mysore**, SAS Programmer<sup>2</sup>

**Laurent Billot**, Director, Statistics Division,<sup>2</sup> and Principal Research Fellow<sup>6</sup>

**Ashleigh Myburgh**, Administrative Assistant<sup>2</sup>

**John Myburgh**, Senior Physician,<sup>1</sup> Director, Critical Care and Trauma Division,<sup>2</sup> and Professor of Critical Care Medicine<sup>3</sup>

1 Department of Intensive Care Medicine, St George Hospital, Sydney, NSW, Australia.

2 The George Institute for Global Health, Sydney, NSW, Australia.

3 St George Clinical School, University of New South Wales, Sydney, NSW, Australia.

4 Wellington Hospital, Wellington, New Zealand.

5 Medical Research Institute of New Zealand, New Zealand.

6 Sydney Medical School, University of Sydney, Sydney, NSW, Australia.

**Correspondence:** m.saxena@unsw.edu.au

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#### Appendix 1. Site-based investigators for audit

Judith Bellapart, Royal Brisbane and Women's Hospital, QLD  
 Celia Bradford, Royal North Shore Hospital, NSW  
 Miranda Hardie, John Hunter Hospital, NSW  
 Anthony Lo, St. George Hospital, NSW  
 Vineet Nayyar, Westmead Hospital, NSW  
 Michael O'Leary, Royal Prince Alfred Hospital, NSW  
 Dorrilyn Rajbandhari, Royal Prince Alfred Hospital, NSW  
 Alan Rashid, John Hunter Hospital, NSW  
 Ian Seppelt, Nepean Hospital, NSW  
 Markus Skirfvars, Liverpool Hospital, NSW