Fever and fever management among intensive care patients with known or suspected infection: a multicentre prospective cohort study

Paul Young, Manoj Saxena, Glenn M Eastwood, Rinaldo Bellomo and Richard Beasley

ABSTRACT

Objective: To describe the duration of fever, fever management, and outcomes among intensive care patients with fever and known or suspected infection.

Design, setting and participants: Prospective observational trial in three tertiary intensive care units over 6 weeks in 2010. Adult patients were screened for eligibility and inclusion if they had a fever of ⩾ 38.0° C and known or suspected infection being treated with antimicrobials; those with neurological injury or elective surgery within 72 hours were excluded.

Main outcome measures: Mean and peak daily temperatures were recorded and the use of antipyretics and other cooling measures were recorded over the first 7 days. Mortality, ICU-free survival, ventilator-free survival and renal replacement therapy-free survival were determined at Day 28.

Results: 51/565 patients (9.0%) were included. The mean daily peak temperature and the proportion of patients with a documented temperature of ⩾ 38.0° C decreased over the first 3 days after first documented fever. Thereafter, the proportion of patients who had daily peak temperatures ⩾ 38.0° C remained about 20%. Paracetamol was administered to 58%–70% of patients per day. Physical cooling was used at least once for 12% of patients. Mean ICU-free survival to Day 28 in eligible patients was 16.0 (SD, 9.2) days. The mortality rate of eligible patients was more than double that of ineligible patients (8/51 [16%] v 36/514 [7%]; $P = 0.05$).

Conclusion: We have described the typical time course of fever in an easily identified cohort of patients with known or suspected infection and have determined that these patients have significant morbidity and mortality. This information is vital to the design of interventional studies for the treatment of fever in ICU.

Crit Care Resusc 2011; 13: 97–102

Fever is a common manifestation of systemic inflammatory response syndrome (SIRS).[1] Although fever is recognised as one of the cardinal signs of infection,[2] it may occur as part of both sepsis and non-infectious SIRS. Non-infectious SIRS is more common than sepsis on admission to the intensive care unit, and more commonly results in death from neurological failure than sepsis.[3] Among patients with neurological injury, elevated body temperature is independently associated with a longer length of ICU stay and increased mortality. Observational studies of patients with neurological injury[4] and mixed critically ill patients[5,6] suggest that an elevated body temperature is independently associated with a longer length of ICU stay and increased mortality. However, the association between temperature and risk of death may be different for patients with infective illnesses.

Phylogenetically, fever can be considered an ancient host response that may result in survival benefit in infective illnesses.[7] In various animal models, increasing body temperature within the physiological range enhances resistance to infection.[2,7] Among critically ill patients, the effect of antipyretics on survival in patients with sepsis is unclear. Although the use of paracetamol to treat fever among patients with presumed severe sepsis may increase the risk of mortality in this setting,[8] two studies have shown that administration of ibuprofen in septic patients does not affect mortality.[9,10] However, antipyretics prolong the duration of illness in chickenpox,[11] parasitaemia in malaria,[12] and viral shedding in rhinovirus infection.[13] On the basis of these data, there is a plausible biological rationale that the presence of fever has different implications in patients with infection compared with those without infection, and that this cohort of patients is of particular interest with respect to further research into strategies of fever control.

Thus, we undertook to prospectively describe the temperature response, the use of antipyretic interventions, source of infection, the use of organ support, and hospital mortality in an Australasian cohort of patients with fever and presumed infection requiring admission to ICU.

Although these data are clinically informative, we postulated that they would also be useful for the design of future interventional ICU trials in patients with suspected infection, and may help determine the feasibility of clinical trials of antipyretics in this population, and facilitate power calculations necessary to estimate the number of patients required for an interventional trial.

Methods

Study design

This study was a multicentre prospective observational cohort study conducted at the ICUs of Wellington Regional Hospital, the Austin Hospital, Melbourne, and St George Hospital, Sydney. These ICUs are all tertiary units in major metropolitan centres — one in New Zealand and two in Australia.

Ethics approval

We obtained prospective hospital Human Research Ethics Committee approval to conduct the audit and collect data related to the study for the Australian hospitals. In New Zealand, it was determined that no ethics review was required as the trial was classified as a "low-risk audit activity". The need for informed patient consent was waived by the ethics committees.

Participants

We prospectively screened all intensive care patients in the three participating hospitals over 6 weeks between September and November 2010. Patients were considered eligible if they fulfilled the following entry criteria:

- Known or suspected infection being treated with antimicrobials;
- Temperature ⩾ 38.0° C (recorded by any route);
- Absence of acute brain injury (defined as any acute traumatic brain injury, subarachnoid haemorrhage, acute ischaemic stroke, acute intracerebral haemorrhage, or acute intracranial infection); and
- Absence of elective surgery within 72 hours of temperature ⩾ 38.0° C.

We recorded the baseline characteristics of eligible patients including the proportion who had sepsis, severe sepsis and septic shock on the basis of standard definitions[14] as well as the sources of infection, Acute Physiology and Chronic Health Evaluation (APACHE) II score and the requirement for organ support at baseline.

Outcome measures

Temperature response and antipyretic use

To determine the duration of fever, we recorded mean, peak and lowest daily temperature for 7 days from the time the entry criteria were first met. The mean daily temperature was determined from temperature recordings taken within 2 hours of four time points — 06:00, 12:00, 18:00 and 24:00 hours. All temperature recordings were "surface" temperatures measured either by the axillary or tympanic route except in two patients where core temperatures were recorded from an intravascular catheter. For these patients, core temperatures were converted to surface temperatures by subtracting 0.4° C.[13] We evaluated the use of antipyretics by reviewing medication charts, and the use of physical cooling by reviewing ICU daily monitoring charts.

Microbiology profile

All microbiology results and additional information that facilitated a precise microbiological diagnosis were collected.

Organ failures and mortality

To determine the morbidity and mortality in this group of patients with suspected infection in the ICU, we examined the following variables at Day 28:

- Ventilation-free survival days;
- Inotrope- or vasopressor-free survival days;
- Renal replacement-free survival days;
- ICU-free survival days; and
- Mortality.

ICU-free days were determined from the date of fulfilling eligibility criteria (Day 0). That is, the number of non-ICU days after ICU discharge, excluding days of ICU readmission, were counted for each day a patient was alive up to Day 28; a patient who died before ICU discharge received a score of 0.

Data collection

Using a standardised case report form, three of us (PY, MS and GME) performed the audit by retrospective chart review following prospective identification of study patients using the study entry criteria. We collected demographic, APACHE II and outcome data for ineligible patients retrospectively using established databases at each study centre.

Statistical analysis

Data were analysed using descriptive and frequency statistical procedures. For between-group comparisons, Fisher exact test and the Mann–Whitney U test were used for categorical and continuous data, respectively. All analyses were performed using InStat 3.1a (GraphPad Software, La Jolla, Calif, USA).

Results

Demographics, microbiological diagnosis and illness severity

All the available 565 adult patients from the three ICUs were prospectively screened. A total of 51 patients (9.0%) fulfilled the eligibility criteria. Eligible patients were younger (54 years [SD, 18 years] v 60 years [SD, 23 years]; $P = 0.01$) and had higher APACHE II scores than ineligible patients (20.1 [SD, 7.7] v 15.1 [SD, 6.9]; $P < 0.001$).

The baseline characteristics of participants with fever and known or suspected infection are shown in Table 1. At

Table 1. Baseline characteristics of participants

Characteristic	No. (%)
Men	32 (63%)
Mean age in years (SD)	54 (18)
Ethnicity	
New Zealand European	13 (25%)
Australian European	28 (55%)
Maori	2 (4%)
Pacific Islander	1 (2%)
Aboriginal or Torres Strait Islander	1 (2%)
Other	6 (12%)
Admission source	
Emergency department	14 (27%)
Ward	15 (29%)
Other hospital intensive care unit	9 (18%)
Other hospital (except ICU)	6 (12%)
Operating theatre after emergency surgery	7 (14%)
Sepsis	
Sepsis	51 (100%)
Severe sepsis	41 (80%)
Septic shock	25 (49%)
Primary source of infection	
Pneumonia	28 (55%)
Urinary tract infection	6 (12%)
Intra-abdominal sepsis	4 (8%)
Bone and joint infection	2 (4%)
Endocarditis	2 (4%)
Line sepsis	1 (2%)
Skin and soft tissue infection	1 (2%)
Unknown	7 (14%)
Illness severity and organ support	
Mean APACHE II score (SD)	20.1 (7.7)
Invasive ventilation	28 (55%)
Inotropic or vasopressor support	28 (55%)
Renal replacement therapy	1 (2%)

APACHE = Acute Physiology and Chronic Health Evaluation.

baseline, inotropic or vasopressor support was used for 28/51 (55%) of patients, 28/51 (55%) were invasively ventilated, and one patient was receiving renal replacement therapy.

All eligible patients met the criteria for SIRS. There were 41/51 patients (80%) who met the criteria for severe sepsis and 25/51 (49%) had septic shock. There were 17/51 patients (33%) who had positive blood cultures that were thought to be related to the initial fever. Pneumonia was the most common cause of infection, accounting for 28/51 cases (55%).

Figure 1. Mean peak daily non-core temperatures of patients in an intensive care unit, Days 0–7 ($n = 51$)

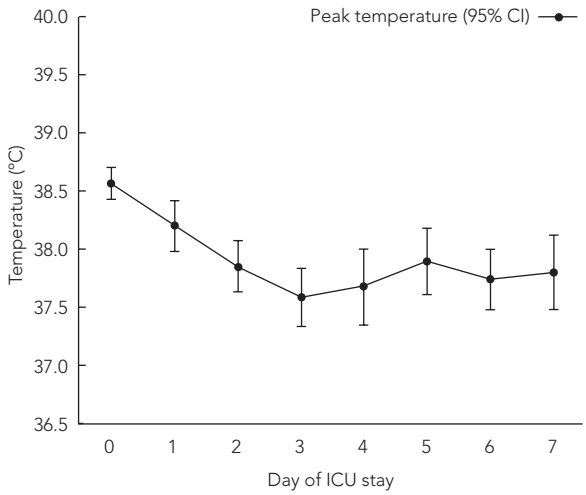
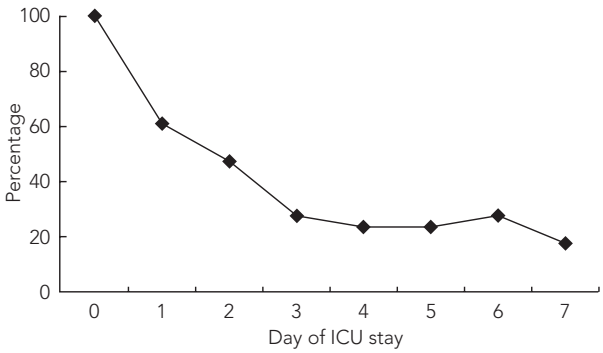


Figure 2. Percentage of patients in an intensive care unit with a peak temperature of at least 38.0° C ($n = 51$)



Fever duration

Daily temperature management data were collected for 244 ICU-days for the 51 patients.

Fever occurred mainly in the first 48 hours after the first documented temperature ⩾ 38.0° C. The mean daily peak temperature of patients who remained in ICU is shown in Figure 1, and the proportion of patients who had a daily peak temperature of ⩾ 38.0° C is shown in Figure 2. Both the mean daily peak temperature and the proportion of patients with a documented daily peak temperature of ⩾ 38.0° C decreased linearly over the first 3 days. Thereafter, for the remainder of the 7 days on which temperature data were collected, the mean daily peak temperature remained elevated between 37.5° C and 38.0° C, and the proportion of patients who had daily peak temperatures

Table 2. Use of paracetamol on Days 1–7 among patients remaining in an intensive care unit

	Day						
	1	2	3	4	5	6	7
Mean daily dose of paracetamol, g (SD)	1.8 (1.6)	2.0 (1.6)	1.9 (1.6)	1.6 (1.6)	1.6 (1.7)	1.7 (1.7)	1.7 (1.7)
Patients who received paracetamol (%)	69%	70%	69%	64%	58%	61%	61%
No. of patients remaining in ICU	51	49	43	37	29	25	24

Table 3. ICU-free survival and ICU support

Outcome	Mean no. of days (SD)
28-day ICU-free survival	16.0 (9.2)
28-day ventilation-free survival	19.5 (9.6)
28-day inotrope or vasopressor-free survival	23.7 (6.6)
28-day renal replacement-free survival	25.4 (6.6)

ICU = intensive care unit.

⩾ 38.0° C remained at around 20%. The mean daily temperature and lowest daily temperature showed a similar trend (data not shown).

Fever management

Paracetamol use was common; however, its use was not associated with the presence of fever (correlation coefficient between daily peak temperature and mean paracetamol dose, $r = 0.037$; $P = 0.89$). The use of paracetamol in the ICU is shown in Table 2.

Physical cooling was used for 6/51 patients (12%) for 2.9/100 ICU-days. The mean peak temperature on days when physical cooling was used was 39.1° C (SD, 0.6° C).

In terms of other medications with potential antipyretic effects, enteral or parenteral steroids were used for 15/51 patients (29%) for 23.0/100 ICU-days and low-dose aspirin (⩽ 300 mg per day) was used for 12/51 patients (24%) for 17.6/100 ICU-days. Other non-steroidal anti-inflammatory drugs (including cyclo-oxygenase 2 inhibitors) were not used during the study period.

Morbidity and mortality data

The mortality for this cohort of patients with temperature at least 38.0° C and known or suspected infection was 8/51 (16%). This was more than double the mortality rate for non-eligible patients over the same period 36/514 (7%) ($P = 0.05$).

The 28-day ICU-free survival and organ-support-free survival of patients with fever and known or suspected infection are shown in Table 3.

Discussion

Through the use of simple eligibility criteria, we identified a group of patients in which 80% had severe sepsis,[14] around half (25/51) had septic shock[14] and a third had positive blood cultures. This cohort had a mortality rate over twice that of other patients in the ICU, and had significant requirements for ICU support.

We determined that the frequency and severity of fever reduced progressively such that by Day 3, fewer than 25% of patients had a peak daily temperature of ⩾ 38.0° C. Most patients in the ICU received at least one dose (1 g) of paracetamol a day, with the mean daily dose ranging from 1.6 to 2.0 g per day throughout the 7 days after initial temperature of ⩾ 38.0° C. The use of paracetamol did not vary with peak daily temperature. Low-dose aspirin and steroids were both administered to over a quarter of patients with fever due to known or suspected infection. Physical cooling was used among 12% of patients with a mean peak temperature of 39.1° C (SD, 0.6° C) on days when physical cooling was used.

Comparison with previous studies

In our study, 9% of patients admitted to the ICU had a fever in association with a known or suspected infection without neurological injury or recent elective surgery. In previous observational studies, the incidence of fever attributable to infection in various critical care settings ranged from 8% to 37%.[5,15-18] These studies defined fever as a temperature of ⩾ 38.2, 38.3 or 38.4° C; however, methods of recording core or surface temperature have been inconsistent. Similarly, in our study, a range of tympanic, axillary and intravascular temperature measurements were used. Also, varying definitions of infection have been used in previous studies. We used a pragmatic definition in which the presence of a known or suspected infection was defined by whether the patient was being treated with antimicrobials for a suspected infection.

The largest study of fever in critically ill patients was a retrospective cohort study conducted in Canada from 2000 to 2006.[15] This study involved 24 204 ICU admission episodes and comprised 20 466 patients. All adults admitted to an ICU in Calgary who had or developed a fever of ⩾ 38.3° C over the 7-year study period were included. The cumulative frequency of fever (incidence density per 100 ICU days) was 44%, and 8% had fever attributable to an infection. However, patients were only defined as having an infection if they had positive cultures. Because many infections may be diagnosed syndromically, have negative cultures or do not have samples sent for culture, their reported

proportion of fevers attributable to an infectious aetiology is likely to be underestimated. In other single-centre trials in Greece,[5] the United Kingdom,[16] Belgium,[17] and the United States,[18] reported rates of fever due to infection were 26%, 37%, 15% and 12%, respectively.

Data regarding the time course of the febrile response were presented in a randomised controlled trial of ibuprofen versus placebo among patients with sepsis.[9] Although this trial did not use a contemporary standard definition of sepsis, about 70% of the patients had a confirmed chest, abdominal or urinary source of sepsis. The pattern of mean temperature versus time seen in the patients in the control arm of this study was similar to that seen in our study. We have determined that in current practice, fever in patients with known or suspected infection in ICU has usually resolved by Day 3. In our study, the proportion of patients with persistent fever in ICU by Day 6 was 24%, similar to previous studies,[15,16] which found a rate of persistent fever of 18% to 23%. We did not observe an increased risk of mortality associated with persistent fever.

Implications

Using simple criteria, we were able to identify a group of ICU patients with sepsis who had significant morbidity and risk of mortality. This group of patients with fever and suspected infection without neurological injury or recent surgery are younger, have higher illness severity and a higher mortality rate than other patients. Although this has clinical relevance in terms of recognition of a group of patients who are at significant risk of complications, it also has implications in terms of potential planning for a randomised controlled trial in febrile ICU patients with infection.

If this group was enrolled in a randomised controlled trial of permissive versus intensive fever management, 9% of our ICU patients would be eligible for the study. As fever tends to reduce rapidly, such a study would need to enrol patients within 6 hours of fever onset. The time course of fever suggests that most patients would require intervention over approximately 3 days. Physical cooling is used in clinical practice for fever $>39.0^{\circ}$C, and trial design will need to account for the potential confounding influence of increased used of physical cooling in the control arm of the trial.

We have calculated that a sample size of 700 patients would give 80% power at an α of 0.05 to detect a 2-day increase in the number of days of "ICU-free survival to Day 28" from 16 to 18, based on a standard deviation of 9.2 and allowing for a 5% drop-out rate. This sample size would also provide 80% power to detect a reduction in 28-day mortality from our observed baseline mortality of 16% to a mortality of 9% at an α of 0.05.

The requirement for organ support in these patients is significant and ventilator-free days, vasoactive-support-free days, and renal replacement-free days are all potentially clinically relevant secondary end points that could be evaluated in phase 2 studies to prepare for a large phase 3 study of permissive versus conventional fever management in ICU.

Strengths and limitations of the study

Our study has several strengths, including prospective identification of eligible patients, standardised data collection methods, robust and verifiable outcomes, and capture of 100% of available eligible patients. We have described important elements of fever and fever management in the intensive care unit and have identified a cohort of patients who are easily identifiable and have significant infection-related morbidity and mortality.

The major limitation of our study is the small sample size; however, despite this, we were able collect data on 244 ICU-days, for which we collected a minimum of four temperature points per day, giving us almost 1000 data points related to patient temperature and a detailed picture of the fever burden in our patients.

Conclusions

We have described the typical time course of fever in an easily identified cohort of patients with sepsis. We have also demonstrated that this cohort has significant ICU support requirements, a mortality rate of 15.7% and 28-day ICU-free survival of 16 (SD, 9.2) days. We have also identified steroid therapy and external cooling as significant potential confounding factors to consider in trials of antipyretic therapy among critically ill patients.

Acknowledgements

We acknowledge the research coordinators who helped with data collection (Leah Peck, Helen Young — Austin Hospital; Lynn Andrews, Di Mackle — Wellington Regional Hospital; Jennene Miller — St George Hospital).

Author details

Paul Young, Intensivist[1]
Manoj Saxena, Intensivist[2]
Glenn M Eastwood, Intensive Care Unit Research Manager[3]
Rinaldo Bellomo, Director of Intensive Care Research[3]
Richard Beasley, Professor[4]

1 Intensive Care Unit, Wellington Regional Hospital, Wellington, New Zealand.
2 Department of Intensive Care Medicine, St George Hospital, Sydney, NSW, Australia.
3 Austin Hospital, Melbourne, VIC, Australia.
4 Medical Research Institute of New Zealand, Wellington, New Zealand.

Correspondence: Paul.Young@ccdhb.org.nz

References

1 Nyström PO. The systemic inflammatory response syndrome: definitions and aetiology. *J Antimicrob Chemother* 1998; 41 Suppl A: 1-7.

2 Kluger MJ. Fever: its biology, evolution and function. Princeton, NJ: Princeton University Press, 1979.

3 Dulhunty JM, Lipman, J Finfer S. Does severe non-infectious SIRS differ from severe sepsis? *Intensive Care Med* 2008; 34: 1654-61.

4 Diringer MN, Reaven NL, Funk SE, Uman GC. Elevated body temperature independently contributes to increased length of stay in neurologic intensive care unit patients. *Crit Care Med* 2004; 32: 1489-95.

5 Kiekkas P, Velissaris D, Karanikolas M, et al. Peak body temperature predicts mortality in critically ill patients without cerebral damage. *Heart Lung* 2010; 39: 208-16.

6 Laupland KB, Shahpori R, Kirkpatrick AW, et al. Occurrence and outcome of fever in critically ill adults. *Crit Care Med* 2008; 36: 1531-5.

7 Mackowiak PA. Fever: blessing or curse? A unifying hypothesis. *Ann Intern Med* 1994; 120: 1037-40.

8 Schulman CI, Namias N, Doherty J, et al. The effect of antipyretic therapy upon outcomes in critically ill patients: a randomized, prospective study. *Surg Infect (Larchmt)* 2005; 6: 369-75.

9 Haupt MT, Jastremski MS, Clemmer TP, et al. Effect of ibuprofen in patients with severe sepsis: a randomized, double-blind, multicenter study. The Ibuprofen Study Group. *Crit Care Med* 1991; 19: 1339-47.

10 Bernard G, Wheeler A, Russell J, et al. The effects of ibuprofen on the physiology and survival of patients with sepsis. *N Engl J Med* 1997; 336: 912-9.

11 Doran T, de Angelis C, Baugardner R, Mellits E. Acetaminophen: more harm than good for chickenpox? *J Pediatr* 1989; 114: 1045-8.

12 Brandts CH, Ndjave M, Graninger W, Kremsner PG. Effect of paracetamol on parasite clearance time in plasmodium falciparum malaria. *Lancet* 1997; 350: 704-9.

13 Stanley E, Jackson G, Panusarn C, et al. Increased virus shedding with aspirin treatment of rhinovirus infection. *JAMA* 1975; 231: 1248-51.

14 Levy MM, Fink MP, Marshall JC, et al; SCCM/ESICM/ACCP/ATS/SIS. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003; 31: 1250-6.

15 Moran JL, Peter JV, Solomon PJ, et al. Tympanic temperature measurements: are they reliable in the critically ill? A clinical study of measures of agreement. *Crit Care Med* 2007; 35: 155-64.

16 Circiumaru B, Baldock G, Cohen J. A prospective study of fever in the intensive care unit. *Intensive Care Med* 1999; 25: 668-73.

17 Peres Bota D, Lopes Ferreira F, Mélot C, Vincent JL. Body temperature alterations in the critically ill. *Intensive Care Med* 2004; 30: 811-6.

18 Barie PS, Hydo LJ, Eachempati SR. Causes and consequences of fever complicating critical surgical illness. *Surg Infect (Larchmt)* 2004; 5: 145-59. ❑