The HEAT trial: a protocol for a multicentre randomised placebo-controlled trial of IV paracetamol in ICU patients with fever and infection

Paul J Young, Manoj K Saxena, Rinaldo Bellomo, Ross C Freebairn, Naomi E Hammond, Frank MP van Haren, Seton J Henderson, Colin J McArthur, Shay P McGuinness, Diane Mackle, John A Myburgh, Mark Weatherall, Steve AR Webb and Richard W Beasley and the ANZICS Clinical Trials Group

ABSTRACT

Background and objective: Paracetamol is commonly administered to febrile critically ill patients with infection. However, there is limited information on the efficacy and safety of using paracetamol in this setting. We describe the study protocol for a Phase IIb multicentre randomised controlled trial (the Permissive Hyperthermia Through Avoidance of Paracetamol in Known or Suspected Infection in ICU [HEAT] trial) comparing intravenous paracetamol to placebo in the treatment of fever in critically ill adults with known or suspected infection.

Design and setting: A pilot study followed by the main trial from November 2012. 700 patients will be recruited for concealed, random, parallel assignment of either 1 g of intravenous paracetamol or placebo (100 mL of 5% dextrose) 6-hourly to treat fever while they remain on antimicrobial therapy in the intensive care unit. The primary end point will be ICU support-free survival at 28 days after randomisation. Secondary end points will include peak daily and mean daily body temperatures, prevalence of liver dysfunction requiring cessation of study treatment, degree of renal injury (based on delta creatinine), other organ failures, and Day 28 and Day 90 mortality. All analyses will be conducted on an intention-to-treat basis.

Results and conclusions: The HEAT trial should generate results that will inform and influence the prescribing of paracetamol. It will also determine if a large-scale Phase III trial of paracetamol is required in this patient group and whether such a trial is feasible.

Trial registration: Australian and New Zealand Clinical Trials Registry (ACTRN12612000513819).

Crit Care Resusc 2012; 14: 290–296

Paracetamol is one of the world's most widely used medicines. Its use in the intensive care setting has been reviewed recently.[1] While the stated aim of administration of paracetamol in septic patients is more commonly analgesia than antipyresis, patients with fever are seven times (95% CI, 2–25; $P = 0.004$) more likely to receive paracetamol than patients without fever.[2] In part, the widespread use of paracetamol among critically ill patients with fever may be nurse driven rather than physician driven, as the threshold for administration of paracetamol for fever in the intensive care unit appears to be lower for nurses than it is for doctors.[3] Irrespective of the reason, in Australian and New Zealand ICUs at least, most patients with fever and suspected infection receive paracetamol.[4]

Despite prevailing practice, there is a sound rationale for the hypothesis that administration of paracetamol to patients with infection is harmful.[5] The development of fever in response to an infection is a preserved physiological response across the animal kingdom from reptiles through to humans.[6] As such, it is presumed that fever confers an adaptive advantage.[6,7] Furthermore, experimental studies in a range of different mammals have shown that suppression of the febrile response to infection with antipyretic therapy increased the risk of mortality in various viral,[8] bacterial,[9] and parasitic infections.[10] Antipyretic therapy increased the risk of mortality by about one-third in animal models of influenza infection[11] and was associated with a twofold increase in mortality in animal models of *Streptococcus pneumoniae* infection.[12] Studies in humans have shown that treatment with paracetamol increased the duration of illness in chickenpox,[13] the duration of parasitaemia in malaria,[14] and rhinovirus shedding in the common cold.[15] Data from a retrospective study of 636 051 patients showed that although the presence of fever in the first 24 hours after ICU admission was associated with an increased risk of mortality in patients without infection, it was associated with a decreased risk of mortality in those with an infection.[16]

Paradoxically, a recent trial of physical cooling to control fever in ventilated adults with septic shock suggested that physical cooling may reduce early mortality in this setting.[17] While it is possible that control of fever in the setting of infection may have beneficial effects related to a reduction in metabolic rate,[18] such as decreased myocardial oxygen demand[19] and decreased minute ventilation,[20] observational data raise the possibility that physical cool-

Table 1. Primary and secondary study end points and proposed subgroup analyses for the HEAT* trial

Primary end point
"Alive ICU-free days" to study Day 28
Secondary end points
28-day mortality
90-day mortality
Intensive care unit length of stay (censored at Day 90)
Hospital length of stay (censored at Day 90)
Mean and maximum axillary temperature
Proportion of patients who stop study treatment due to the development of liver dysfunction†
C-reactive protein levels measured on Days 1, 3, 5 and 7
Proportion of patients with creatine kinase > 5000 units measured on Days 1, 3, 5 and 7
Degree of acute kidney injury (based on delta creatinine‡)
ICU support-free survival to Day 28
Hospital-free days to Day 28
Mechanical ventilation-free days to Day 28
Inotrope- or vasopressor-free days to Day 28
Predefined subgroups for primary and secondary outcome analyses
Patients with severe hyperthermia at randomisation (temperature ⩾ 39°C)
Patients with ICU-acquired versus community-acquired versus other hospital-acquired infection
Patients with septic shock
Patients taking aspirin at baseline versus patients not taking aspirin at baseline

* Permissive Hyperthermia Through Avoidance of Paracetamol in Known or Suspected Infection in ICU. † Defined as an aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level elevated to five times the upper limit of normal or a bilirubin level of twice the upper limit of normal. ‡ Difference between the prerandomisation creatinine level and the peak creatinine level measured during the first 7 days in ICU.

Table 2. Inclusion criteria for the HEAT* trial

Patients must be in the intensive care unit and must fulfil all of the following criteria:
Age ⩾ 16 years
Standardised body temperature ⩾ 38.0°C within the previous 12 hours
Receiving antimicrobial therapy for a known or suspected infection (this does *not* include patients who are receiving postoperative antibiotics for the purposes of prophylaxis rather than treatment)

* Permissive Hyperthermia Through Avoidance of Paracetamol in Known or Suspected Infection in ICU.

ing reduces mortality risk while antipyretic therapy increases it.[21]

At present, it is unknown how using paracetamol to treat fever in patients with sepsis affects patient-centred outcomes.[22] Despite paracetamol being one of the most commonly administered medications in the ICU, no placebo-controlled trial of paracetamol use in febrile ICU patients with known or suspected infection has been performed to establish its safety or its capacity to improve patient-centred end points. The only previous study investigating the effect of paracetamol on infective complications in ICU patients compared an aggressive antipyretic strategy with a permissive one and was stopped by the data safety and monitoring board after an interim analysis identified a trend towards increased risk of infection and death in patients being cooled more aggressively.[23]

We describe the study protocol for the Permissive Hyperthermia Through Avoidance of Paracetamol in Known or Suspected Infection in ICU trial (the HEAT trial).

Study design and outcomes

The HEAT trial is a prospective, Phase IIb, multicentre, concealed, parallel-groups, randomised controlled trial comparing the administration of paracetamol for antipyresis with a permissive temperature strategy in critically ill patients with known or suspected infection. The trial has a simple, pragmatic design with allocation concealment, blinding, and minimisation of ascertainment bias and loss to follow-up, and will be analysed on an intention-to-treat basis. It aims to recruit 700 adult patients from 21 ICUs throughout Australia and New Zealand in an anticipated recruitment period of 24 months. Adult patients with fever and known or suspected infection who fulfil other eligibility criteria will be allocated at random to receive 1 g of intravenous paracetamol or placebo (100 mL of 5% dextrose) as outlined in detail in the section on study treatments. As a Phase IIb trial, the principal objective of the study is to determine whether to proceed to a Phase III trial with a patient-centred primary outcome, such as 90-day mortality.

Table 1 summarises the primary and secondary end points as well as the predefined subgroup analyses. The primary end point will be "alive ICU-free days" to Day 28 (the day of randomisation is defined as Day 0). The number of ICU-free days will be calculated as 28 minus the number of days in ICU (excluding days of ICU readmission). All patients who die before the Day 90 follow-up will be counted as having zero ICU-free days on the basis that patients who die should be assigned the worst possible outcome.

Secondary end points will include death from all causes at Day 28 and Day 90, and ICU and hospital length of stay

Table 3. Exclusion criteria for the HEAT* trial

Patients who fulfil any of the following criteria will be excluded:
AST or ALT greater than five times the upper limit of normal, or bilirubin greater than twice the upper limit of normal, or any other contraindication to 4 g paracetamol per day
A requirement for ongoing use of non-steroidal anti-inflammatory drugs (in excess of low-dose aspirin)
Admission to the intensive care unit following a cardiac arrest which is currently being treated with therapeutic hypothermia or where a need for therapeutic hypothermia is anticipated
Evidence of acute brain injury during the current hospital admission (defined as any acute traumatic brain injury, subarachnoid haemorrhage, acute ischaemic stroke, acute intracerebral haemorrhage, or acute intracranial infection)
Hyperthermic syndromes including heat stroke; current biochemical evidence of thyrotoxicosis (thyroid function tests are not required before recruitment into the trial unless clinically indicated); malignant hyperthermia, neuroleptic malignant syndrome, or other drug-induced hyperthermia
Limitation of therapy order or aggressive treatment is deemed unsuitable
Moribund; death is perceived to be imminent (within 24 hours)
Rhabdomyolysis deemed by the treating clinician to be clinically significant
Transferred from another ICU where they spent > 12 hours and fulfilled all inclusion criteria while there
Pregnant
Previously enrolled in the HEAT trial or previously eligible for enrolment during the current ICU admission but not enrolled in the study (ie, patients who were not enrolled within 12 hours of onset of fever in association with satisfying other eligibility criteria may not be enrolled at a later point in the ICU admission)

AST = aspartate aminotransferase. ALT = alanine aminotransferase.
* Permissive Hyperthermia Through Avoidance of Paracetamol in Known or Suspected Infection in ICU.

(censored at day 90). Additionally, hospital-free days, mechanical ventilation-free days, inotrope- or vasopressor-free days, and ICU support-free days will all be assessed at Day 28. ICU-support is defined as any of the following provided in ICU: any form of positive pressure ventilation, including both invasive and non-invasive ventilation; any inotropic or vasopressor drug administered by infusion; any form of continuous renal replacement therapy (including sustained low-efficiency dialysis). In the case of ICU support-free days, a patient will need to be free of any ICU support for an entire calendar day and will need to remain free from such supports until the time of physical discharge from the ICU to be deemed support-free, as this is of relevance to the readiness for ICU discharge and has resource implications. For the other "free-day" measures, the number of individual hours of particular supports will be used to calculate the number of support-free days to Day 28. All patients who die during study follow-up will be assigned zero free days for all free-day outcome measures.

Physiological secondary outcome variables include mean and peak daily body temperature. All temperatures measured in the study will be measured using Protec BX/144 digital thermometers (Protec Solutions) and will be measured via the axillary route. The axillary route has been chosen because it is the most common route of temperature measurement in patients without brain injury in Australian and Zealand ICUs.[24] The use of a standardised route and device will make temperature measurements comparable across study centres.

Other secondary outcome variables include renal failure, based on delta creatinine (the difference between the pre-randomisation creatinine level and the peak creatinine level measured during the first 7 days in ICU), and the proportion of patients who stop study treatment due to development of liver dysfunction, defined as an aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level elevated to five times the upper limit of normal or a bilirubin level of twice the upper limit of normal. C-reactive protein levels and the proportion of patients with creatine kinase levels of greater than 5000 units will also be compared as secondary outcome variables.

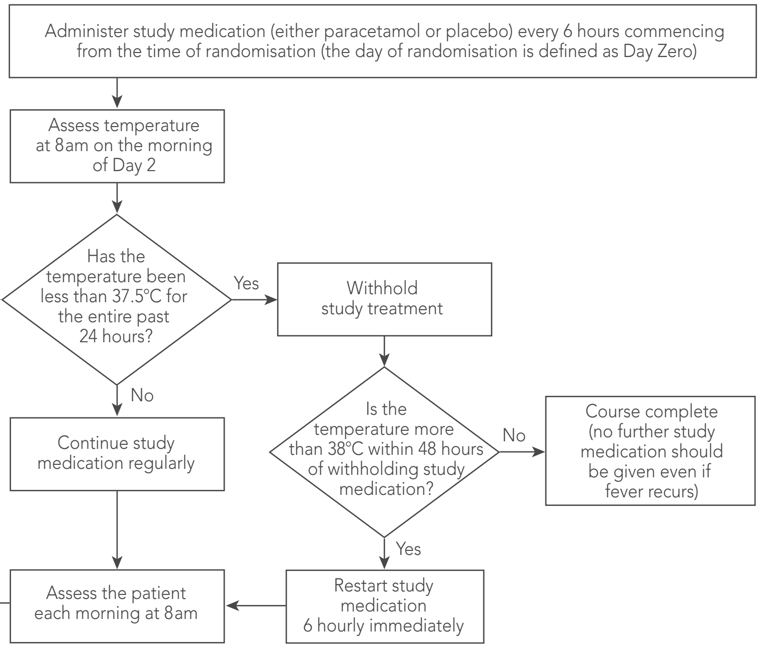
Participants

Adult ICU patients will be eligible to be included in this study if their body temperature measured via the axillary route using the prescribed thermometer is at least 38.0°C within the previous 12 hours and they are receiving antimicrobial therapy for a known or suspected infection. Major exclusion criteria include contraindications to paracetamol, the presence of an acute brain injury (as there is an established association between the presence of fever and worsened outcome in patients with brain injury[25]), or a diagnosis of a hyperthermic syndrome. Tables 2 and 3 list the full inclusion and exclusion criteria.

Study treatments

After randomisation, patients will receive either a placebo (100 mL of 5% dextrose) or 1 g of intravenous paracetamol every 6 hours until the earliest of the following occurs: development of a contraindication to paracetamol or permissive hyperthermia, cessation of antimicrobial therapy, discharge from ICU, Day 28 (672 hours after randomisation), or the resolution of fever and completion of study treatment (Figure 1). Provided that the patient remains in the ICU on antimicrobial therapy and does not develop a contraindication to study treatment, they will receive paracetamol or placebo until at least the morning of Day 2. On

Figure 1. Flow diagram illustrating the process for determining resolution of fever and duration of study therapy for the HEAT* trial



*If antimicrobial therapy is stopped, or the patient is discharged from the intensive care unit, or the patient develops a contraindication to paracetamol or permissive hyperthermia, the course of study medication is deemed complete (irrespective of when this occurs). If the patient reaches Day 28 (672 hours) after randomisation, the study medication course is complete. * Permissive Hyperthermia Through Avoidance of Paracetamol in Known or Suspected Infection in ICU.*

Figure 2. Study medications (paracetamol and placebo), concealed by using identical bottles and labels except for an identifying numerical code

the morning of Day 2, the patient will be assessed. If the patient has not had a temperature of < 37.5°C for the previous 24 hours, they will continue to receive paracetamol or placebo 6 hourly and will be assessed on each subsequent morning to determine if they have had a temperature of < 37.5°C for the entire previous 24 hours. If, at the time of assessment, the patient has had a temperature of < 37.5°C for the entire past 24 hours, further study treatment will be withheld. If the patient does not develop a fever of ⩾ 38°C within 48 hours from the time study treatment has been withheld, they will be deemed to have completed the course of study medication. If, on the other hand, the patient does develop a temperature of ⩾ 38°C within 48 hours of study treatment being withheld, the study medication will be restarted and, thereafter, the patient will be assessed each morning to determine whether their temperature has been < 37.5°C for a period of 24 hours. When this occurs, the medication will again be withheld until a temperature of ⩾ 38°C develops. If such a temperature does not develop within 48 hours, the course of medication will be deemed complete. While the patient is receiving study medication, use of open-label paracetamol is not permitted. Alternative analgesics will be used. Once the patient has completed the course of study medication, they may receive open-label paracetamol at the discretion of the treating clinician. Rescue physical cooling measures are allowed at the discretion of the treating clinician when the body temperature exceeds 39.5°C.

Medication will be allocated in packs that each hold 12 bottles containing the same treatment. Paracetamol and placebo bottles will be identical in appearance (Figure 2) so that study treatments are concealed. Each pack will be identified by a unique five-digit number, and each bottle within the pack will be labelled with the same five-digit number. In addition, each bottle will have a suffix from one to 12 corresponding to the bottle number within the treatment pack. The initial and subsequent allocation of packs will be determined by a web-based randomisation system. The information regarding what treatment each box number corresponds to will be maintained by the information technology employees responsible for the design of the online randomisation system and will also be maintained in a secure location at the coordinating centre by the information technology manager. If, for reasons of patient safety, unblinding of study treatment is required, procedures will be in place for this to occur.

Table 4. Data to be collected in the HEAT* trial

Baseline information
Age, sex and ethnicity
Baseline APACHE II score
Where participants were admitted to the intensive care unit from (ICU admission source)
ICU admission diagnosis
Whether the patient has severe sepsis and/or septic shock
Presumed or known site of infection, type of infecting agent, any positive blood cultures
Baseline laboratory values (creatinine, bilirubin, PT and AST level)
Organ supports (inotropic or vasopressor support, invasive ventilation, non-invasive ventilation, renal replacement therapy, other extracorporeal support)
Whether the patient is receiving steroids
Comorbidities (ischaemic heart disease, congestive heart failure, chronic pulmonary disease [requiring long-term steroids or bronchodilators], end-stage renal failure [on long-term dialysis], neurological dysfunction severely affecting ambulation or day-to-day functioning, cirrhosis, diabetes, cancer, HIV)
Daily data
Body temperature (6 hourly until Day 7)
Maximum body temperature (daily until Day 28)
Mean arterial pressure and heart rate (6 hourly until Day 3; daily for Days 4–7)
Minute ventilation (6 hourly until Day 3; daily for Days 4–7)
C-reactive protein and creatine kinase (Days 1, 3, 5, 7)
Creatinine, bilirubin, PT and AST or ALT level daily until day 7
Renal replacement therapy use (daily)
Potential confounding factors including use of steroids, aspirin, antimicrobials, extracorporeal circuits, open-label paracetamol, NSAIDS, and physical cooling (daily)
Day 28 and Day 90 follow-up
Alive ICU-free days to Day 28 (primary end point)
ICU support-free days to Day 28
Hospital-free days to Day 28
Mechanical ventilation-free days to Day 28
Inotrope- or vasopressor-free days to Day 28
Vital status at Day 28 and Day 90, date of death and proximate cause of death
Adverse reactions and protocol deviations
Description, timing and resolution of any adverse events
Nature, timing and corrective actions taken in response to identified protocol violations

PT = prothrombin time. ASP = aspartate aminotransferase. ALT = alanine aminotransferase. NSAIDS = non-steroidal anti-inflammatory drugs.
* Permissive Hyperthermia Through Avoidance of Paracetamol in Known or Suspected Infection in ICU.

Data collection and management

Data collection will be conducted by trained staff at each study centre and will be entered into a web-based case report form (see Table 4 for details of the data to be collected). Information collected will include eligibility criteria at randomisation, baseline patient demographics and medical information to ensure balance of randomisation and to allow categorisation into subgroups of interest. Medical information collected at baseline will include ICU admission source and diagnosis, Acute Physiology and Chronic Health Evaluation (APACHE) II score,[26] and underlying comorbid conditions. Microbiological data being collected include the site of infection, the infecting organism (where identified), and whether the patient is bacteraemic.

While the patient is in ICU, the mean and peak body temperature will be measured to demonstrate the antipyretic efficacy of paracetamol in critically patients with known or suspected infection. The highest measured daily temperature will be recorded daily until Day 28. Additionally, temperature data will be collected 6 hourly for the first 7 days. Data on baseline organ support and function will also be collected. Daily organ support requirements will be collected to allow calculation of inotrope- or vasopressor-free days, mechanical ventilation support-free days and ICU support-free days at Day 28. Average daily mean arterial pressure, heart rate and minute ventilation (for patients who are mechanically ventilated) will be measured over the first 72 hours. C-reactive protein and creatine kinase will be measured at baseline and on Days 1, 3, 5, and 7, while creatinine, bilirubin, prothrombin time (PT) and AST or ALT (depending on local preference) will be measured daily until Day 7. Vital status (alive or dead) will be determined at Day 28 and Day 90.

Data on potential confounding factors, including the use of open-label paracetamol, physical cooling measures, non-steroidal anti-inflammatory drugs, low-dose aspirin, steroids, and antimicrobials, will be collected daily for the first 28 days.

The web-based data-management system allows for automatic validation and ad hoc consistency checks by study monitors. This will ensure the accuracy and completeness of data. An online screening log will record the details of all patients who are eligible but not enrolled in the study, as well as the number of excluded patients and the reason for exclusion.

Study medication and logistics

All blinded study treatment will be manufactured according to good manufacturing practice requirements for investigational medicinal products and will be produced and distributed by Biomedical Services New Zealand Limited. Management of the study medication will be coordinated using the study website. This system tracks which treatment packs have been distributed to each participating centre and the allocation of these treatment packs to patients who are allocated to a study group. The computerised tracking of treatment packs allows the coordinating centre to monitor supplies of study treatment at each study site and ensure amounts of stock delivered to individual sites are appropriate.

Ethical issues

It is anticipated that most patients in this trial will be critically unwell and unable to give consent at the time that they are enrolled into the trial. Wherever practical, families and/or legal representatives will be informed and given the opportunity to express their views before the patient is enrolled. However, in situations where it is approved by the local human research ethics committee, if it is not possible to obtain informed consent from the patient or a substitute person before enrolment, delayed consent will be obtained as soon as is reasonably possible. Irrespective of the consent of surrogates, the patients themselves will be given the opportunity to provide informed consent as soon as it is possible for them to do so. Where local ethics committees do not have provision for delayed consent, consent will be obtained only before recruitment.

Sample size and power

A prospective cohort study of ICU patients with fever and known or suspected infection[2] found the mean (SD) of the nominated primary outcome variable "ICU-free survival to Day 28" was 16.0 (9.2) days. In this cohort study there was widespread use of paracetamol. Our nominated sample size of 700 patients (350 per study group) can detect a 2-day difference at 80% power, with a type I error rate of 5%, and allows for a 5% dropout rate. In a secondary power calculation, the sample size provides 80% power, with a type I error rate of 5%, to detect a reduction in 28-day mortality from the mortality rate observed in the cohort study, 16%,[2] to 9%. Although this is a relatively large difference in mortality (relative risk, 0.56) the only previous randomised trial of paracetamol in critically ill febrile patients showed a reduction in mortality from 16% to 3% ($P = 0.06$) with a less aggressive cooling strategy.[23]

Statistical analysis

A report outlining the planned statistical methodology in detail will be published before the completion of participant recruitment.

Data and safety monitoring

The Data Monitoring Committee (DMC) will be chaired by Dr Geoffrey Robinson. Other members are Professor Brian Anderson and Professor Mark Weatherall. A detailed set of guidelines for the conduct of the DMC have been produced and agreed to by the DMC and the management committee. The DMC will undertake general safety monitoring and make recommendations to the management committee on prespecified interim analyses. Additionally, the DMC will review data provided by the management committee in relation to informed consent, failures to complete assigned treatment, and any other protocol deviations. The DMC will make recommendations on these data where they feel that these issues may threaten the appropriate ethical conduct of the trial or the scientific validity of the trial results.

The DMC will review summaries of adverse events provided by the management committee. However, given the potential for type 1 error that exists in examining multiple adverse events and the considerable existing knowledge base about the safety of paracetamol and its common use in routine practice,[1] it is not anticipated that the DMC will make recommendations to stop the clinical trial early on the basis of reported adverse events suspected to be due to paracetamol unless circumstances are exceptional.

Funding and support

The HEAT trial is endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group, and is funded by a grant from the Health Research Council of New Zealand. All analyses and reports will be conducted independently of the funder. This study is supported by The George Institute for Global Health (Sydney, Australia), and the Medical Research Institute of New Zealand (Wellington, New Zealand).

Summary

The HEAT trial is a placebo-controlled study of paracetamol use in ICU patients with infection and fever. There is a sound scientific basis for the hypothesis that fever is a natural host defence against a broad range of infectious diseases. Despite this, antipyretics in the form of paracetamol are commonly administered to ICU patients with infections. This study is part of a research program that will determine whether administration of paracetamol to critically ill patients with fever and known or suspected infection is beneficial or harmful.

Competing interests

None declared.

Author details

Paul J Young, Intensive Care Specialist[1,2]
Manoj K Saxena, Intensive Care Specialist[3,4]
Rinaldo Bellomo, Director of Intensive Care Research[5]
Ross C Freebairn, Intensive Care Specialist[6]
Naomi E Hammond, Research Fellow[3]
Frank MP van Haren, Intensive Care Specialist[7]
Seton J Henderson, Intensive Care Specialist[8]
Colin J McArthur, Director[9]
Shay P McGuinness, Intensive Care Specialist[10]
Diane Mackle, Research Co-ordinator[1]
John A Myburgh, Director[3]
Mark Weatherall, Professor of Medicine[11]
Steve AR Webb, Intensive Care Specialist[12]
Richard W Beasley, Director[2]
and the ANZICS Clinical Trials Group

1 Intensive Care Unit, Wellington Regional Hospital, Wellington, New Zealand.
2 Medical Research Institute of New Zealand, Wellington, New Zealand.
3 Critical Care Division, The George Institute for Global Health, Sydney, NSW, Australia.
4 Intensive Care Unit, St George Hospital, Sydney, NSW, Australia.
5 Intensive Care Unit, Austin Hospital, Melbourne, VIC, Australia.
6 Intensive Care Unit, Hawkes Bay Hospital, Hastings, New Zealand.
7 Intensive Care Unit, Canberra Hospital, Canberra, ACT, Australia.
8 Intensive Care Unit, Christchurch Hospital, Christchurch, New Zealand.
9 Department of Critical Care Medicine, Auckland City Hospital, Auckland, New Zealand.
10 Cardiovascular Intensive Care Unit, Auckland City Hospital, Auckland, New Zealand.
11 Wellington School of Medicine, University of Otago, Wellington, New Zealand.
12 Intensive Care Unit, Royal Perth Hospital, Perth, WA, Australia.

Correspondence: paul.young@ccdhb.org.nz

References

1 Jefferies S, Saxena M, Young P. Paracetamol in critical illness: a review. *Crit Care Resusc* 2012; 14: 74-80.
2 Selladurai S, Eastwood GM, Bailey M, Bellomo R. Paracetamol therapy for septic critically ill patients: a retrospective observational study. *Crit Care Resusc* 2011; 13: 181-6.
3 Saxena MK, Hammond NE, Taylor C, et al. A survey of fever management for febrile intensive care patients without neurological injury. *Crit Care Resusc* 2011; 13: 238-43.
4 Young P, Saxena M, Eastwood GM, et al. Fever and fever management among intensive care patients with known or suspected infection: a multicentre prospective cohort study. *Crit Care Resusc* 2011; 13: 97-102.
5 Young PJ, Saxena MK, Beasley RW. Fever and antipyresis in infection. *Med J Aust* 2011; 195: 458-9.
6 Mackowiak PA. Fever: blessing or curse? A unifying hypothesis. *Ann Intern Med* 1994; 120: 1037-40.
7 Kluger MJ, Kozak W, Conn CA, et al. The adaptive value of fever. *Infect Dis Clin North Am* 1996; 10: 1-20.
8 Kurosawa S, Kobune F, Okuyama K, Sugiura A. Effects of antipyretics in rinderpest virus infection in rabbits. *J Infect Dis* 1987; 155: 991-7.
9 Vaughn LK, Veale WL, Cooper KE. Antipyresis: its effect on mortality rate of bacterially infected rabbits. *Brain Res Bull* 1980; 5: 69-73.
10 van der Zee CE, van Dam RH, Dwinger RH, et al. Flurbiprofen and immunosuppression of *Trypanosoma brucei* infection in the goat. *Vet Immunol Immunopathol* 1985; 8: 341-50.
11 Eyers S, Weatherall M, Shirtcliffe P, et al. The effect on mortality of antipyretics in the treatment of influenza infection: systematic review and meta-analysis. *J R Soc Med* 2010; 103: 403-11.
12 Jefferies S, Weatherall M, Young P, et al. Systematic review and meta-analysis of the effects of antipyretic medications on mortality in *Streptococcus pneumoniae* infections. *Postgrad Med J* 2012; 88: 21-7.
13 Doran TF, De Angelis C, Baumgardner RA, Mellits ED. Acetaminophen: more harm than good for chickenpox? *J Pediatr* 1989; 114: 1045-8.
14 Brandts CH, Ndjave M, Graninger W, Kremsner PG. Effect of paracetamol on parasite clearance time in *Plasmodium falciparum* malaria. *Lancet* 1997; 350: 704-9.
15 Graham NM, Burrell CJ, Douglas RM, et al. Adverse effects of aspirin, acetaminophen, and ibuprofen on immune function, viral shedding, and clinical status in rhinovirus-infected volunteers. *J Infect Dis* 1990; 162: 1277-82.
16 Young PJ, Saxena M, Beasley R, et al. Early peak temperature and mortality in critically ill patients with or without infection. *Intensive Care Med* 2012; 38: 437-44.
17 Schortgen F, Clabault K, Katsahian S, et al. Fever control using external cooling in septic shock: a randomized controlled trial. *Am J Respir Crit Care Med* 2012; 185: 1088-95.
18 Horvath SM, Spurr GB, Hutt BK, Hamilton LH. Metabolic cost of shivering. *J Appl Physiol* 1956; 8: 595-602.
19 Greisman SE. Cardiovascular alterations during fever. In: Mackowiak PA, editor. Fever: basic mechanisms and management. 2nd ed. Philadelphia: Lippincott-Raven, 1997: 143-65.
20 Bernard GR, Wheeler AP, Russell JA, et al. The effects of ibuprofen on the physiology and survival of patients with sepsis. The Ibuprofen in Sepsis Study Group. *N Engl J Med* 1997; 336: 912-8.
21 Lee BH, Inui D, Suh GY, et al. Association of body temperature and antipyretic treatments with mortality of critically ill patients with and without sepsis: multi-centered prospective observational study. *Crit Care* 2012; 16: R33.
22 Jefferies S, Weatherall M, Young P, et al. The effect of antipyretic medications on mortality in critically ill patients with infection: a systematic review and meta-analysis. *Crit Care Resusc* 2011; 13: 125-31.
23 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.
24 Hammond NE, Saxena M, Young P, et al. Temperature management for patients without brain injury in Australian and New Zealand ICUs: a point prevalence study [poster presentation]. *Crit Care* 2012; 16 Suppl 1: P58.
25 Greer DM, Funk SE, Reaven NL, et al. Impact of fever on outcome in patients with stroke and neurologic injury: a comprehensive meta-analysis. *Stroke* 2008; 39: 3029-35.
26 Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; 13: 818-29. ❑