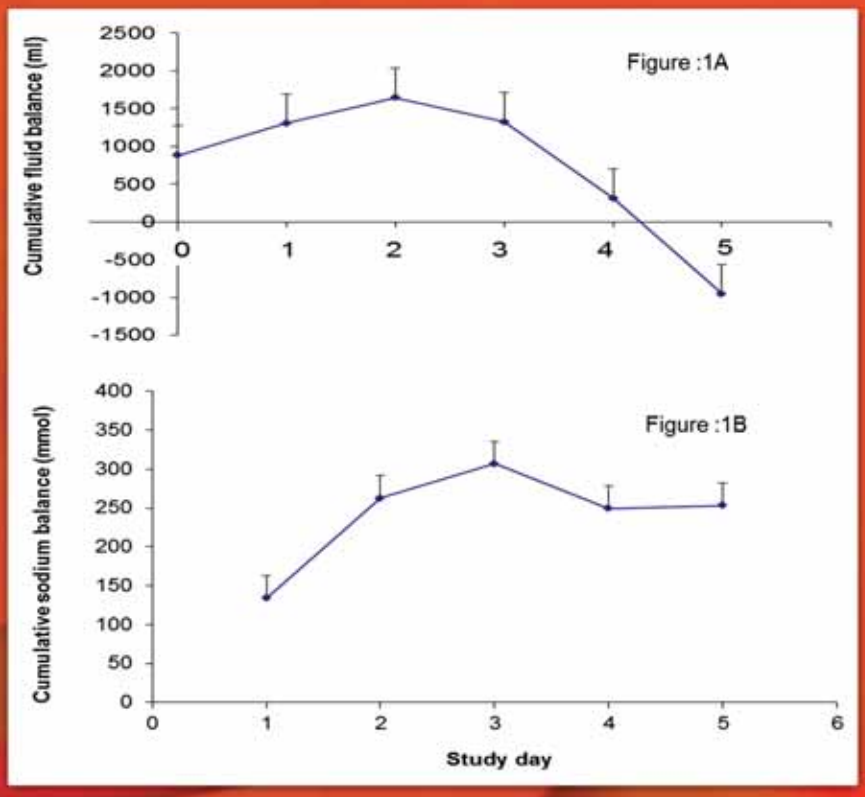
Critical Care and Resuscitation
Volume 15 Number 4 December 2013



Journal of the College of Intensive Care Medicine of Australia and New Zealand

PRINT POST APPROVED
PP:255003/07984

Take Control of Temperature Management

ZOLL's Intravascular Temperature Management (IVTM™) system rapidly reaches target temperature and precisely maintains it, providing the control needed to treat critically ill patients. There's no need to worry about changing cooling pads or ice packs, just set the desired temperature and the console does the rest.

IVTM is fast, accurate, and convenient:

- Rapidly, precisely, and automatically manage patient temperature to target
- Focus on treating the patient rather than the patient's temperature
- Reduce nursing time and improve patient access
- Safe and effective, complication rates are comparable to those seen with surface methods.[1,2]

To learn more, visit zoll.com.au or phone us on 1 800 605 555

[1] Patel N, et al. *Conn Med.* 2013 Jan;*77*(1):35–41.
[2] Diringer MN, et al. *Crit Care Med.* 2004;(32)2:559–564.

ZOLL®

CriticalCare and Resuscitation

Critical Care and Resuscitation submission goes electronic

The College of Intensive Care Medicine is pleased to announce that we have partnered with Rose Technology (ICON) to launch an online submission software for the *Critical Care and Resuscitation* journal.

This enables all authors submitting an article to the journal to logon and easily check the status of their submission at any stage, make changes and update information. Other useful features include email alerts sent to authors as the status of articles change, and the ability to access the site from any mobile device.

This new software will lead to a more efficient process when submitting articles to the journal. Articles can be submitted in 3 steps: provide submission details including an abstract; register authors; and upload the manuscript and associated diagrams.

This new site and user instructions will be accessible via a link on the resources section of College of Intensive Care Medicine website, www.cicm.org.au, as of **Monday 2 December 2013**.

College of Intensive Care Medicine of Australia and New Zealand

CICM CALENDAR OF EVENTS 2014

MARCH

14th	**Communications Course – Adelaide**
26th & 27th	**CICM Management Skills – Melbourne**

JUNE

12th	**ICU Update – Brisbane**
13th to 15th	**2014 Annual Scientific Meeting – Brisbane** Registrations open January 2014, visit the ASM Website for full program details. http://www.cicm-asm.org.au/

JULY

11th	**Communications Course – Sydney**

AUGUST

	New Fellows Conference

SEPTEMBER

4th to 5th	**Education Conference**

OCTOBER

3rd	**Communications Course – Perth**

NOVEMBER

18th to 19th	**Paediatrics Basic Course – Melbourne**

For further information on all courses and events, visit the cicm website http://www.cicm.org.au/courses or contact **stephg@cicm.org.au**

Critical Care and Resuscitation

EDITORIALS

ORIGINAL ARTICLES

BRIEF COMMUNICATION

LETTER

FRI 13TH JUNE > SUN 15TH JUNE

2014 CICM ASM BRISBANE

INTENSIVE CARE: IT'S A RISKY BUSINESS

Making decisions when there are no right answers

The conference theme "Intensive Care Medicine – it's a RISKY BUSINESS" will identify decision points in intensive care clinical practice at which there is no risk-free solution, outline how the various risks of a complex ICU can be mitigated and try to build consensus on how to practice in a risk-averse but overambitious healthcare system.

WHATS NEW IN 2014

- Adult and Paediatric concurrent sessions
- Paediatric simulation sessions
- Trainee sessions

IMPORTANT DATES

Abstract Submissions – Are Now Open

Abstract submissions can be submitted in the following categories

- Felicity Hawker Presentations
- Free Paper Presentations
- 5x5 Poster Session (Accepted posters will be presented as 5 slides in 5 minutes)

Early Bird Registrations Open – January 14th 2014

INTERNATIONAL SPEAKERS

Professor Brian Cuthbertson
Chief of Critical Care, Sunnybrook Health Sciences Centre, Toronto, Canada

Professor Anders Perner
Intensivist, University of Copenhagen, Denmark

Dr Duncan Young
Intensivist, University of Oxford, United Kingdom

Dr Allan Goldman
Chairman of the Cardiorespiratory ICU – Great Ormond Street Hospital for Children, United Kingdom

The College would like to thank our Sponsors of the 2014 ASM

GE Healthcare

Breakfast Session Sponsor

mayohealthcare australia

Coffee Sponsor




BRISBANE CONVENTION & EXHIBITION CENTRE

VISIT THE ASM WEBSITE www.asm.cicm.org.au/2014

Starch solutions in Australia: the empire strikes back

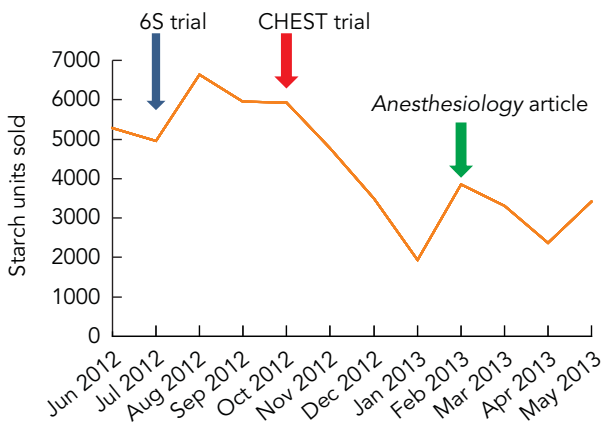
Rinaldo Bellomo

> All who drink of this remedy will recover … except those whom it does not help, who will die. Therefore, it is obvious that it fails only in incurable cases
>
> — Galen

On 12 July 2012 in the *New England Journal of Medicine*, Scandinavian investigators led by Anders Perner reported the results of a double-blind, multicentre, randomised controlled trial (DB MC RCT) of hydroxyethyl starch (HES) in a balanced crystalloid solution versus the balanced crystalloid solution itself.[1] They found that patients who received HES had an increased risk of death and of acute kidney injury requiring treatment with renal replacement therapy. Did these findings affect the use of starch in Australia? Absolutely not (Figure 1).

About 3 months later, on 17 October 2012, the results of the Crystalloid Versus Hydroxyethyl Starch Trial (CHEST)[4] were published in the *New England Journal of Medicine*.[2] CHEST, also a DB MC RCT, confirmed that HES increased the incidence of acute kidney injury requiring renal replacement therapy. These findings, coming from Australia and New Zealand, led to a 19.5% decrease in sales of Voluven and Volulyte (the HES preparations marketed in Australia) in the following month, and a 67.4% decrease by January 2013 (Figure 1).

Figure 1. Changes in sales of hydroxyethyl starch-containing fluid in Australia



After publication of the Scandinavian (6S) trial,[1] there were no changes. Sales plummeted after the Crystalloid Versus Hydroxyethyl Starch Trial (CHEST) trial.[2] However, stability was restored after release of the Anesthesiology *article.[3] (Data available from http://www.imshealth.com/portal/site/imshealth upon payment.)*

This looked like a promising scenario for those "in a galaxy far, far away" who believe that practice should be based on high-level evidence. They were wrong. In an article published in *Anesthesiology* in early February this year, the other side focused on patients having surgery and on short-term physiological changes to demonstrate (in a warped logic that would have made Galen proud) that all was well with starch fluids, if they were only used in the operating theatres (a large area of starch sales).[3] Despite intense protests by various correspondents about the profound flaws of this analysis,[5,6] and concern because the four main authors reported conflicts of interest in relation to HES producers, it "worked". HES sales in Australia in February 2013 doubled compared with January. They remained essentially stable until May 2013 (the last month for which data were available) — 3415 units (equivalent to about A$40 000) were sold in May. Whether recent decisions by various regulatory authorities to restrict or remove HES from use[7] will prove successful remains to be seen. As reported by the *Financial Times*, it is likely that HES manufacturers will fight restrictions to the bitter end.[8] It makes one almost filled with admiration for Lilly, who pulled Xigris from the market the day after the results of the PROWESS-SHOCK trial were made public.[9] The lesson is clear: evidence is but a tiny part of the practice puzzle. When translating best evidence into practice is in conflict with the commercial interests of large and wealthy multinational companies, the game is much rougher than issuing guidelines or writing erudite reviews. It is much more like Star Wars than one could ever imagine. It remains to be seen whether the poorly armed and poorly resourced clinician – investigator with only the best interests of his or her patients at heart will, like the rebels, eventually win the war.

Competing interests

None declared.

Author details

Rinaldo Bellomo, Codirector,[1] and Professorial Fellow[2]

1 Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, VIC, Australia.

2 Department of Medicine, University of Melbourne, Melbourne, VIC, Australia.

rinaldo.bellomo@austin.org.au

References

1 Perner A, Haase N, Guttormsen AB, et al; 6S Trial Group; Scandinavian Critical Care Trials Group. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 2012; 367: 124-34.

2 Myburgh JA, Finfer S, Bellomo R, et al; CHEST Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 2012; 367: 1901-11.

3 Martin C, Jacob M, Vicault E, et al. Effect of waxy maize-derived hydroxyethyl starch 130/0.4 on renal function in surgical patients. *Anesthesiology* 2013; 118: 387-94.

4 Myburgh J, Li Q, Heritier S, et al; Crystalloid Versus Hydroxyethyl Starch Trial (CHEST) Management Committee. Statistical analysis plan for the Crystalloid Versus Hydroxyethyl Starch Trial (CHEST). *Crit Care Resusc* 2012; 14: 44-52.

5 Groeneveld ABJ, Navickis RJ, Wilkes MM. Hyroxyethylstarch 130/0.4 and postoperative acute kidney injury. *Anesthesiology* 2013; 119: 733-5.

6 Wiedermann CJ. Hydroxyethyl starch 130/0.4: safe for the kidney of surgical patients? *Anesthesiology* 2013; 119: 735-6.

7 Aubron C, Bellomo R. Infusion of hydroxyethyl starch-containing fluids. *Minerva Anestesiol* 2013; 79: 1088-92.

8 Jack A. German healthcare group in row over research findings. *Financial Times* 2013; 30 Sep. http://www.ft.com/intl/cms/s/0/07ea35f0-29ca-11e3-9bc6-00144feab7de.html (accessed Oct 2013).

9 Bellomo R, Lipscey M. Xigris 2011: déjà vu all over again? *Crit Care Resusc* 2011;13: 211-2 ❑

Critical Care and Resuscitation

Journal of the College of Intensive Care Medicine of Australia and New Zealand • Chief Editor: Rinaldo Bellomo

Copyright transfer statement

The copyright to this article is transferred to the *College of Intensive Care Medicine of Australia and New Zealand* effective if and when the article is accepted for publication. The copyright transfer covers the exclusive right to reproduce and distribute the article, including reprints, translations, photographic reproductions, microform, electronic form (offline, online) or any other reproductions of similar nature.

We the undersigned declare that the material presented in the attached paper has not been published previously (nor is it currently being assessed for publication) by any journal other than *Critical Care and Resuscitation*.

MANUSCRIPT TITLE

. . . . . .

. . . . . .

. . . . . .

. . . . . .

. . . . . .

AUTHORS' NAMES (Print)

. . . . . .

. . . . . .

. . . . . .

. . . . . .

. . . . . .

. . . . . .

. . . . . .

. . . . . .

AUTHORS' SIGNATURES (and Date)

. . . . . .

. . . . . .

. . . . . .

. . . . . .

. . . . . .

. . . . . .

. . . . . .

. . . . . .

Is maintenance fluid therapy in need of maintenance?

David J Gattas and Manoj K Saxena

Acute illness can cause decreased fluid intake and increased fluid and electrolyte loss, and can be associated with alterations in cardiovascular and other vital organ functions. The stress response to acute illness activates inflammatory, endocrine and other pathways that result in the retention of sodium and water. In this context, what are the daily sodium and water needs of a critically ill patient, and how are they different to normal requirements for salt and water intake during recovery and in health? And if these needs are different, how do we recognise the clinical transition from stress to recovery phase?

In health, the average daily sodium intake for adults in Australia and New Zealand is around 150 mmol/day. The National Health and Medical Research Council recommend an intake of between 20 and 40 mmol/day, and up to 100 mmol/day is considered reasonable.[1] Sodium balance is regulated in part by the renin–angiotensin–aldosterone and sympathetic nervous systems. Intrarenal mechanisms also contribute via regulation of intramedullary and regional renal blood flow. Daily sodium intake is balanced by daily excretion through urinary and cutaneous (sweat) losses, although other mineral intakes (potassium and calcium) have effects on urinary loss of sodium.

In this issue of *Critical Care and Resuscitation,* Bihari and colleagues describe the epidemiology of sodium administration among a broad cross-section of intensive care unit patients in Australia and New Zealand.[2] Previously, in the findings of a single-centre exploratory study,[3] two of these authors have reported that sodium and fluid balance are not predictably related in ICU patients and that sodium accumulation may be associated with morbidity. The current report extends our understanding of sodium and fluid intake during the usual clinical care of critically ill patients. It also demonstrates the value of investing in research infrastructure and capacity — in this case, the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG) Point Prevalence Program.[4-6]

This report describes sodium intake in 356 patients from 40 Australian and New Zealand ICUs on a single day and has several key findings. First, the median amount of administered sodium was 224.5 mmol/day (interquartile range, 144.9–367.6 mmol/day), which is well in excess of the recommended daily sodium intake in health. Second, this daily dose appears to persist throughout intensive care admission. Third, although maintenance fluid is the main source of sodium administration (around 35%), a significant amount of sodium is administered with fluid boluses (around 20%), in vehicles for drugs and in flushes (around 30%). Fourth, sodium administration varies markedly among different ICUs, suggesting significant practice variation as part of usual care. Finally, hypernatraemia was more prevalent than hyponatraemia.

We administer fluid and sodium to patients concurrently, but ICU clinicians think and prescribe predominantly in terms of fluid volume only. There is clinical evidence of an association between positive cumulative fluid balance and adverse clinical outcomes in ICU patients,[7-9] but these data from Bihari and coworkers raise the question of whether sodium balance is also important to help understand the association between fluid accumulation and morbidity. Is it possible that maintenance fluid (together with the fluid used as a vehicle for drugs and electrolytes) is an iatrogenic factor that "maintains" sodium and fluid overload? Is maintenance fluid an intervention whose volume and composition can influence the outcomes of patients in hospital?

Bihari et al also observed that bolus fluid resuscitation was the second most significant source of intravenous sodium input, particularly on the second and third days after intensive care admission. The requirement for bolus fluid resuscitation varies during the course of critical illness, and clinicians determine whether bolus fluid is indicated using vital signs and their assessment of perfusion. However, recent clinical investigation is making it less clear what the net benefits of bolus fluid administration are for patients in the ICU. Colloids offer no general superiority over crystalloids.[10] Specific colloids are associated with harm.[11] Bolus fluid resuscitation is an established practice for early management of sepsis[12] (perhaps albumin has an advantage[13]), but there is a case to be made for reviewing established practice in this diagnostic group.[14] How should we apply evidence from a recent high-quality, large-scale clinical trial which showed that bolus fluid resuscitation (albumin or saline) is associated with increased mortality in children with severe febrile illness presenting to resource-limited clinics in Africa?[15] The study by Bihari et al documents that sodium administration is substantial in ICU patients and suggests an association with some adverse outcomes. We cannot be certain of the importance of these findings, but they contribute to an emerging theme of unclear benefits and possible harms associated with liberal bolus fluid use.

An impressive cross-section of patients has been arrayed from across two countries on a single day, but the study is limited by its inability to report sodium balance; some sources

of sodium input have not been captured, and there are no data for sodium output. The ability of these data to associate sodium with patient outcomes is hypothesis-generating at best. There is no reason to think that recommended daily intake for sodium during health should apply in critical illness, but the physiological rationale for reducing high and persistent levels of sodium administration in the recovery phase of critical illness is plausible. We need to ask the question: what are we maintaining with maintenance fluid? The unknown medical wit who said that the dumbest kidney is still smarter than the smartest doctor may be correct, but this is no excuse for us to stop trying to constantly improve fluid administration to our critically ill patients.

Competing interests

None declared.

Author details

David J Gattas, Intensive Care Physician,[1] Clinical Associate Professor,[2] and Honorary Fellow[3]

Manoj K Saxena, Research Fellow,[3] and Intensive Care Physician[4,5]

1 Intensive Care, Royal Prince Alfred Hospital, Sydney, NSW, Australia.

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

3 Critical Care and Trauma Division, The George Institute for Global Health, Sydney, NSW, Australia.

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

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

Correspondence: david.gattas@sydney.edu.au

References

1 Australian Government National Health and Medical Research Council, New Zealand Ministry of Health. Sodium. Nutrient reference values for Australia and New Zealand including recommended dietary intakes. http://www.nrv.gov.au/resources/_files/n35-sodium.pdf (accessed Sep 2013).

2 Bihari S, Peake SL, Seppelt I, et al. Sodium administration in critically ill patients in Australia and New Zealand: a multicentre point-prevalence study. *Crit Care Resusc* 2013; 15: 294-300.

3 Bihari S, Baldwin CE, Bersten AD. Fluid balance does not predict estimated sodium balance in critically ill mechanically ventilated patients. *Crit Care Resusc* 2013; 15: 89-96.

4 The George Institute for Global Health. Point Prevalence Program. http://www.georgeinstitute.org.au/projects/point-prevalence-program (accessed Oct 2013).

5 Elliott D, Aitken LM, Bucknall TK, et al. Patient comfort in the intensive care unit: a multicentre, binational point prevalence study of analgesia, sedation and delirium management. *Crit Care Resusc* 2013; 15: 213-9.

6 Hammond NE, Saxena MK, Taylor C, et al. Temperature management of non-elective intensive care patients without neurological abnormalities: a point prevalence study of practice in Australia and New Zealand. *Crit Care Resusc* 2013; 15: 228-33.

7 Boyd JH, Forbes J, Nakada TA, et al. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. *Crit Care Med* 2011; 39: 259-65.

8 Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; 354: 2564-75.

9 Murphy CV, Schramm GE, Doherty JA, et al. The importance of fluid management in acute lung injury secondary to septic shock. *Chest* 2009; 136: 102-9.

10 Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev* 2013; (2): CD000567.

11 Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 2012; 367: 124-34.

12 Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012. *Crit Care Med* 2013; 41: 580-637.

13 Delaney AP, Dan A, McCaffrey J, Finfer S. The role of albumin as a resuscitation fluid for patients with sepsis: a systematic review and meta-analysis. *Crit Care Med* 2011; 39: 386-91.

14 Hilton AK, Bellomo R. A critique of fluid bolus resuscitation in severe sepsis. *Crit Care* 2012; 16: 302.

15 Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. *N Engl J Med* 2011; 364: 2483-95. ❑

Can social media bridge the gap between research and practice?

Paul J Young, Christopher P Nickson and Dashiell C Gantner

If it doesn't spread, it's dead[1]

The ultimate aim of all clinical research should be to improve patient outcomes. Effective translation of evidence into practice is a prerequisite for this objective to be achieved. In many respects, performing a definitive, large-scale, randomised controlled trial (RCT) is a worthless endeavour unless clinicians implement the study's findings.

Gaps between evidence and practice are increasingly recognised in all areas of medicine. Health research funding bodies, cognisant of this, frequently require grant applicants to plan the dissemination of their results before completion of the trial, and there are a growing number of funding streams specifically for knowledge translation research (eg, National Health and Medical Research Council Translating Research Into Practice fellowships).

The spotlight fell on such research–practice gaps in 2001 with the report *Crossing the quality chasm*, which described the widespread failure to implement high-level evidence in the United States health care system.[2] This report highlighted the finding that the average lag time between the demonstration of an effective treatment and its implementation into practice was 17 years![3] The archetypal example is the use of thrombolytic therapy in acute myocardial infarction.[4] The first trial to report the efficacy of thrombolysis in acute myocardial infarction was published in 1959.[5] A meta-analysis of 24 RCTs of 6000 patients published by 1985 demonstrated that intravenous thrombolytic therapy reduced the relative risk of early death by 22% ($P < 0.001$).[6] However, even after more than 55 000 patients had been randomly allocated to trials of thrombolysis for acute myocardial infarction, and after publication of several more meta-analyses demonstrating benefit, large observational studies conducted across Europe and the US found implementation rates ranging from only 18%–55% into the mid 1990s.[7-9]

Knowledge translation is difficult to achieve for many reasons including financial barriers, entrenched institutional practices and the nature of medical education.[10] However, perhaps the foremost component of knowledge translation is winning the hearts and minds of practitioners. The publication of trial results in a high-profile journal alone does not achieve this. Ironically, the precise, understated conclusions that are the hallmark of high-quality scientific writing may actually impede this aim. Consider the following statement from the NICE-SUGAR study:[11] "our findings suggest that a goal of normoglycemia for glucose control does not necessarily benefit critically ill patients and may be harmful". This measured conclusion comes from a definitive randomised trial demonstrating a significant treatment effect on patient mortality, yet does not convey any urgency with respect to practice change.

This is important because the results of clinical trials are likely to be weighed against the biases of individual clinicians and against anecdotes. For example, the impact of the results of the DECRA trial[12] might be undermined by the narrative of an individual patient, treated with early decompressive craniectomy when death appeared imminent, who subsequently made a "miraculous recovery". Doctors, like all humans, are captivated by stories; it is easy for an RCT and a good story to assume equal weight in the battle to win their hearts and minds. This is partly because of the inherent cognitive biases that influence our decision making, such as the "availability heuristic",[13] in which the more easily something comes to mind, the more probable it seems.

Publication of high-quality trials in high-impact journals is important, but it is only a single step on the path of achieving beneficial practice change. The reality is that knowledge translation results from teaching at the bedside and conversations between clinicians. Traditionally, these conversations happened in hospital corridors, but increasingly they are occurring online, using social media and free, open-access medical education internet resources.[14] These virtual corridor conversations are potentially the most rapid means of achieving widespread dissemination of trial results to a global audience.

Social media and the internet are the modern communication paradigm and are already being used for knowledge translation in critical care. The CRASH-2 trial[15] investigators are using several internet-based strategies to increase the uptake of tranexamic acid into clinical practice in major trauma patients. These include a user-friendly study website with slides for download, links to various study-related videos, as well as a brief podcast outlining the trial results, and even a song![16] Meanwhile, the ARISE trial investigators[17] are tweeting updates on Twitter as @TheARISEstudy, and updates for the HEAT trial[18] are regularly tweeted by @DogICUma.

Researchers need to harness social media and the internet in a systematic way to sell their messages and make them stick, so that their research findings are translated into practice. In essence, this is a marketing exercise that needs to be carefully planned.

Clearly there are risks. Consider the example of delayed sequence intubation. Scott Weingart published his approach, described as procedural sedation to achieve oxygenation, in 2011 in the *Journal of Emergency Medicine* with minimal fanfare.[19] He subsequently created a podcast[20] on the topic that led to worldwide discussion, debate, early adoption and rapid refinement of the technique. All of this occurred despite a lack of any evidence stronger than theoretical plausibility and case reports. This could mean that more patients are receiving benefits sooner, but there are obvious dangers. Conventional translation is slow but traditional mechanisms of translation, including confirmatory studies and meta-analyses, reduce the likelihood of translating poor-quality evidence.

Even among high-profile trials, medical reversals (when therapies initially thought to be effective are found to be ineffective or harmful) are common.[21] The risk with social media is that knowledge dissemination and practice change may occur prematurely. Although this risk is real, rapid dissemination by social media and internet-based communication is here to stay, whether or not researchers get involved. There is also the opportunity to accelerate the reversal process through free and open discussion". Clinician–researchers are often recognised as opinion leaders and have the potential to be influential in the online environment. While some may feel uncomfortable with the ethics of self-marketing, researchers, despite potential conflicts of interest, are still arguably in a better position than most to weigh up evidence.

A structured approach to knowledge translation that harnesses social media and the internet may have tangible, practical benefits for researchers. Increased social media activity within the first 3 days of an article being published is associated with an increased citation rate.[22] Moreover, a recent study demonstrated that a release of research articles by social media increases the number of people who view and download those articles in the subsequent week.[23] Facebook, Twitter and various critical care blogs and podcasts including lifeinthefastlane.com, intensivecarenetwork.com, emcrit.org, and crit-iq.com.au provide the means to deliver research directly to the end user, complementing traditional disemination methods. They provide researchers with a means to tell clinicians around the world what they believe their research means for clinical practice in a frank, honest and open way.

Researchers and clinicians must embrace this opportunity because there is a moral imperative to close the gap between research and practice. To defeat dogma and improve patient outcomes, we need to enter the battle for hearts and minds wherever it takes place, whether that is in the hospital corridors or on the internet.

Competing interests

None declared.

Author details

Paul J Young, Intensive Care Specialist,[1] and Senior Research Fellow[2]
Christopher P Nickson, Senior Registrar[3]
Dashiell C Gantner, Senior Registrar,[3] PhD Candidate,[4] and Centre of Excellence in Traumatic Brain Injury Research Fellow[5]

1 Intensive Care Unit, Wellington Hospital, Wellington, New Zealand.
2 Medical Research Institute of New Zealand, Wellington, New Zealand.
3 Intensive Care Unit, The Alfred Hospital, Melbourne, VIC, Australia.
4 Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, VIC, Australia.
5 National Trauma Research Institute, Melbourne, VIC, Australia.
Correspondence: paul.young@ccdhb.org.nz

References

1 Michelle Lin, Editor-in-Chief, Academic Life in Emergency Medicine. Tweet. Blog: http://academiclifeinem.com; @m_lin.
2 National Research Council. Applying evidence to health care delivery. In: Crossing the quality chasm: a new health system for the 21st century. Washington DC: National Academy Press, 2001: 145-63. http://www.nap.edu/catalog.php?record_id=10027 (accessed Oct 2013).
3 Balas EA, Boren SA. Managing clinical knowledge for health care improvement. In: Bemmel J, McCray AT, editors. Yearbook of medical informatics 2000: patient-centred systems. Stuttgart, Germany: Schattauer Verlagsgesellschaft mbH, 2000: 65-70. http://www.ihi.org/_layouts/ihi/login/login.aspx?ReturnURL=%2fknowledge%2fPages%2fPublications%2fManagingclinicalknowledgeforhealthcareimprovement.aspx (accessed Oct 2013).
4 Antman EM, Lau J, Kupelnick B, et al. A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts. Treatments for myocardial infarction. *JAMA* 1992; 268: 240-8.
5 Fletcher AP, Sherry S, Alkjaersig N, et al. The maintenance of a sustained thrombolytic state in man. II. Clinical observations on patients with myocardial infarction and other thromboembolic disorders. *J Clin Invest* 1959; 38: 1111-9.
6 Yusuf S, Collins R, Peto R, et al. Intravenous and intracoronary fibrinolytic therapy in acute myocardial infarction: overview of results on mortality, reinfarction and side-effects from 33 randomized controlled trials. *Eur Heart J* 1985; 6: 556-85.
7 Pashos CL, Normand SL, Garfinkle JB, et al. Trends in the use of drug therapies in patients with acute myocardial infarction: 1988 to 1992. *J Am Coll Cardiol* 1994; 23: 1023-30.
8 Ketley D, Woods KL. Impact of clinical trials on clinical practice: example of thrombolysis for acute myocardial infarction. *Lancet* 1993; 342: 891-4.
9 European Secondary Prevention Study Group. Translation of clinical trials into practice: a European population-based study of the use of

thrombolysis for acute myocardial infarction. *Lancet* 1996; 347: 1203-7.
10 Pierson DJ. Translating evidence into practice. *Respir Care* 2009; 54: 1386-401.
11 NICE-SUGAR Study Investigators; Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009; 360: 1283-97.
12 Cooper DJ, Rosenfeld JV, Murray L, et al. Decompressive craniectomy in diffuse traumatic brain injury. *N Engl J Med* 2011; 364: 1493-502.
13 Tversky A, Kahneman D. Judgment under uncertainty: heuristics and biases. *Science* 1974; 185: 1124-31.
14 Nickson CP. FOAM [Free Open Access Meducation]. http://lifeinthefastlane.com/foam/ (accessed Sep 2013).
15 CRASH-2 trial collaborators; Shakur H, Roberts I, Bautista R, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 2010; 376: 23-32.
16 London School of Hygiene & Tropical Medicine. CRASH 2 [Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage]. http://www.crash2.lshtm.ac.uk/ (accessed Sep 2013).
17 Delaney AP, Peake SL, Bellomo R, et al. The Australasian Resuscitation in Sepsis Evaluation (ARISE) trial statistical analysis plan. *Crit Care Resusc* 2013; 15: 162-71.
18 Young PJ, Saxena MK, Bellomo R, et al. The HEAT trial: a protocol for a multicentre randomised placebo-controlled trial of IV paracetamol in ICU patients with fever and infection. *Crit Care Resusc* 2012; 14: 290-6.
19 Weingart SD. Preoxygenation, reoxygenation, and delayed sequence intubation in the emergency department. *J Emerg Med* 2011; 40: 661-7.
20 Weingart SD. EMCrit Podcast 40 – Delayed sequence intubation (DSI). http://emcrit.org/podcasts/dsi/ (accessed Sep 2013).
21 Prasad V, Vandross A, Toomey C, et al. A decade of reversal: an analysis of 146 contradicted medical practices. *Mayo Clin Proc* 2013; 88: 790-8.
22 Eysenbach G. Can tweets predict citations? Metrics of social impact based on Twitter and correlation with traditional metrics of scientific impact. *J Med Internet Res* 2011; 13: e123.
23 Allen HG, Stanton TR, Di Pietro F, Moseley GL. Social media release increases dissemination of original articles in the clinical pain sciences. *PLOS One* 2013; 8: e68914. ❑

Intensive care unit mobility practices in Australia and New Zealand: a point prevalence study

Susan C Berney, Megan Harrold, Steven A Webb, Ian Seppelt, Shane Patman, Peter J Thomas and Linda Denehy

ABSTRACT

Objectives: To develop a comprehensive set of items describing physiotherapy mobilisation practices for critically ill patients, and to document current practices in intensive care units in Australia and New Zealand, focusing on patients having > 48 hours of mechanical ventilation.

Design: Prospective, observational, multicentre, single-day, point prevalence study.

Participants and setting: All patients in 38 Australian and New Zealand ICUs at 10 am on one of three designated days in 2009 and 2010.

Main outcome measures: Demographic data, admission diagnosis and mobilisation practices that had occurred in the previous 24 hours.

Results: 514 patients were enrolled, with 498 complete datasets. Mean age was 59.2 years (SD, 16.7 years) and 45% were mechanically ventilated. Mobilisation activities were classified into five categories that were not mutually exclusive: 140 patients (28%) completed an in-bed exercise regimen, 93 (19%) sat over the side of the bed, 182 (37%) sat out of bed, 124 (25%) stood and 89 (18%) walked. Predefined adverse events occurred on 24 occasions (5%). No patient requiring mechanical ventilation sat out of bed or walked. On the study day, 391 patients had been in ICU for > 48 hours. There were 384 complete datasets available for analysis and, of these, 332 patients (86%) were not walked. Of those not walked, 76 (23%) were in the ICU for ⩾ 7 days.

Conclusion: Patient mobilisation was shown to be low in a single-day point prevalence study. Future observational studies are required to confirm the results.

Crit Care Resusc 2013; 15: 260–265

Immobility, deconditioning and muscle weakness are a consequence of critical illness. This results in longstanding impaired physical function for survivors of intensive care.[1,2] Early mobilisation for patients who are intubated and receiving mechanical ventilation in the intensive care unit is advocated as a treatment intervention that may attenuate the development of weakness.[3-6] To date, several cohort studies have shown that early mobilisation for these patients is feasible and safe,[6-8] and is associated with a reduction in ICU length of stay, hospital length of stay[6] and hospital readmission up to 1 year after discharge.[9] There are few large randomised controlled trials showing the effects of early mobilisation on patient-centred outcomes.

Survey data suggest that physiotherapists incorporate mobilisation as part of their clinical practice in the ICU.[10] No widespread prospective audit of mobilisation in the ICU has occurred in Australia or New Zealand. Our aim was to document current physiotherapy mobilisation practices across a large sample of general (medical and surgical) ICU patients and focus specifically on mobilisation practices in patients requiring prolonged mechanical ventilation, defined as more than 48 hours.

Methods

Sites and ethics approval

Our study was conducted within the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG) point prevalence program and was endorsed by the ANZICS CTG. All ICUs in Australia and New Zealand were invited to participate. The point prevalence program is a mechanism to conduct multiple prospective one-day observational epidemiological studies and was approved by the appropriate institutional, state or national multicentre ethics committee for each participating hospital, with the need for participant consent waived. Data were de-identified before submission to the coordinating centre.

Survey

Our study was performed in each site on one of three designated days in 2009 and 2010. A 30-item general case report form (CRF) was completed by a research nurse, and a 25-item physiotherapy-specific CRF was completed by a research nurse or physiotherapist. The physiotherapy CRF consisted of two items about service provision, two about respiratory care, 10 about mobilisation practices (including respiratory support and barriers to mobilisation), 11 items about factors interfering with physiotherapy (such as renal replacement therapy or procedures outside the ICU), and two items about unplanned or adverse events occurring during physiotherapy. The survey questions are available from the author.

Table 1. Safety assessment for patient mobilisation, using selected elements of the SOFA score[11] and RASS[12] for patients with an ICU LOS > 48 hours

Characteristic	Measurement		
SOFA score	0	1	2
PaO_2/FIO_2	> 400	301–400	201–300;* < 301†
Cardiovascular parameters	MAP > 70 mmHg	MAP < 70 mmHg	Dopamine ⩾ 5 µg/kg/min‡
RASS	–1	0	1
Assessment	Drowsy§	Alert, calm	Restless¶

SOFA = sequential organ failure assessment. RASS = Richmond agitation and sedation score. ICU = intensive care unit. LOS = length of stay. MAP = mean arterial pressure. * With respiratory support. † Without respiratory support. ‡ Or any dose of dobutamine, milrinone or levosimendan. § Not fully alert but sustained (10-second) awakenings with eye contact to voice. ¶ Anxious or apprehensive, movements not aggressive or vigorous.

Data on all mobility and rehabilitation activities undertaken by patients in the previous 24 hours were collected from the nursing or physiotherapy notes, or from the daily observation chart. Each activity was predefined, using a data dictionary. Mobilisation activities included in-bed exercise activity, sitting in bed or sitting out of bed, and all walking that occurred. "Walking" was defined as taking three steps on the spot or away from the bedside.

Patients

All adult patients (aged 16 years or over) who were admitted to the ICU at a 10 am census point on the designated day were included. Demographic data including age, sex and admission diagnosis were recorded. Admission diagnoses were categorised by the Acute Physiological and Chronic Health Evaluation (APACHE) II score in the 24 hours before the study day, and according to whether the patient was admitted to or discharged from the ICU on the study day. A subset of patients in the ICU for more than 48 hours was analysed separately to determine the prevalence of early mobilisation in patients with prolonged stays in the ICU.

Safety criteria

Safety criteria were developed and defined by five of us (four of whom had over 10 years' clinical ICU experience): two senior ICU staff specialists and three experienced ICU physiotherapists. Criteria were developed using available data from the general section of the CRF, and were based on parameters used in clinical trials that had examined ICU patient mobilisation and on two of our Australian trials that were then underway. These criteria were presented to the ANZICS CTG in 2009 and agreed on by senior medical, nursing and physiotherapy clinicians present. The definitions of these criteria are shown in Table 1.

We retrospectively applied the safety criteria using the Richmond agitation and sedation score (RASS) and the respiratory and cardiovascular components of the sequential organ failure assessment (SOFA) score to each patient, and classified patients as safe or unsafe to mobilise. We used these safety criteria to investigate if consistent safety criteria were used in the decision to sit patients out of bed or walk them away from the bed, and to determine if there was potential for greater levels of mobilisation.

Analysis

Statistical analysis was performed using SAS version 9.1 (SAS Institute). Variables that were normally distributed were reported as means with standard deviations, and non-normally distributed data were reported as medians with interquartile ranges. Proportions were reported as percentages.

Results

ICU and patient data

Thirty-eight units participated in the point prevalence study (33 in Australia and five in New Zealand). All were closed multidisciplinary ICUs, with patient management supervised by accredited ICU specialists. There are 182 ICUs in Australia and New Zealand. The sample from our study represented 30 of 35 tertiary units in Australia and New Zealand (86%), six of 39 metropolitan units (15%), one of 49 rural and regional units (2%), and one of 59 private hospital units (2%).

Figure 1. Ventilatory status of all patients

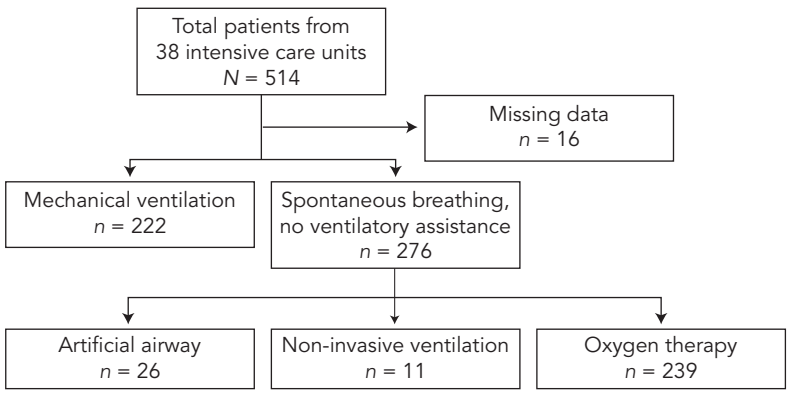


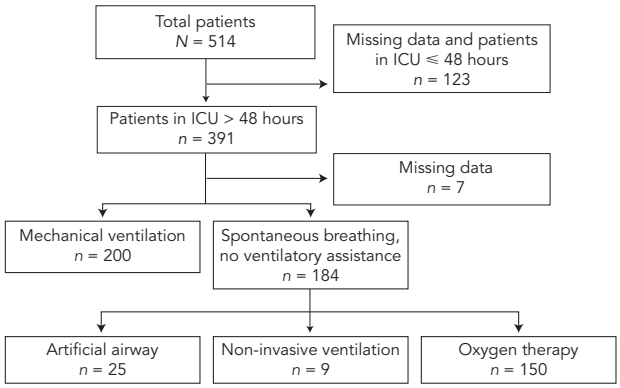
Table 2. Demographic data of ICU patients

Characteristic	*n* (%)*
Mean age, years (*n* = 504)	
20–59	219 (43%)
60–79	236 (47%)
> 80	49 (10%)
Overall mean 59.2 years; SD, 16.7 years	
Weight, kg (*n* = 513)	
< 70	150 (29%)
70–100	294 (57%)
> 100	69 (13%)
APACHE II (*n* = 480) score	
< 10	53 (11%)
10–20	232 (48%)
21–29	149 (31%)
⩾ 30	46 (10%)
Source of ICU admission (*n* = 514)	
Emergency department	133 (26%)
Elective surgery	127 (25%)
Emergency surgery	86 (17%)
Other	168 (33%)
Reason for ICU admission (*n* = 465)	
Postoperative care	213 (46%)
Sepsis	123 (26%)
Trauma	77 (17%)
ALI	26 (6%)
ARDS	26 (6%)
Length of ICU stay, days (*n* = 419)	
< 2	177 (42%)
2–7	106 (25%)
> 7	136 (32%)

ICU = intensive care unit. ALI = acute lung injury. ARDS = acute respiratory distress syndrome. APACHE = Acute Physiology and Chronic Health Evaluation. * Percentages may not total 100 due to rounding.

Data were collected on 514 patients who had spent any time in the ICU after 10 am on the study day. Of the 514 patients, 16 had some missing data. Of the remaining 498 patients, 222 (45%) were receiving mechanical ventilatory support and 276 (55%) patients were breathing spontaneously with oxygenation but not ventilatory assistance (Figure 1). The demographic data for the cohort are shown in Table 2. For 90% of patients, this was their first ICU admission during that hospital stay.

Figure 2. Ventilatory status of patients in the intensive care unit (ICU) for > 48 hours

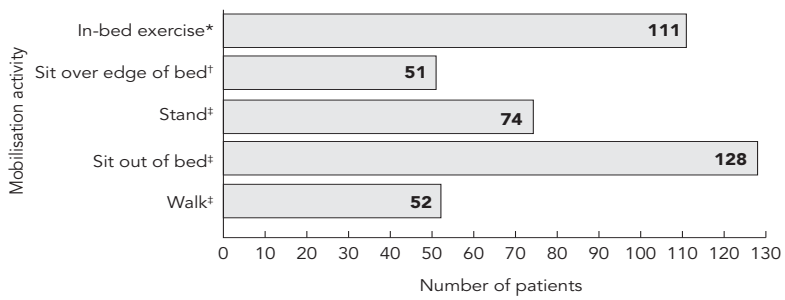


Mobilisation activities

Mobilisation activities of all 498 patients were classified into five categories that were not mutually exclusive: 140 (28%) completed an in-bed exercise regimen; 93 (19%) sat over the side of the bed; 182 (37%) sat out of bed; 124 (25%) stood and 89 (18%) walked.

Predefined adverse events occurred on 24 occasions (5%). No serious adverse event occurred resulting in death, cardiac or respiratory arrest or a patient fall. Of the 24 adverse events recorded, patients were returned to bed on seven occasions (30%) because of a reduction in mean arterial blood pressure. On six occasions (25%), the patient required an increase in positive end-expiratory pressure (PEEP) to > 10 cmH_2O, or > 20% increase in PEEP if already > 10 cmH_2O. The remaining 11 adverse events included arrhythmia, bronchospasm and deterioration in mental state. No loss of airway or intravascular line occurred during mobilisation exercises. Physiotherapists were involved in mobilisation activities, including sitting out of bed, on 90% of occasions.

Figure 3. Frequency of mobilisation activities undertaken by patients in the intensive care unit for > 48 hours



MV = mechanical ventilation. * Fifty-four patients of 111 (49%) were on MV. † Six patients of 51 (12%) were on MV. ‡ No patient on MV stood, sat out of bed or walked.

Table 3. Main reasons for not sitting out of bed or walking

Reason	Not sitting out of bed *n* (%)	Not walking *n* (%)
Unconscious or unresponsive	49 (20%)	5 (7%)
Sedated or agitated	42 (17%)	NA
No RASS recorded	5	NA
RASS recorded	37	NA
RASS –1 to –3	22	NA
RASS < –4	11	NA
RASS > 0	4	NA
No stated barrier	33 (13.4%)	31 (41%)
Haemodynamic instability	28 (11.4%)	NA
No inotropic support detailed	23	NA
Weakness	23 (9.4%)	22 (29%)
Unstable trauma	11 (4.5%)	2 (3%)
Severe respiratory failure	11 (4.5%)	NA
With ARDS	2	NA
No ARDS or ALI	9	NA
Renal replacement therapy	8 (3.3%)	NA
Femoral access	2	NA
Subclavian or jugular access	6	NA

RASS = Richmond agitation and sedation score. ARDS = acute respiratory distress syndrome. ALI = acute lung injury.

Table 4. Safety criteria for sitting out of bed

	Sat out of bed		Walked	
Criterion	Yes	No	Yes	No
Within SOFA and RASS parameters (*n* = 125*)	69	56	30	93 (88)†
Not within SOFA and RASS parameters (*n* = 266*)	59	207	22	245
Total	128	263	52	388

SOFA = sequential organ failure assessment. RASS = Richmond agitation and sedation score. * SOFA parameters: cardiovascular 0–2, respiratory 0–2; RASS parameters: 1 to –1 (1 = restless, anxious, movements not aggressive; 0 = alert, calm; –1 = drowsy, not fully alert but has sustained awakenings). † Due to trauma such as spinal cord injury and stroke in five patients, only 88 patients were potentially able to walk.

Respiratory support during out-of-bed mobilisation

No patients on mechanical ventilation were sat out of bed or walked. Twenty patients with artificial airways, but not mechanical ventilation, were mobilised out of bed. Two of the 20 patients had an endotracheal tube in situ and were sat out of bed, and one was mobilised; both patients were on T-piece oxygenation at the time. Eighteen patients with a tracheostomy tube in situ were sat out of bed, and eight of these were also mobilised. One hundred and fifty patients (30%) were mobilised on face mask oxygen, and one was mobilised while receiving non-invasive ventilation. On 10 occasions, respiratory support was not recorded.

Out-of-bed mobilisation for patients in the ICU > 48 hours

All further results pertain to a subgroup of the original 514 patients, the 391 patients (76%) who were in the ICU > 48 hours. Seven had missing data, and of the 384 complete data sets, 200 (52%) were receiving mechanical ventilatory support. The ventilatory status of these patients is given in Figure 2.

The numbers of patients undertaking different mobilisation activities are shown in Figure 3. Of the 384 patients, 332 (86%) were not walked. Of these 332 patients, 76 (23%) were in the ICU for 7 days or longer. All predefined adverse events previously described occurred in this longer-stay cohort of patients. Similarly to what was observed in the entire cohort, physiotherapists performed mobilisation activities on 81% of occasions.

Of the 150 patients receiving oxygen therapy via a face mask, 85 (57%) sat out of bed and 45 (30%) walked. All previously described out-of-bed mobilisation activities for patients with an artificial airway in situ occurred in patients whose length of stay in ICU was > 48 hours.

The barriers to sitting patients out of bed and/or walking them were reported by the clinical staff caring for the patients and are shown in Table 3.

Application of objective safety criteria

Of the 384 patients with a length of stay > 48 hours and complete datasets (Figure 2), 125 patients (33%) met the predefined safety criteria to sit out of bed and walk (Table 4). Sixty-nine sat out of bed and 30 walked.

Of the 266 patients (68%) who did not meet the predefined safety criteria, 59 sat out of bed, and 22 of those 59 walked. On 58 occasions, the patient did not meet the respiratory criteria, and on one occasion, the patient did not meet the cardiovascular criteria. On one occasion, mobilisation occurred when the patient did not meet the respiratory and RASS safety criteria, and on all other occasions one safety criterion was not met. No patient who sat out of bed or was mobilised when they did not meet the safety criteria experienced an adverse event.

On 73 occasions, patients had a procedure in the ICU or were transported outside the ICU, and these procedures may have interfered with mobilisation in the 24 hours of data collection. Thirty-eight of these occasions (52%) were associated with imaging, which on three occasions resulted in a surgical procedure being performed in the ICU. On 16 occasions (22%), patients underwent surgical procedures in

the operating room. On 11 occasions (15%), these patients were sat out of bed or mobilised, and on 15 occasions (21%) these patients met safety criteria but were not mobilised.

Discussion

Recent evidence suggests that survivors of intensive care may suffer longstanding muscle weakness.[1,13] Early mobilisation, particularly walking, that begins in the ICU in patients who are intubated and ventilated is advocated as a treatment intervention to attenuate muscle weakness and improve patient outcomes.[3,6,14] The results of our point prevalence study indicate that critically ill patients in Australia and New Zealand perform a range of mobilisation activities either in bed or sitting out in a chair. However, only 18% of all patients in the ICU walked and, for those staying in the ICU for >48 hours, this decreased to 13%. No patient requiring mechanical ventilation either sat out of bed or walked on the day of our study.

This was a mixed medical and surgical cohort, and about 40% of patients were postoperative. We were most interested in physiotherapy practices for patients admitted for > 48 hours, rather than for patients admitted for routine postoperative surveillance who were likely to be discharged within 24 hours. Physiotherapists in Australia and New Zealand are part of the multidisciplinary team. They provide respiratory care and rehabilitation for patients in the ICU. Most ICUs in Australia have at least one physiotherapist on staff, with half the therapists having >5 years of clinical experience in intensive care.[10,15] No data describing the profile of physiotherapists in New Zealand ICUs has been published but we would expect it to be similar.

Self-reporting surveys of physiotherapists working in the critical care setting have described the provision of mobilisation practices.[10,16-18] A survey by Skinner and colleagues of Australian mobility practices in ICUs reported that 94% of physiotherapists would routinely prescribe mobilisation exercise for patients.[10] That survey of 111 physiotherapists reported that 103 respondents (93%) would prescribe in-bed mobilisation exercises, 100 (90%) would sit patients over the edge of the bed, and over 100 (90%) would walk patients on the spot or away from the bed. Skinner and colleagues also reported that, in patients who were mechanically ventilated, 56 of 102 physiotherapists (55%) would mobilise the patient away from the bed. Our results do not support those results, with fewer than 50% of patients in our study having received any form of mobilisation activity.

United Kingdom survey data reported similar findings to those of Skinner and colleagues, with almost all physiotherapists surveyed stating that they provide mobilisation exercises in the ICU. These results may highlight potential issues with self-reporting surveys compared with prospective data. To date, no prospective data are available to compare physiotherapy practices in the UK.

The results of this study reflect a lack of consensus on safety criteria for mobilising patients, particularly for sitting out them of bed and walking them, in ICUs across Australia and New Zealand. This was reflected by the number of patients who did not meet our predefined safety criteria and who sat out of bed (46%) and walked (42%). While there was broad agreement about which patients were *not* safe to sit out of bed or walk, there was little agreement about who *was* safe to mobilise out of bed. In our study, using our safety criteria, 15% more patients could have sat out of bed and 36% more could have walked. This is despite the low rate of adverse events reported in our study and in the literature on early mobilisation of patients in the ICU.[6,7,19] The low rate of adverse events reported in our study is consistent with other studies of functional mobility practices in the critical care setting, with reported rates between 0% and 5%.[6,8,19]

An alternative explanation for our low observed rates of ICU patients sitting out of bed and walking may be that we have not yet developed a culture of early mobility across Australia and New Zealand. Haemodynamic instability was reported on 28 occasions as a reason for the patient not to sit out of bed, but 23 of these patients were not receiving inotropic support. On 45 of the 76 occasions that patients were not walked once they were sitting in the chair, no reason was given for why they were not walked. These barriers may reflect a reluctance of staff to engage in early mobilisation of patients who are critically ill, and there may be many variables that have an impact on ICU mobilisation practices.

A solution may be to develop stepwise protocols that prescribe mobilisation activity based on the cognitive level and physical capacity of the patient. Protocols such as these have been safely and effectively introduced into clinical practice.[6] In one centre in the United States, they have resulted in patients walking at least 3 days sooner, an adverse event occurrence of <1% and an increase in mobility of up to twofold.[6] In another US centre, an increase in routine mobilisation occurred.[19]

Patients were unavailable for part of the 24 hours of data collection on 73 occasions. While we acknowledge that some of the procedures affecting our data collection, such as surgical interventions in the operating theatre, may have had an impact on ICU patient mobilisation, they were not common enough to influence the overall results of our study.

Limitations

There are several limitations to our study. Point prevalence data may not be representative of usual practice, but in this study we documented all mobilisation in the previous 24

hours, not just what had occurred at a single time on the study day. Prevalence data (compared with incidence data) can be biased in favour of long-term patients, but in our study this was precisely our group of interest, and even with this bias, our observed number of mobilisation episodes was low.

At different sites, physiotherapists and research nurses carried out the data collection, and the variation in training of these two professions may introduce bias in the reporting. There were also missing data in the cases, which changes the sample size for different responses. This may also introduce bias in results. The pragmatic safety criteria that were applied to the data retrospectively to determine if further mobilisation may have been possible were not comprehensive. We were limited to information already collected as part of the point prevalence survey and, although based on safety criteria used in trials of early mobilisation, we acknowledge that other potentially important factors may have contributed to the observed rates of mobilisation.

Conclusion

On a single day in 38 ICUs in Australia and New Zealand, the number of patients mobilised was low, and much lower than predicted by our prespecified safety criteria and previous self-reported descriptions of practice. By restricting a patient's capacity to sit out of bed and walk, we may be limiting their functional recovery. A further program of research starting with a prospective observational study is required to confirm these data. We are awaiting similar audit data to compare our results with international ICU cohorts.

Competing interests

None declared.

Author details

Susan C Berney, Associate Professor,[1] and Physiotherapy Manager[2]
Megan Harrold, Lecturer,[3] and Senior Physiotherapist[4]
Steven A Webb, Senior Staff Specialist,[4] and Clinical Professor, School of Medicine and Pharmacology[5]
Ian Seppelt, Senior Staff Specialist,[6] Director of Clinical Research,[7] and Senior Research Fellow[8]
Shane Patman, Associate Professor,[9] and Senior Physiotherapist[10]
Peter J Thomas, Senior Physiotherapist[11]
Linda Denehy, Head[1]

1 Department of Physiotherapy, School of Health Sciences, University of Melbourne, Melbourne, VIC, Australia.
2 Austin Health, Melbourne, VIC, Australia.
3 Curtin University, Perth, WA, Australia.
4 Royal Perth Hospital, Perth, WA, Australia.
5 University of Western Australia, Perth, WA, Australia.
6 Intensive Care Medicine, Nepean Hospital, Sydney, NSW, Australia.
7 Sydney West Area Health Service, Sydney, NSW, Australia.
8 The George Institute for Global Health, Sydney, NSW, Australia.
9 School of Physiotherapy, University of Notre Dame, Perth, WA, Australia.
10 Fremantle Hospital and Health Service, Perth, WA, Australia.
11 Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia.
Correspondence: l.denehy@unimelb.edu.au

References

1 Cuthbertson BH, Roughton S, Jenkinson D, et al. Quality of life in the five years after intensive care: a cohort study. *Crit Care* 2010; 14: R6.
2 Herridge MS, Tansey CM, Matté A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011; 364: 1293-304.
3 Needham DM. Mobilizing patients in the intensive care unit: improving neuromuscular weakness and physical function. *JAMA* 2008; 300: 1685-90.
4 Needham DM, Korupolu R, Zanni JM, et al. Early physical medicine and rehabilitation for patients with acute respiratory failure: a quality improvement project. *Arch Phys Med Rehabil* 2010; 91: 536-42.
5 Morris PE, Herridge MS. Early intensive care unit mobility: future directions. *Crit Care Clin* 2007; 23: 97-100.
6 Morris PE, Goad A, Thompson C, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. *Crit Care Med* 2008; 36: 2238-43.
7 Bailey P, Thomsen GE, Spuhler VJ, et al. Early activity is feasible and safe in respiratory failure patients. *Crit Care Med* 2007; 35: 139-45.
8 Thomsen GE, Snow GL, Rodriguez L, Hopkins RO. Patients with respiratory failure increase ambulation after transfer to an intensive care unit where early activity is a priority. *Crit Care Med* 2008; 36: 1119-24.
9 Morris PE, Griffin L, Berry M, et al. Receiving early mobility during an intensive care unit admission is a predictor of improved outcomes in acute respiratory failure. *Am J Med Sci* 2011; 341: 373-7.
10 Skinner EH, Berney S, Warrillow S, Denehy L. Rehabilitation and exercise prescription in Australian intensive care units. *Physiotherapy* 2008; 94: 220-9. doi: 10.1016/j.physio.2007.11.004.
11 Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; 22: 707-10.
12 Sessler CN, Grap MJ, Brophy GM. Multidisciplinary management of sedation and analgesia in critical care. *Semin Respir Crit Care Med* 2001; 22: 211-26.
13 Needham DM, Davidson J, Cohen H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Crit Care Med* 2012; 40: 502-9.
14 Schweickert WD, Kress JP. Implementing early mobilization interventions in mechanically ventilated patients in the ICU. *Chest* 2011; 140: 1612-7.
15 Wiles L, Stiller K. Passive limb movements for patients in an intensive care unit: a survey of physiotherapy practice in Australia. *J Crit Care* 2010; 25: 501-8.
16 Nava S. Rehabilitation of patients admitted to a respiratory intensive care unit. *Arch Phys Med Rehabil* 1998; 79: 849-54.
17 Lewis M. Intensive care unit rehabilitation within the United Kingdom: review. *Physiotherapy* 2003; 89: 531-8.
18 Norrenberg M, Vincent JL. A profile of European intensive care physiotherapists. European Society of Intensive Care Medicine. *Intensive Care Med* 2000; 26: 988-94.
19 Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet* 2009; 373: 1874-82. ❑

Missed medical emergency team activations: tracking decisions and outcomes in practice

Jessica L Guinane, Tracey K Bucknall, Judy Currey and Daryl A Jones

ABSTRACT

Background: Despite extensive work to improve early recognition of and response to abnormal vital signs, a failure or delay in response to clinical deterioration by activating a medical emergency team (MET) can affect patient safety.

Objectives: To determine incidence, management and outcomes of patients having vital signs fulfilling MET call criteria during their entire admission, and to compare baseline characteristics and outcomes of patients who fulfilled MET call criteria with patients who did not.

Design: A retrospective chart audit was conducted in a private Melbourne hospital. All patients hospitalised for $\geqslant$ 24 hours in general wards and discharged in the 7-day study period were included. Medical records were reviewed for all patients who fulfilled MET criteria to assess escalation of care.

Results: Of the sample ($N = 568$), 82 patients (14%) had one or more documented vital signs fulfilling MET criteria. Hospital length of stay (LOS) for these patients was twice that of those who did not (8.6 days versus 4.3 days; $P < 0.001$). Medical patients were more likely to meet MET criteria than surgical patients ($P = 0.03$), and there were no significant differences for sex or between elective and emergency admissions. In the 79 patients not reviewed by the MET, the primary nurse escalated care for 36 patients (46%). Nurses independently initiated treatment for 23 of these patients (64%) and when unable to, they referred the patient for medical review (36%). Presence of MET criteria had resolved within 1 hour for 37 patients (45%) who fulfilled criteria.

Conclusions: Despite one in seven patients fulfilling MET criteria, MET activation occurred infrequently. The presence of MET criteria was associated with a doubling of the hospital LOS. Escalation of care in response to detection of MET criteria fulfilment was variable. Further research tracking patient management is needed to understand the decision-making process that occurs in the presence of clinical deterioration.

Crit Care Resusc 2013; 15: 266–272

Despite efforts to improve early recognition of abnormal vital signs and response to the affected patient, ward patients are still at risk of deterioration, which can lead to a serious adverse event. One model to identify and respond to this is the medical emergency team (MET). An MET is activated based on the measurement and recognition of clinical deterioration by clinicians, and their response. Clinical deterioration is identified by predefined vital sign derangements or subjective concern for a patient's condition. The MET consists of critical care clinicians who make time-critical decisions. These might include continuing current treatment; transferring a patient to an area for higher acuity patients; implementing a limitation-of-medical-therapy directive; or facilitating a transition to palliative care.[1,2] Failed MET activation or delayed MET calls commonly occur and are associated with worse patient outcomes.[3-5] Patients who are subject to an MET call or who fulfil MET criteria have an inhospital mortality rate of around 25%[6-8] and about 10% will require intensive care unit services.[6-7] Despite this observation, compliance with activation remains suboptimal.[9]

To our knowledge, no study has assessed the proportion of patients who fulfil MET criteria during their admission in a private institution, or how clinicians respond to abnormal vital signs if MET activation does not occur. Buist and colleagues have prospectively reported the incidence of abnormal clinical observations for patients' entire admission durations.[10] However, this study took place in a public setting and the major aim was to assess the association between abnormal vital signs and subsequent inhospital mortality.

We assessed the incidence of patients fulfilling MET criteria during their hospital admission, and their outcomes. We also compared the outcomes of patients with documented vital signs which fulfilled MET criteria, with the outcomes of patients whose documented vital signs did not fulfil MET criteria. Finally, we examined the actions that staff took in response to documented vital signs fulfilling MET criteria, and the time taken for aberrant vital signs to resolve.

Methods

Following ethics approval (approval 03-26-10-09), an observational study using a retrospective chart audit was

Table 1. Study inclusion criteria for adult and paediatric vital sign values

Vital sign	Value
Adult	
Systolic blood pressure (mmHg)	< 90
Heart rate (beats/minute)	> 130
Respiratory rate (breaths/minute)	> 30 or < 6
Oxygen saturation	< 90% on oxygen therapy
Paediatric	
Systolic blood pressure (mmHg)	
Age term–3 months	< 50
4–12 months	< 60
1–4 years	< 70
5–12 years	< 80
⩾ 12 years	< 90
Heart rate (bradycardia; tachycardia) (beats/minute)	
Age term–3 months	< 100; > 180
4–12 months	< 100; > 180
1–4 years	< 90; > 160
5–12 years	< 80; > 140
⩾ 12 years	< 60; > 130
Respiratory rate (breaths/minute)	
Age term–3 months	> 60
4–12 months	> 50
1–4 years	> 40
5–12 years	> 30
⩾ 12 years	> 30
Oxygen saturation	< 90% on oxygen therapy

conducted for patients hospitalised between 10 and 16 October 2009. Data were collected using a standardised case report form (CRF). Vital sign charts were reviewed to determine if patients had documented vital signs that fulfilled the MET calling criteria at any stage during their admission. The study parameters included systolic blood pressure, heart rate, respiratory rate and oxygen saturation. Only objective MET criteria from the institution were reviewed. Subjective criteria were purposely excluded; this decision was based on the knowledge that there is generally a large discrepancy in the interpretation and measurement of these criteria by nursing staff. Further, it would have been difficult to ensure reliability and consistency in results by retrospectively collecting these data, as they may not have been documented. The adult and paediatric MET calling criteria are shown in Table 1. Patients who fulfilled MET criteria were cross-referenced with the ICU database to determine whether they received an MET review.

Setting

Our study was conducted in a private health care facility in Melbourne, Australia. The hospital has about 400 beds, an emergency department (ED), a coronary care unit and a 12-bed ICU. The hospital implemented an MET in 2003, and all staff were trained in when and how to activate an MET call and the reason for doing so. MET training is compulsory for all new staff during their hospital orientation. The MET can be activated by any staff member if a patient fulfils one or more of the objective criteria or for any subjective concern. At the time of our study, vital signs were transcribed on a hospital-specific observation chart in a horizontal manner, so no graphical trends were possible to establish. Hospital policy stated that observations were to be performed 4-hourly for all patients, and were to include temperature, heart rate, respiration rate, blood pressure and pulse oximetry, unless otherwise ordered by medical staff or determined by the patient's clinical status.

Participants

Adult, paediatric and neonatal medical and surgical patients were included in the study if they were hospitalised for 24 hours or more in general ward areas or the postanaesthetic care unit (PACU), and discharged from the hospital during the 7-day study period.

Patients were excluded if they were hospitalised for less than 24 hours (eg, day oncology, day procedure unit or ED short-stay patients) or had a documented not-for-resuscitation order. If a patient had a concurrent ward and ICU admission, vital signs taken during the ICU stay were excluded.

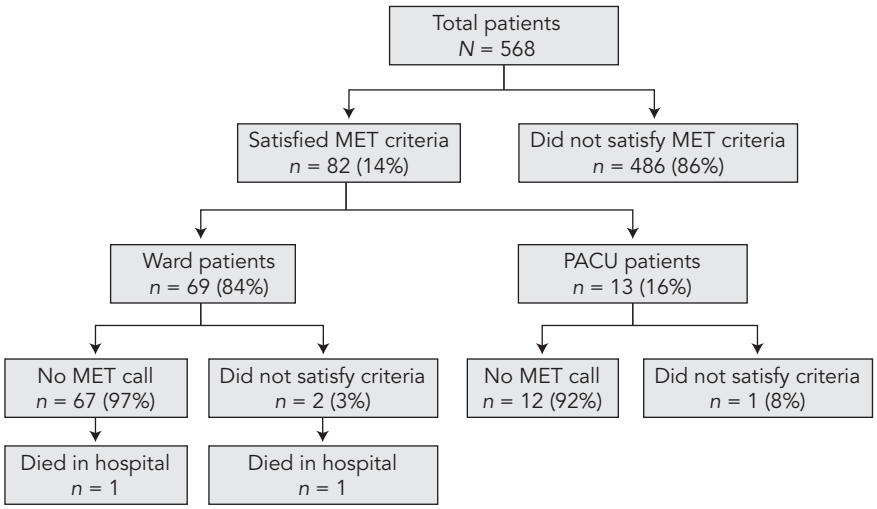
Data collection

Patient characteristics and demographics were recorded for every patient. For patients who fulfilled MET criteria, the date and time of the criteria being met and specific vital signs were documented. If MET activation did not occur, patient progress notes and intravenous and medication charts were reviewed to ascertain if other clinical escalation responses occurred. Alternative escalation responses were categorised as follows:

- the nurse in charge or doctor was notified and treatment ordered
- the primary nurse managed the patient
- the nurse in charge or doctor was notified and no treatment orders were made
- there was no documentation of recognition or response.

The time taken for the aberrant vital sign to resolve was determined as the time from the initial documented time that the vital sign parameter fulfilled an MET call criterion, to the documented time that the parameter returned to normal (did not fulfil an MET call criterion).

Figure 1. Summary of numbers of patients who did and did not satisfy MET activation criteria (*N* = 568)



MET = medical emergency team. PACU = postanaesthetic care unit.

Outcome measures

Our primary aim was to determine the incidence of patients who had vital signs that fulfilled the MET activation criteria at any stage during their admission, and the proportion who received an MET review.

We compared differences in baseline characteristics (gender, admission type and parent unit) and outcomes (length of stay [LOS] and inhospital mortality) for patients who fulfilled MET criteria with patients who did not. If MET activation failed, we examined if any alternative interventions occurred. Finally, we documented the time taken for aberrant vital signs to resolve.

Data analysis

All data were analysed using SPSS version 16 (SPSS Inc). Categorical variables (gender, admission type and parent unit) were analysed using the χ^2 value for determining significance, and obtained using the Yates correction for continuity. The *P* value set at 0.05 was considered statistically significant. Continuous variables (age and LOS) were compared using student *t* tests based on two independent samples.

Results

Patient characteristics

Of the sample (*N* = 568), 82 patients (14%) had an aberrant vital sign during their admission that fulfilled MET criteria; 69 patients (84%) were situated on a ward, and 13 (16%) were located in the PACU. Only 3 of 82 patients (4%) had a documented MET review; one patient in the PACU and the other two on wards. One ward patient with an MET activation was transferred to the ICU and the other patient was stabilised and remained on the ward. The patient reviewed in the PACU was transferred to the ward once haemodynamic stability was achieved.

Two patients of the sample of 568 (0.35%) died while in hospital, both with vital signs fulfilling MET criteria; only one patient received an MET review (Figure 1).

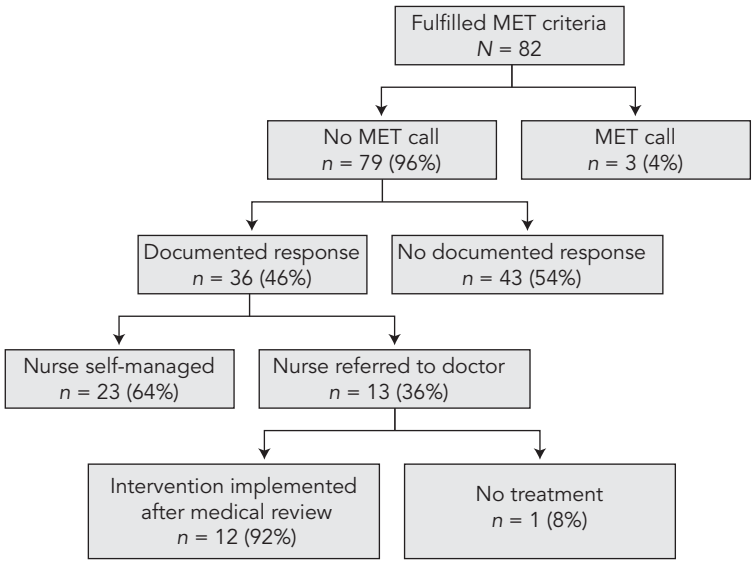
Hospital LOS for patients who fulfilled MET criteria was double that of patients who did not (8.6 days versus 4.3 days, respectively; $P < 0.001$). Medical patients were more likely to fulfil MET call criteria compared with surgical patients (18% versus 11%, respectively; $P = 0.03$). Although not statistically significant, more female than male patients fulfilled MET call criteria (16.8% versus 11.9%; $P = 0.121$). The mean ages for patients who did and did not fulfil MET call criteria were similar (61.5 years versus 60.8 years; $P = 0.782$).

Alternative escalation processes in the absence of an MET review

When an MET was not activated in response to aberrant vital signs, the primary nurse escalated care in 36/79 cases (46%). Of those 36, a nurse-initiated response occurred for 23 patients (64%) and, when an intervention outside the nursing scope of practice was required, a referral to the patient's treating doctor was made in 13 cases (36%). Subsequently, treatment was ordered for 12 of the 13 patients (92%) (Figure 2).

The four study parameters (blood pressure, heart rate, respiratory rate and oxygen saturation) were grouped to ascertain the overall proportion that fulfilled MET criteria and resolved in less than 1 hour. Notably, we found 37 patients (45%) demonstrated clinical improvement within 1 hour and no longer fulfilled MET criteria. Of that proportion, 26 (70%) had documentation indicating that the aberrant measurement was recognised and that a subsequent intervention had taken place. Most instances were responded to by the nurse initiating treatment (21; 81%) and, in five patients (19%), the nurse referred the patient to medical staff (Figure 3). Nursing interventions included administering or increasing supplemental oxygen supply in response to hypoxia, and patients who were hypotensive

Figure 2. Nurse response to aberrant vital signs (*N* = 82)



MET = medical emergency team.

received repositioning and an increased frequency of blood pressure measurements. In response to tachycardia a 12-lead electrocardiogram (ECG) was recorded, and the treating doctor was asked to review the patient. In all cases, the nurse reassessed the patient's vital signs and condition to ensure clinical stability was achieved after the intervention.

No documentation indicated that aberrant vital sign measurements were only reported to the nurse in charge. Typically, the doctor and nurse in charge were simultaneously notified of a problem, and the documentation reflected the treating doctor's assessment and orders.

Vital sign parameters fulfilling MET criteria

For the 82 patients who fulfilled the MET criteria, the most common vital signs documented as meeting the criteria were, in descending order: systolic blood pressure (42; 51%), oxygen saturation (27; 33%), heart rate (11; 13%) and respiratory rate (2; 2%).

Of the 42 patients whose blood pressure was the trigger for an MET activation, 33 patients (79%) had a systolic blood pressure < 90 mmHg and no documentation indicating recognition or escalation to senior nursing or medical staff (Figure 4). For five patients (12%) who were hypotensive, the primary nurse intervened by placing the patient in the Trendelenburg position and increased the frequency of blood pressure measurements until clinical stability was assured. A further five patients (12%) were referred to medical staff and in response received intravenous fluid therapy.

Documentation showed nursing staff were most responsive to low oxygen saturations. Of the 27 patients whose oxygen saturation was the trigger for an MET activation, 17 patients (63%) had a nurse who responded immediately by administering or increasing supplemental oxygen, and made frequent assessments to ensure the patient responded appropriately. In all 17 patients, oxygen saturations increased within 1 hour. Another five patients (19%) with documented hypoxia were referred to medical staff for review. All these patients were administered bronchodilators and attended medical imaging for a chest x-ray to further investigate their condition.

Of the 11 patients with documented tachyarrhythmia, two (18%) were referred to and reviewed by a doctor. In response, an ECG was recorded and antiarrhythmic agents were administered to treat the diagnosed clinical condition. For these patients, clinical stability was achieved in less than 3 hours. A further six patients who satisfied MET criteria for an aberrant heart rate did not have documentation indicating that nursing or medical staff had been alerted or that an intervention took place. Reasons for this remain unknown.

Two patients fulfilled MET criteria with tachypnoea, and neither had any documentation suggesting this was responded to.

Discussion

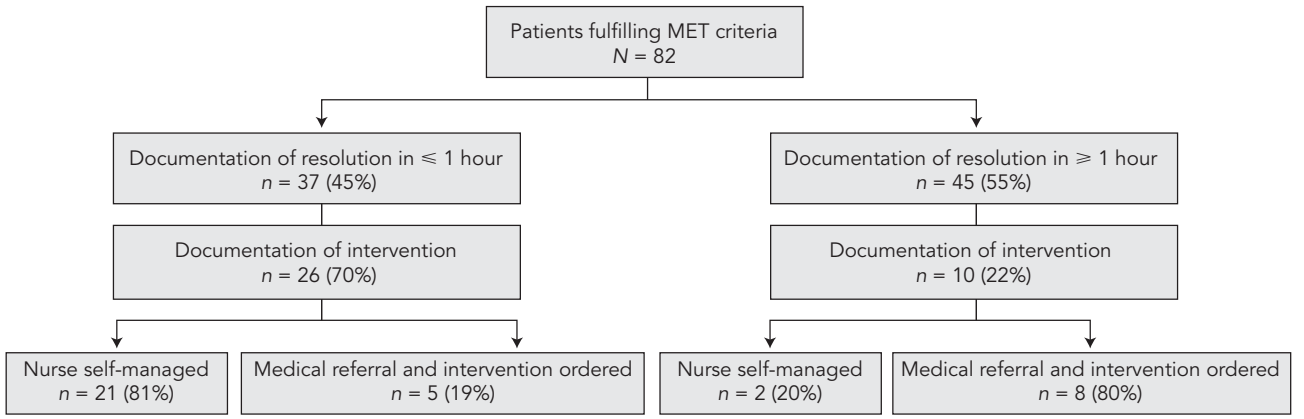
Major findings

We conducted a retrospective observational study to determine the incidence and outcomes of patients fulfilling MET criteria during their entire hospital admission. We found that one in seven patients (14%) had vital signs that fulfilled one or more MET call criteria. Only three patients received an MET review. Despite the low MET activation rate, aberrant vital signs were still responded to in 46% of the cohort. During the study period, two patients died in hospital. Significantly, hospital LOS for patients who fulfilled MET criteria was double that of patients who did not.

Comparison with previous studies

Our findings add to previous research reporting that 3%–27% of patients had vital signs fulfilling MET criteria.[9,11-13] In a single-centre study in Sweden and Denmark, the point prevalence of MET criteria being met was 4.5% and 18%, respectively. The study of Casamento and colleagues prospectively examined the prevalence of patients who fulfilled hospital-specific criteria for MET action, and reported that 3.26% of the 1688 patients had vital signs sufficient to warrant an MET review.[7] A study by Vetro and

Figure 3. Proportion of aberrant vital signs documented to have resolved in less than 1 hour (*N* = 82)



MET = medical emergency team.

colleagues revealed that of 22 patients who had a cardiac arrest, six patients (27%) had had vital signs fulfilling MET criteria in the preceding 6 hours but none had had an MET call.[14]

Differences in these reported incidences may relate to differences in MET criteria thresholds and patient demographics. The studies reporting MET incidence reviewed only a proportion of patient vital signs taken at their admission. Similarly to our study, Buist and colleagues prospectively assessed patients' vital signs from five general wards for their entire admission duration.[10] He reported that 8.9% of the cohort had had abnormal bedside observations, of which 67% spontaneously resolved and 21.6% were brought back to normal with treatment on the ward. The higher proportion of patients with abnormal vital signs and the proportion that spontaneously resolved could be attributed to the larger sample size, institutional variances and a longer study period.

Implications

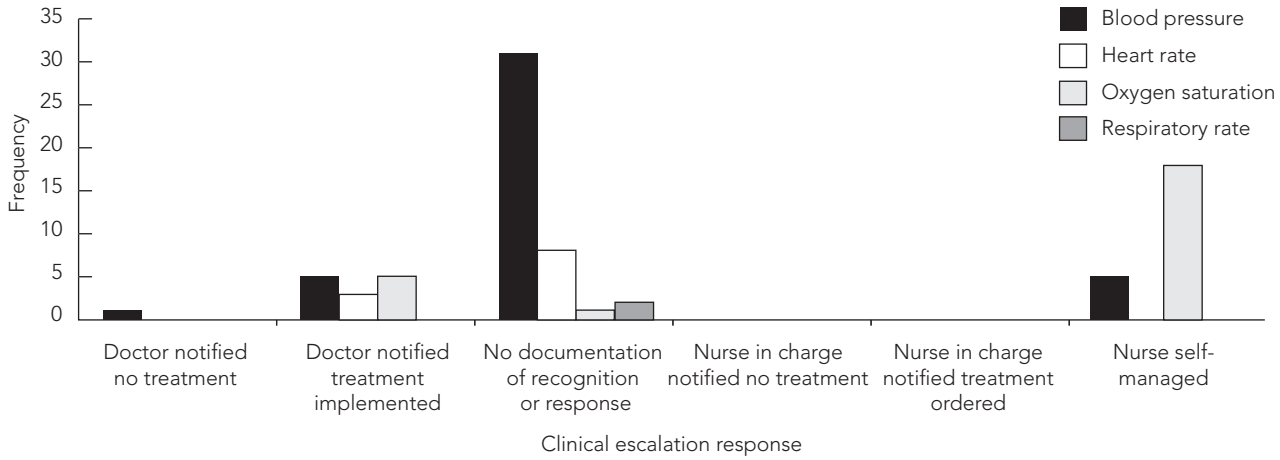
We found that one in seven patients fulfilled one or more MET criteria during their hospital admission. Therefore, the likelihood of nurses encountering patients who may deteriorate during a routine shift is high. In addition, patients with vital signs fulfilling MET criteria had an associated LOS that was double that of patients who did not. Similarly, Fuhrmann and colleagues reported a significant association between patients with abnormal vital signs and hospital LOS (median difference, 7 days; $P < 0.0001$).[9] An increased LOS has implications for patient morbidity, hospital resources and bed availabilities. Both these findings emphasise the importance of nurses recognising signs of clinical deterioration and valuing the importance of early escalation and intervention.

We found that MET activation occurred in a minority of patients fulfilling MET criteria, which initially suggested that nurses may not consistently recognise the clinical significance of or urgency in responding to aberrant vital signs. It was encouraging that half of patients had documentation indicating that nurses interpreted the meaning behind aberrant vital sign measurements and escalated care in ways other than activating an MET. Nurses mostly responded within their scope of practice or referred patients to medical staff for review and treatment orders. Importantly, in many patients, MET criteria resolved in less than 1 hour. This indicates that clinicians felt confident managing certain clinical situations without activating an MET. Nurses at the study institution favoured a multitiered response, as proposed by the Australian Commission on Safety and Quality in Health Care.[15] Similarly, Kansal and Havill reported an increase of 50% in escalation of care with the implementation of a two-tiered rapid-response system (along with new observation charts and MET calling criteria) for patients who were at risk of deteriorating.[16]

We found that hypotension and hypoxia were the most common parameters which fulfilled MET criteria. This finding was also reported in Buist's study, in which decreased oxygen saturation comprised 51% of all events and hypotension accounted for 17.3%.[10] Only two patients in our study had a documented respiratory rate fulfilling MET criteria for tachypnoea. Despite a large body of evidence indicating that an abnormal respiratory rate is an important predictor of serious adverse events,[17-20] neither of these patients had documentation indicating responsiveness in terms of therapeutic management or further investigation of causes.

We found that respiratory rate was infrequently documented and often missing as part of a full set of vital sign

Figure 4. Escalation responses to individual study parameters when medical emergency team activation failed



measurements. It is unknown if this represents infrequent assessment or poor documentation, both of which have been reported in previous studies.[20-23] Incomplete vital sign measurement undermines the objective basis of ascertaining the clinical status of a patient and the value associated with a response system.[24] Medical students and clinicians should be taught that respiratory rate is the most useful marker for identifying patients at risk of serious adverse events, and therefore warrants frequent assessment and documentation.

Further research

Further research is needed to understand the decision-making processes of nurses when they are faced with clinical deterioration of a patient. Other factors that need investigating are those influencing which clinicians summon an MET call immediately compared with those who do not. Insight into the routine documentation practices of clinicians would be useful, to ascertain the intervention, referral and management decisions that are formally documented and those that are not.

Research to inform the optimal frequency of vital sign measurement to ensure clinical deterioration does not go unrecognised and to prevent associated complications would be beneficial. Understanding the factors that contribute to a doubling of LOS would benefit patient management and outcome decisions.

Strengths and limitations

To our knowledge, our study is the first to review the incidence and outcomes of patients fulfilling MET criteria for their entire hospital LOS in a private population. The private setting may have restricted our ability to generalise our findings, but the study institution represents a typical large metropolitan private hospital in a developed country. Therefore, the results and study methodology may be relevant to other institutions with similar characteristics. We cannot comment on the proportion of objective concerns that were not escalated.

Our results further contribute to existing MET literature by investigating the trajectory of care provided in the absence of an MET review. Our CRF had predefined questions to efficiently capture information so that we could meet our research aims and make data collection consistent. Clinicians were not aware of the study taking place, so their decision making was not altered by the presence of researchers.

Documentation bias is a potential limitation of our study. Data obtained from this chart review relied on accurate measurement and documentation of vital signs, escalation procedures and interventions implemented by clinicians. While this documentation is a legal requirement for nurses, we recognise that it may not always occur accurately and completely. The data collection period occurred during 1 week in October, therefore seasonal and institutional variations cannot be accounted for. We had limited information on admission and presence of baseline comorbidities. We cannot comment on whether intervention by the MET would have resulted in a reduction in the increased LOS observed.

Conclusions

The MET is a major component of the modern health care system. Recognising the significance of altered physiological observations and responding appropriately is a highly complex process, and involves nurses integrating knowledge with clinical experience. Patients fulfilling MET criteria had twice the hospital LOS. Further research is needed to

assess nurse decision making in the context of abnormal vital signs, and the actions taken in the absence of MET review.

Competing interests

None declared.

Author details

Jessica L Guinane, PhD Candidate[1]
Tracey K Bucknall, Professor of Nursing, Alfred Deakin Centre for Nursing Research, Alfred Health[1]
Judy Currey, Leader, Postgraduate Critical Care and Perioperative Programs, Faculty of Health[1]
Daryl A Jones, Intensive Care Specialist, Adjunct Senior Research Fellow and PhD Candidate[2]
1 Deakin University, Melbourne, VIC, Australia.
2 Austin Health, Melbourne, VIC, Australia.
Correspondence: j.guinane@deakin.edu.au

References

1 Smith GB. Increased do not attempt resuscitation decision making in hospitals with a medical emergency teams system — cause and effect? *Resuscitation* 2008; 79: 346-7.
2 Jones DA, McIntyre T, Baldwin I, et al. The medical emergency team and end-of-life care: a pilot study. *Crit Care Resusc* 2007; 9: 151-6.
3 McQuillan P, Pilkington S, Allan A, et al. Confidential inquiry into quality of care before admission to intensive care. *BMJ* 1998; 316: 1853-8.
4 Buist MD, Jarmolowski E, Burton PR, et al. Recognising clinical instability in hospital patients before cardiac arrest or unplanned admission to intensive care. A pilot study in a tertiary-care hospital. *Med J Aust* 1999; 171: 22-5.
5 Goldhill DR, Worthington L, Mulcahy A, et al. The patient-at-risk team: identifying and managing seriously ill ward patients. *Anaesthesia* 1999; 54: 853-60.
6 Calzavacca P, Licari E, Tee A, et al. Features and outcome of patients receiving multiple Medical Emergency Team reviews. *Resuscitation* 2010; 81: 1509-15.
7 Casamento AJ, Dunlop C, Jones DA, Duke G. Improving the documentation of medical emergency team reviews. *Crit Care Resusc* 2008; 10: 29.
8 Buist MD, Moore GE, Bernard SA, et al. Effects of a medical emergency team on reduction of incidence of and mortality from unexpected cardiac arrests in hospital: preliminary study. *BMJ* 2002; 324: 387-90.
9 Fuhrmann L, Lippert A, Perner A, Østergaard D. Incidence, staff awareness and mortality of patients at risk on general wards. *Resuscitation* 2008; 77: 325-30.
10 Buist M, Bernard S, Nguyen TV, et al. Association between clinically abnormal observations and subsequent in-hospital mortality: a prospective study. *Resuscitation* 2004; 62: 137-41.
11 Harrison GA, Jacques TC, Kilborn G, McLaws ML. The prevalence of recordings of the signs of critical conditions and emergency responses in hospital wards—the SOCCER study. *Resuscitation* 2005; 65: 149-57.
12 Bell MB, Konrad D, Granath F, et al. Prevalence and sensitivity of MET-criteria in a Scandinavian University Hospital. *Resuscitation* 2006; 70: 66-73.
13 Bucknall TK, Jones D, Bellomo R, Staples M. Responding to medical Emergencies: System Characteristics Under Examination (RESCUE): a prospective multi-site point prevalence study. *Resuscitation* 2013; 84: 179-83.
14 Australian Commission on Safety and Quality in Health Care. National consensus statement: essential elements for recognising and responding to clinical deterioration. Sydney: ACSQHC, 2010. http://www.safetyandquality.gov.au/publications/national-consensus-statement-essential-elements-for-recognising-and-responding-to-clinical-deterioration (accessed Sep 2013).
15 Vetro J, Natarajan DK, Mercer I, et al. Antecedents to cardiac arrests in a hospital equipped with a medical emergency team. *Crit Care Resusc* 2011; 13: 162-6.
16 Kansal A, Havill K. The effects of introduction of new observation charts and calling criteria on call characteristics and outcome of hospitalised patients. *Crit Care Resusc* 2012; 14: 38-43.
17 Cretikos M, Chen J, Hillman K, et al. The objective medical emergency team activation criteria: a case-control study. *Resuscitation* 2007; 73: 62-72.
18 Fieselmann JF, Hendryx MS, Helms CM, Wakefield DS. Respiratory rate predicts cardiopulmonary arrest for internal medicine inpatients. *J Gen Intern Med* 1993; 8: 354-60.
19 Goldhill DR, McNarry AF, Mandersloot G, McGinley A. A physiologically-based early warning score for ward patients: the association between score and outcome. *Anaesthesia* 2005; 60: 547-53.
20 Hodgetts TJ, Kenward G, Vlachonikolis IG, et al. The identification of risk factors for cardiac arrest and formulation of activation criteria to alert a medical emergency team. *Resuscitation* 2002; 54: 125-31.
21 Hogan J. Why don't nurses monitor the respiratory rates of patients? *Br J Nurs* 2006; 15: 489-92.
22 McBride J, Knight D, Piper J, Smith GB. Long-term effect of introducing an early warning score on respiratory rate charting on general wards. *Resuscitation* 2005; 65: 41-4.
23 Ryan H, Cadman C, Hann L. Setting standards for assessment of ward patients at risk of deterioration. *Br J Nurs* 2004; 13: 1186-90.
24 Leuvan CH, Mitchell I. Missed opportunities? An observational study of vital sign measurements. *Crit Care Resusc* 2008; 10: 111-5. ❑

Mortality of rapid response team patients in Australia: a multicentre study

The ANZICS-CORE MET dose investigators

ABSTRACT

Background: Most studies of the rapid response team (RRT) investigate the effect of introducing an RRT on outcomes of all hospitalised patients. Less information exists on RRT patient epidemiology, or changes in RRT call numbers with time.

Objectives: To estimate the inhospital mortality of patients subject to RRT review, the proportion of inhospital deaths reviewed by the RRT, and changes in annual RRT call numbers with time.

Method: Retrospective observational study in adult RRT-equipped Australian hospitals for up to 10 years (2000–2009).

Participants and outcome measures: Thirty-four per cent (35/102) of the Australian adult RRT-equipped hospitals provided annual hospital admissions and deaths, intensive care unit admissions and RRT calls. They also provided the number of patients reviewed by the RRT and the number of inhospital deaths in such patients.

Results: Over the study period, there were 4.91 million hospital admissions, 196 488 ICU admissions and 99 377 RRT calls. Most data arose from Victoria, New South Wales and Western Australia, and from public tertiary hospitals. Among the 27 hospitals contributing at least 4 years of data, annual RRT calls per 1000 admissions was higher in the last year compared with the first year of data submission in 23 hospitals (range of increase, 11.9%–777.4%; median, 90%; interquartile range, 40%–180%). In the remaining four hospitals, annual RRT calls per 1000 admissions were lower in the last year compared with the first year (range of decrease, – 5.5% to – 29.8%). Among the 70 924 RRT patients for whom the outcome was known, there were 17 260 deaths (24.3%). We calculate that the RRT reviewed 17 260 of 79 476 patients (21.7%) who died in hospital over the study period. In the 2008–09 financial year, there were 18 800 RRT calls for at least 14 743 patients.

Conclusions: Annual RRT calls are increasing in many Australian hospitals, and now affect more than 14 700 patients annually. Inhospital mortality of RRT patients is about 25%, and about 20% of patients who die in hospital are reviewed by the RRT. Further research is needed to understand the reason for the high inhospital mortality of RRT patients.

Crit Care Resusc 2013; 15: 273–278

Rapid response teams (RRTs) have been introduced in hospitals to identify and treat deteriorating patients. Such teams have been introduced in many countries around the world, including the United States, Canada,[1] the Netherlands,[3] Brazil[4] and Sweden,[5] as well as Australia and New Zealand.[6] Most studies of RRTs have focused on what happens to the outcomes of an entire hospital population when an RRT is introduced. The most commonly studied outcomes include unexpected deaths, unplanned intensive care unit admissions and cardiac arrest rates. There is much less information on the resource implications of introducing an RRT service or the characteristics and outcome of patients who are actually reviewed by the RRT.[7]

Three single-centre studies have reported a progressive increase in the use of an RRT service with time,[8-10] but no studies exist to assess such time-related changes over several years in multiple hospitals. Other single-centre studies suggest that the inhospital mortality of adult patients subject to RRT review is about 20%[11-13] — much greater than the 11% inhospital mortality typically reported for ICU admissions in Australia.[14] If these findings were true in multiple hospitals, this would have major implications for workload and resource use (particularly for ICUs[15,16]) as well as for public health.

We conducted a retrospective observational study in 35 Australian adult hospitals to estimate the mortality of patients subject to RRT review from financial year 2000–01 to 2009–2010. In addition, we assessed the broader resource implications of RRT services, by assessing the changes in annualised RRT reviews. Finally, we investigated the role of the RRT in end-of-life care, by calculating the proportion of inhospital deaths that were seen by the RRT.

Methods

We obtained ethics approval from all participating hospital research and ethics committees and from Monash University (CF10/1531 – 2010000820). The need for informed patient consent was waived by all committees. This study is part of a larger study of 39 hospitals.[15] Of these, for the present study, we excluded three paediatric hospitals and one hospital that was not able to provide data.

Table 1. Hospital admissions, intensive care unit admissions and total rapid response team (RRT) calls for 35 adult Australian hospitals over a 10-year period

	Hospital admissions	ICU admissions	Total RRT calls
Total number	4 914 746	196 488	99 377
ICU classification			
Metropolitan	27.1%	14.2%	16.5%
Private	9.1%	10.0%	3.3%
Rural/regional	21.0%	15.6%	12.3%
Tertiary	42.8%	60.2%	67.9%
Jurisdiction			
Australian Capital Territory	1.5%	2.4%	2.7%
New South Wales	26.1%	23.3%	25.9%
Northern Territory	0.7%	1.3%	0.2%
Queensland	11.7%	6.3%	5.1%
South Australia	8.3%	9.7%	8.5%
Tasmania	0.9%	0.7%	0.3%
Victoria	36.6%	45.6%	45.1%
Western Australia	14.1%	10.7%	12.2%
ICU level			
1	0.6%	0.8%	0.4%
2	33.6%	23.8%	19.8%
3	65.8%	75.4%	79.7%

Study infrastructure and coordination

The study was coordinated from the Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation (ANZICS-CORE). A management committee (Appendix) oversaw all aspects of the study, including study design and development, obtaining funding, development, review and distribution of the study protocol and data dictionary, collation of results, query resolution with participating sites, data analysis, and manuscript writing.

Staff from the 102 adult hospitals known to have an RRT were invited to participate via email in early 2010, and the protocol and data dictionary were finalised in May 2010. At each hospital, the investigators obtained site-specific data from clinical information systems and inhouse RRT databases. These were collated into a Microsoft Excel spreadsheet, and emailed to the coordination centre. Data enquiries were handled by one or more site investigators at each hospital (Appendix).

Funding was obtained from the Australian Commission on Safety and Quality in Health Care (ACSQHC) to fund a part-time research officer, and cover partial costs at participating sites.

Data collected

At each site, the investigators obtained retrospective data for each financial year (1 July to 30 June) as aggregate numbers, collated in a Microsoft Excel spreadsheet. The 2000–01 financial year is represented by the year 2000. Only aggregate data were provided, and no individual patient data were submitted to the management committee. All sites provided identical data and a data dictionary was provided to investigators to standardise data collection. Only years where data were available for the complete financial year were included. Thus, data for each year were classified as "unavailable" if the hospital did not collect data for that year, or if data were only available for part of the year.

At each site, investigators collected data on numbers of hospital admissions lasting more than 24 hours (excluding day cases, endoscopies, same-day dialysis and chronic/rehabilitation patients), inhospital deaths in acute patients, ICU admissions and total RRT calls.

In addition to collecting data on annual RRT calls or admission numbers, we also calculated the inhospital mortality of RRT patients. To achieve this, site investigators collated data on the number of "RRT patients where the inhospital mortality was known". This group calculated the number of patients subject to RRT review by excluding repeat RRT reviews (so outcome was not counted twice), and excluding RRT calls where the inhospital outcome was not known.

Finally, site investigators collected data on "RRT call patient deaths", which was the number of patient deaths

Table 2. Comparison of site characteristics for study participants and non-participants over a 10-year periodICY =

	Non-participant	Participant	Total	*P**
Jurisdiction				
Australian Capital Territory	1 (1.5)	1 (2.9)	2 (2.0)	
New South Wales	23 (34.3)	6 (17.1)	29 (28.4)	
Northern Territory	0 (0)	1 (2.9)	1 (1.0)	
Queensland	18 (26.9)	3 (8.6)	21 (20.6)	0.07
South Australia	4 (6.0)	4 (11.4)	8 (7.8)	
Tasmania	2(3.0)	1 (2.9)	3 (2.9)	
Victoria	15 (22.4)	15 (42.9)	30 (29.4)	
Western Australia	4 (6.0)	4 (11.4)	8 (7.8)	
ICU classification				
Metropolitan	14 (20.9)	8 (22.9)	22 (21.6)	
Private	29 (43.3)	6 (17.1)	35 (34.3)	0.02
Rural/regional	16 (23.9)	10 (28.6)	26 (25.5)	
Tertiary	8 (11.9)	11 (31.4)	19 (18.6)	
Public/private				
Private	29 (43.3)	6 (17.1)	35 (34.3)	0.008
Public	38 (56.7)	29 (82.9)	67 (65.7)	
ICU level				
1	6 (9.0)	1 (2.9)	7 (6.9)	
2	33 (49.3)	16 (45.7)	49 (48.0)	0.41
3	28 (41.8)	18 (51.4)	46 (45.1)	
Total	67	35	102	

ICU = intensive care unit. * Significance, < 0.05.

among the group of "RRT patients where the inhospital mortality was known". Mortality in RRT patients was estimated by dividing the number of deaths by the number of RRT patients where this outcome measure was known.

Data analysis and statistics

We present descriptive statistics as crude numbers and percentage of totals, and distributions are presented as median and interquartile range (IQR). Details on hospital admissions, ICU admissions and total RRT calls are presented as aggregate data, and according to hospital type, jurisdiction of Australia, and College of Intensive Care Medicine level (1, 2 or 3).[14]

Annual RRT reviews were presented as RRT calls per 1000 admissions. We present the range, median and IQR for call numbers overall. Additionally, in hospitals that contributed data for at least four consecutive years, we plot the trend for annual RRT calls per 1000 admissions versus year since implementation, and describe changes in annual RRT reviews by comparing calls per 1000 admissions in the last versus the first year of data submitted.

Inhospital mortality was derived by dividing deaths over admissions for years where both data were available, and are expressed as a percentage. RRT call patient mortality was obtained by dividing RRT call patient deaths by the number of RRT patients where the inhospital mortality was known (also expressed as a percentage).

Statistical analysis was performed using SAS version 9.2 (SAS Institute). Comparison of proportions was performed using χ^2 tests for equal proportion with Yates' continuity correction, and a two-sided $P < 0.05$ was taken to indicate statistical significance.

Results

Details of overall cohort

At the time of study enrolment, 102 adult hospitals were known to have an RRT and, of these, 35 (34.3%) participated in the study. Based on the known RRT start date at each hospital, data were available for 198 of 270 (73.3%) possible years. In the 2000–01 financial year, five sites contributed data, and this increased to 35 sites in the 2008–09 financial year.

Overall, there were 4.91 million hospital admissions, 196 488 ICU admissions, and 99 377 RRT calls (Table 1). Most data arose from hospitals in Victoria, New South Wales and Western Australia, and from level 2 and 3 ICUs (Table 1 and Table 2). Participating sites were more likely to be public and tertiary level hospitals (Table 2).

Change in annualised RRT reviews

The annualised RRT reviews varied almost 53-fold, from 1.35 per 1000 admissions in a rural/regional hospital in 2007–08, to 71.32 per 1000 admissions in a tertiary-level hospital in 2009–10. The median number of RRT reviews was 14.0 (IQR, 8.0–30.0) calls per 1000 admissions.

Among the 35 participating sites, 27 contributed at least 4 years of data (Figure 1). Among these 27 hospitals, in 23 hospitals, the annualised number of RRT reviews per 1000 admissions was higher in the last year compared with the first year of data submission (range of increase, 11.9%–777.4%; median, 90%; IQR, 40%–180%). In the remaining four hospitals, the annualised number of RRT reviews per 1000 admissions was lower in the last year

compared with the first year (range of decrease, – 5.5% to – 29.8%).

Inhospital mortality of hospital admissions and patients subject to RRT review

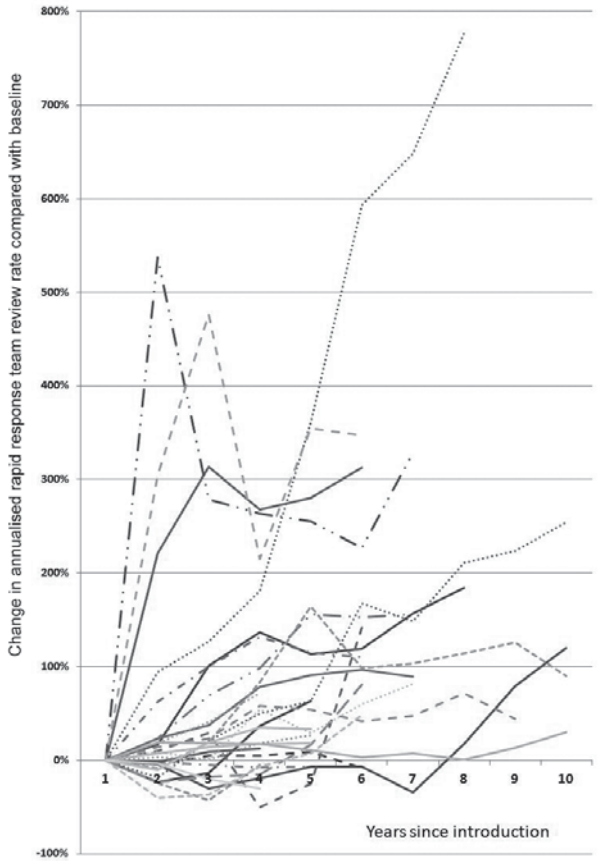
Over the 10-year period, there were 4 818 277 hospital admissions where the inhospital mortality was known; among these, there were 79 476 deaths (1.6%). Among the 99 377 RRT calls, there were 70 924 RRT patients for whom the outcome was known; among these, there were 17 260 deaths (24.3%).

As there were 79 476 hospital deaths and 17 260 RRT-related deaths, we calculate that the RRT services reviewed 21.7% of the patients who died in the participating hospitals over the 10-year study period.

Details of data from the 2008–09 financial year

In the 2008–09 financial year, all 35 hospitals contributed data. During the year, there were 862 886 hospital admissions, 33 842 ICU admissions and 18 800 RRT calls. Among the 14 743 RRT patients for whom the outcome was known, there were 3305 deaths (22.4%). In the 2008–09 financial year, the RRT reviewed at least 3305/13 611 (24.3%) of all patients who died in hospital.

Figure 1. Percentage change in annualised rapid response team review rate compared with baseline for 27 hospitals contributing at least 4 years of continuous data



Discussion

We studied 35 RRT-equipped Australian adult hospitals over a 10-year period. We found that in 23 hospitals there was an increase in annual RRT calls after adjusting for hospital admissions. We further found that the mortality of RRT patients was around 24%, and that the RRT reviewed about one in five of all hospital deaths. As these findings now affect more than 14 000 patients annually, they have important public health implications.

Our findings suggest that patients reviewed by the RRT are at increased risk of death, with inhospital mortality greater than the 11% typically reported for ICU admissions in Australia[14] but less than the 80% mortality seen in patients who suffer cardiac arrest.[17,18] It is likely that many of the patients subject to RRT review had limitations of medical therapy and do-not-resuscitate orders. A previously published multicentre study has shown that RRT patients with limitations of medical therapy have an inhospital mortality of about 50%.[19]

Other studies have also shown high mortality in adult patients subject to RRT review, ranging from 23.6% to 31.8%.[11-13,19] The mortality presented here (24.3%) is very similar to that seen in a recently published seven-hospital multinational prospective observational study (23.6%).[19] It is also similar to that of patients urgently admitted to the ICU from the ward.[20]

Our findings suggest that RRT reviews are increasing in a substantial number of hospitals and now involve more than 14 000 patients in Australia every year. As the study hospitals represented here comprise about a third of adult RRT-equipped hospitals, it is highly likely that this number is substantially larger.

Given the high inhospital mortality of patients subject to RRT review, our findings suggest that novel strategies are required to prevent patients deteriorating before RRT criteria are fulfilled, and to optimise the outcome of patients reviewed by the RRT. If part of the mortality is related to not-for-resuscitation orders, then there is a need for systematic improvements of ward-based end-of-life care. As only a quarter of these hospitals are specifically funded to provide such services,[15] our findings also suggest there may be a need to better resource RRTs. Finally, as RRT patients represent a large proportion of ICU workload and are subject to high inhospital mortality, there may also be a need to develop centralised databases

for RRT calls similar to that performed for ICU admissions in Australia and New Zealand.[21]

Our study has a number of strengths. It involved 35 hospitals, a 10-year inception period, and examined and compared the outcomes of more than 4.8 million hospital admissions and 70 000 RRT call patients. It is the largest multicentre study to demonstrate high inhospital mortality in RRT patients. It involved the collection of simple aggregate data sets, use of a data dictionary to standardise data collection, and data queries to optimise data quality.

Despite these strengths, our study has important limitations, including its retrospective design, single-country representation, incomplete data sets, low participation rate, and disproportionate representation from limited jurisdictions and large teaching hospitals. Thus, we cannot comment on the details of the breakdown of the relative numbers of repeat RRT calls and patients for whom the outcome was not known. Despite these limitations, the overall RRT call mortality observed accords well with a recently published multinational prospective observational study[19] and a single centre study from Sweden.[5]

A further limitation was our inability to provide explanations for the high mortality, the timing of death in relation to RRT review, and inability to comment on the proportion of patients subject to end-of-life care and the impact of these factors on RRT patient mortality. We were also not able to comment on factors contributing to the variability of annual RRT rates between hospitals, including local cultural factors, differences in maturation effects, release of guidelines and published studies on the RRT.

Further research is required to better elucidate the epidemiology of patients reviewed by the RRT in order to identify patient, disease and system factors that may contribute to a patient needing RRT review, which can be addressed to improve patient outcomes. Importantly, strategies need to be developed to prevent deterioration in the period before RRT review. In addition, the findings of our study require confirmation in similar studies from other countries.

Our study suggests that RRT calls are increasing in number in many adult Australian hospitals. Further studies are required to identify patient, disease and system factors that contribute to the high mortality of RRT patients, and to develop strategies to reduce it. In addition, improved resources are likely to be required to treat this at-risk group of patients.

Acknowledgement

Funding for this study was provided by the ACSQHC. The funder had no role in the conception, design, conduct, analysis or writing phases of the study.

Competing interests

Daryl Jones received a research grant from the ACSQHC for RRT research in 39 Australian hospitals, and consultancy fees from Eastern Health. Rinaldo Bellomo works as a paid consultant for Philips Medical Systems in the development of monitoring technology for general wards.

Author details

The ANZICS-CORE MET dose investigators
*Correspondence:*Daryl.Jones@austin.org.au

References

1 Steel AC, Reynolds SF. The growth of rapid response systems. *Jt Comm J Qual Patient Saf* 2008; 34: 489-95.
2 Lobos AT, Costello J, Gilleland J, et al. An implementation strategy for a multicentre pediatric rapid response system in Ontario. *Jt Comm J Qual Patient Saf* 2010; 36: 271-80.
3 Ludikhuize J, Hamming A, de Jonge E, Fikkers BG. Rapid response systems in The Netherlands. *Jt Comm J Qual Patient Saf* 2011; 37: 138-44.
4 Boniatti MM, Azzolini N, da Fonseca DL, et al. Prognostic value of the calling criteria in patients receiving a medical emergency team review. *Resuscitation* 2010; 81: 667-70.
5 Jäderling G, Calzavacca P, Bell M, et al. The deteriorating ward patient: a Swedish-Australian comparison. *Intensive Care Med* 2011; 37: 1000-5.
6 Jones D, George C, Bellomo R, et al. Introduction of Medical Emergency Teams in Australia and New Zealand: a multi-centre study. *Crit Care* 2008; 12: R46.
7 DeVita M. Medical emergency teams: deciphering clues to crises in hospitals. *Crit Care* 2005; 9: 325-6.
8 Jones D, Bates S, Warrillow S, et al. Effect of an education programme on the utilization of a medical emergency team in a teaching hospital. *Intern Med J* 2006; 36: 231-6.
9 Jones D, Mitra B, Barbetti J, et al. Increasing the use of an existing medical emergency team in a teaching hospital. *Anaesth Intensive Care* 2006; 34: 731-5.
10 DeVita MA, Braithwaite RS, Mahidhara R, et al. Use of medical emergency team responses to reduce hospital cardiopulmonary arrests. *Qual Saf Health Care* 2004; 13: 251-4.
11 Calzavacca P, Licari E, Tee A, et al. Features and outcome of patients receiving multiple Medical Emergency Team reviews. *Resuscitation* 2010; 81: 1509-15.
12 Casamento AJ, Dunlop C, Jones DA, Duke G. Improving the documentation of medical emergency team reviews. *Crit Care Resusc* 2008; 10: 29.
13 Buist MD, Moore GE, Bernard SA, et al. Effects of a medical emergency team on reduction of incidence of and mortality from unexpected cardiac arrests in hospital: preliminary study. *BMJ* 2002; 324: 387-90.
14 Drennan K, Hicks P, Hart GK. Intensive Care Resources & Activity: Australia & New Zealand 2007/2008. ANZICS, Melbourne. http://www.anzics.com.au/core/reports (accessed Aug 2011).
15 The ANZICS-CORE MET dose Investigators; Jones D, Drennan K, Hart GK, et al. Rapid Response Team composition, resourcing and calling criteria in Australia. *Resuscitation* 2012; 83: 563-7.
16 Jacques T, Harrison GA, McLaws ML. Attitudes towards and evaluation of medical emergency teams: a survey of trainees in intensive care medicine *Anaesth Intensive Care* 2008; 36: 90-5.

17 McGrath RB. In-house cardiopulmonary resuscitation–after a quarter of a century. *Ann Emerg Med* 1987; 16: 1365-8.
18 Peberdy MA, Ornato JP, Larkin GL, et al. Survival from in-hospital cardiac arrest during nights and weekends. *JAMA* 2008; 299: 785-92.
19 Jones DA, Bagshaw SM, Barrett J, et al. The role of the medical emergency team in end-of-life care: a multicenter, prospective, observational study. *Crit Care Med* 2012; 40: 98-103.
20 Flabouris A, Hart G, George C. Observational study of patients admitted to intensive care units in Australia and New Zealand after interhospital transfer. *Crit Care Resusc* 2008; 10: 90-6.
21 Stow PJ, Hart GK, Higlett T, et al; ANZICS Database Management Committee. Development and implementation of a high-quality clinical database: the Australian and New Zealand Intensive Care Society Adult Patient Database. *J Crit Care* 2006; 21: 133-41. ❑

Appendix. ANZICS-CORE MET dose investigators

Writing and management committee

Daryl A Jones (Chair), Kelly Drennan, Michael Bailey, Graeme K Hart, Rinaldo Bellomo, Steven A R Webb

Site investigators (hospitals are in Victoria unless specified)

The Alfred: Sandy Zalstein, Kathleen Collins
Alice Springs (NT): Penny Stewart, Wendy Corkill
Austin: Antoine Schneider, Paolo Calzavacca
Ballarat Health Services: Andrew Thomas, Dianne Hill, Sofia Jasiowski
Barwon Health: David Green, Peter Stow
Bendigo: Jason Fletcher, Julie Smith
Cairns Base (Qld): Drew Wenck, Catherine Pearce
Calvary Mater Newcastle (NSW): Melissa Lintott, Katrina Ellem
Calvary Wakefield (SA): Amanda Rischbieth, Katherine Davidson
Canberra (ACT): Imogen Mitchell, Nicole Slater, David Elliott
Central Gippsland: Jenny Dennett, Tim Coles
Children's at Westmead (NSW): Bradley Ceely, Stephen Jacobs
Dandenong: Yvonne Kearley, Kate Shepherd, Bridget O'Bree
Epworth Freemasons: Nerina Harley, Megan Robertson, Lenise Banner, Kristy Green
Flinders (SA): Andrew Bersten, Elisha Matheson
Flinders Private (SA): Merle Carter, Andrew Holt
Fremantle (WA): Frank Breheny
Gosford (NSW): John Albury, Robert Cameron
Goulburn Valley: Lynn Morcom, Julie Mathewson, Mathew Piercy
Hornsby (NSW): Jay Halkhoree, James Fratzia
Joonalup (WA): Bev Ewens, Brad Power
Lismore (NSW): Di Goldie, Craig McCalman
Liverpool (NSW): Sharon Micallef, Nicholas Mifflin, Michael Parr
Lyell McEwin (SA): Josette Wood, Peter Thomas, Sam Clausen
Nepean (NSW): Stuart Lane, Janet Scott
North West Regional (Tas): Trudy Segger, Alan Rouse
Redcliffe (Qld): Leeona Smith, Hamish Pollock
Repatriation General (SA): Jayne Williams, Andrew Bersten
Royal Children's: Warwick Butt, Carmel Delzoppo, Sophie Sydall
Royal Melbourne: Nerina Harley, Peter Morley, Jennifer Bell
Sir Charles Gairdner (WA): Mary Pinder, Anne Brinkworth, Brigit Roberts
St John of God Ballarat: Barry Flynn
St John of God (Subiaco, WA): Kim Lawrence, David Morgan
St Vincent's: John Santamaria
Townsville Health Service District (Qld): Geoff Gordon, Katharine Hutchinson
Wangaratta: Brett Johnson
Warrnambool: Marcia Beard
Warringal Private: Jenny Broadbent
Women's and Children's (SA): Katrina Welbing, Michael Yung, Neil Matthews ❑

Statistical analysis plan for the HEAT trial: a multicentre randomised placebo-controlled trial of intravenous paracetamol in intensive care unit patients with fever and infection

Paul J Young, Mark Weatherall, Manoj K Saxena, Rinaldo Bellomo, Ross C Freebairn, Naomi E Hammond, Frank M P van Haren, Seton J Henderson, Colin J McArthur, Shay P McGuinness, Diane Mackle, John A Myburgh, Steve A R Webb and Richard W Beasley and the Australian and New Zealand Intensive Care Society Clinical Trials Group

ABSTRACT

Background and objective: We describe the statistical analysis plan (SAP) for the Permissive Hyperthermia through Avoidance of Paracetamol in Known or Suspected Infection in the Intensive Care Unit (HEAT) trial, a 700-patient, prospective, randomised, Phase 2b, multicentre, double-blind, parallel-groups, placebo-controlled trial of paracetamol administration for the treatment of fever in critically ill patients with known or suspected infection.

Methods: The data fields described are those outlined in the study protocol published previously. We describe the plan for the presentation and comparison of baseline characteristics, process measures and outcomes. We describe baseline characteristics, and define and categorise trial outcomes according to their assigned importance.

Results and conclusions: We developed an SAP for the HEAT trial, and produced a mock Consolidated Standards of Reporting Trials diagram and tables. Our prespecified SAP accords with high-quality standards of internal validity and should minimise future analysis bias.

Crit Care Resusc 2013; 15: 279–286

This article outlines the statistical analysis plan for the Permissive Hyperthermia through Avoidance of Paracetamol in Known or Suspected Infection in the Intensive Care Unit (HEAT) trial; a multicentre, double-blind, randomised, placebo-controlled trial of intravenous (IV) paracetamol in intensive care unit patients with fever and known or suspected infection.[1]

This trial is endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG). Publication of a statistical analysis plan (SAP) before analysis of study data has been used for previous randomised controlled trials conducted by the ANZICS CTG, including the Randomised Evaluation of Normal versus Augmented Level of Replacement Therapy (RENAL) study,[2] the Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study,[3] and the Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care (CHEST) study.[4] Use of a prespecified SAP in the HEAT study aims to reduce the risk of analysis bias arising from knowledge of the study findings as they emerge during analysis of the study data.[5]

The SAP for the HEAT trial was developed by the chief investigator (P Y) in consultation with the study statistician (M W) at the Medical Research Institute of New Zealand, before completion of the first interim analysis by the data safety and monitoring board (DSMB), and was approved by the study management committee.

Overview

Design

The HEAT trial is a prospective, Phase IIb, multicentre, parallel-groups, double-blind, randomised, placebo-controlled trial of IV paracetamol for the treatment of fever in critically ill patients with known or suspected infection. The primary outcome variable used in the study is "alive ICU-free days" to Day 28. The trial was prospectively registered (ACTRN12612000513819) and the study protocol has been previously published.[1]

Funding and support

The HEAT trial is primarily funded by a grant from the Health Research Council of New Zealand. In addition, funding has been provided by the Intensive Care Foundation and the Waikato Medical Research Foundation. The funding bodies had no input into the design or conduct of the trial or into the SAP, and all analyses and reports will be conducted independently of them. The George Institute for Global Health and the Medical Research Institute of New Zealand are providing subsidised project management and monitoring.

Table 1. Summary and time schedule of data to be collected in the electronic case report form

Time of study	Data collected
Baseline	Date and time of randomisation, demographic data, comorbid conditions, date and time of ICU admission, ICU admission source, physiological and laboratory data, physiological support received, sepsis status, microbiological data.
Day 0–Day 28	Peak temperature: Day 0–Day 28. Temperature: 6-hourly, Day 0–Day 7. Mean arterial pressure, heart rate, minute ventilation: 6-hourly, Day 0–Day 3; daily, Day 4–Day 7. Hours of individual ICU supports (inotropes/vasopressors, mechanical ventilation, RRT, other extracorporeal supports): Day 0–Day 28. Daily use of steroids, NSAIDs, aspirin, antimicrobial agents, physical cooling, study medication, open-label paracetamol: Day 0–Day 28. Creatinine, bilirubin, prothrombin time, AST or ALT: Day 0–Day 7. CRP, CK: Day 1, Day 3, Day 5, Day 7.
End of study	Vital status at Day 28 and Day 90, cause of death, ICU length of stay, hospital length of stay, ICU-free days, ICU support-free days, hospital-free days, mechanical ventilation support-free days, inotrope/vasopressor support-free days, RRT-free days.
Adverse events	Description, timing and resolution of adverse events from randomisation until Day 90.
Protocol deviations	Randomisation of an ineligible patient, use of an incorrect treatment pack, double randomisation, other deviations.

ICU = intensive care unit. RRT = renal replacement therapy. NSAID = non-steroidal anti-inflammatory drug. AST = aspartate aminotransferase. ALT = alanine aminotransferase. CRP = C-reactive protein. CK = creatine kinase.

Study population and treatment

A total of 700 ICU patients aged 16 years or older will be enrolled in the study, at 22 centres in Australia and New Zealand. All potential participants are being screened for study eligibility. A patient who fulfils eligibility criteria is randomly assigned to receive IV paracetamol or placebo (5% dextrose) every 6 hours until he or she:

- develops a contraindication to paracetamol or permissive hyperthermia
- ceases antimicrobial therapy
- is discharged from the ICU
- reaches study Day 28 (672 hours after randomisation), or
- achieves resolution of fever.

Randomisation is achieved using a secure, password-protected, encrypted, internet-based randomisation system with 24-hour on-call back-up provided by the study management committee and project team. Randomisation is stratified by study centre.

Inclusion criteria

Patients being treated in one of the study ICUs are eligible for inclusion in the study if they meet all the following criteria:

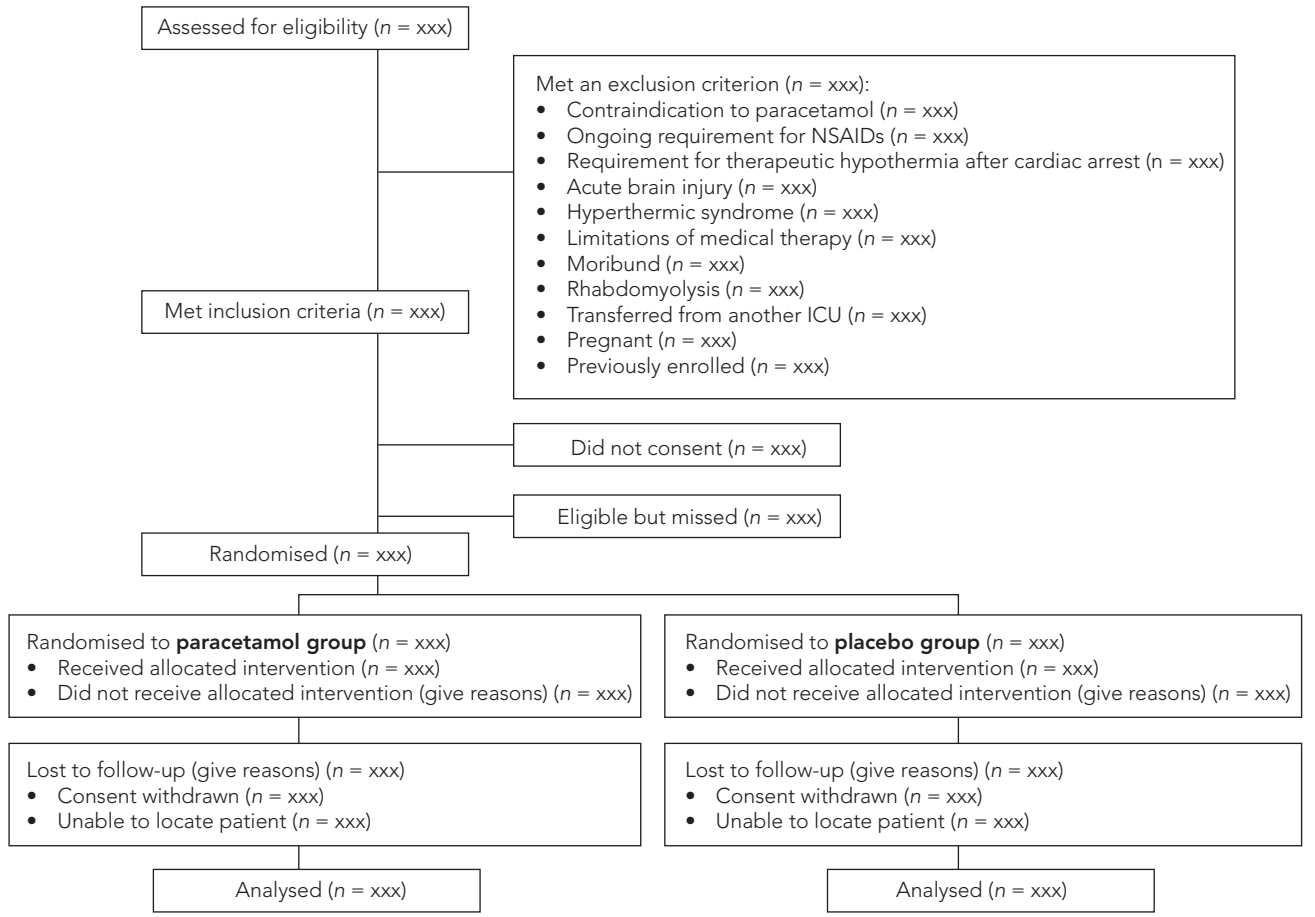
- they are aged 16 years or older
- their body temperature was $\geq 38°C$ in the ICU within the previous 12 hours, and
- they are receiving antimicrobial therapy for a known or suspected infection.

Exclusion criteria

Patients are excluded from the study if they meet one or more of the following criteria:

- their aspartate aminotransferase or alanine aminotransferase level is > 5 times the upper limit of normal, or their bilirubin level is > 2 times the upper limit of normal, or they have any other contraindication to receiving paracetamol 4 g/day
- there is a requirement for a non-steroidal anti-inflammatory drug or for aspirin use in excess of 300 mg/day
- admission to the ICU follows a cardiac arrest being treated with therapeutic hypothermia, or such a need is anticipated
- there is evidence of acute brain injury (any acute traumatic brain injury, subarachnoid haemorrhage, acute ischaemic stroke, acute intracerebral haemorrhage or acute intracranial infection) diagnosed during the current hospital admission
- there is a hyperthermic syndrome such as heat stroke, thyrotoxicosis, malignant hyperthermia, neuroleptic malignant syndrome or other drug-induced hyperthermia
- there is a limitation-of-therapy order in place or aggressive treatment is deemed unsuitable
- the patient is moribund and death is perceived to be imminent (within 24 hours)
- rhabdomyolysis is present and deemed clinically significant
- the patient was transferred from another ICU, fulfilled all inclusion criteria in the other ICU, and spent > 12 hours in the other ICU before transfer
- the patient is pregnant, or
- the patient was previously randomised into the HEAT trial, or was previously eligible for enrolment during the current ICU admission but not enrolled in the study.

Figure 1. Flow of participants through the HEAT trial



HEAT = Permissive Hyperthermia through Avoidance of Paracetamol in Known or Suspected Infection in the Intensive Care Unit trial. NSAIDs = non-steroidal anti-inflammatory drugs.

Aims

Primary aim

Our primary aim is to estimate the difference in alive ICU-free days to Day 28 attributable to the administration of paracetamol in a population of ICU patients with fever and known or suspected infection.

Secondary aims

Our secondary aims are to:

- estimate the difference in the 28-day and 90-day all-cause mortality attributable to paracetamol administration, and to use the estimates for a sample size calculation for a Phase III study
- estimate the effect of paracetamol administration on ICU and hospital support requirements
- estimate the effect of paracetamol administration on body temperature, development of liver dysfunction, creatinine levels, and C-reactive protein (CRP) levels
- determine if there are differences in outcomes in four patient subgroups (those with severe hyperthermia at baseline [temperature ⩾ 39°C]; ICU-acquired versus community-acquired versus other hospital-acquired infection; septic shock; and those taking aspirin)
- estimate the likely recruitment rate at Australian and New Zealand sites for a Phase III trial using the current study design.

Definitions of outcome variables

Primary outcome variable

Our primary outcome variable is alive ICU-free days to Day 28.[6] The number of ICU-free days will be calculated as 28 minus the number of days or part-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 they should be counted as having the worst possible outcome.

Table 2. Baseline patient characteristics

Characteristic	Paracetamol	Placebo
Age (years)	xx (SD)	xx (SD)
Sex (male)	*n* (%)	*n* (%)
Weight (kg)	xx (SD)	xx (SD)
New Zealand–European ethnicity	*n* (%)	*n* (%)
Australian–European ethnicity	*n* (%)	*n* (%)
Maori ethnicity	*n* (%)	*n* (%)
Pacific Islander ethnicity	*n* (%)	*n* (%)
Aboriginal or Torres Strait Islander ethnicity	*n* (%)	*n* (%)
Other ethnicity	*n* (%)	*n* (%)
Comorbid conditions		
Cancer	*n* (%)	*n* (%)
Chronic pulmonary disease	*n* (%)	*n* (%)
Congestive heart failure	*n* (%)	*n* (%)
Diabetes	*n* (%)	*n* (%)
End-stage renal failure	*n* (%)	*n* (%)
HIV	*n* (%)	*n* (%)
Ischaemic heart disease	*n* (%)	*n* (%)
Severe neurological dysfunction	*n* (%)	*n* (%)
Intensive care unit admission data		
From emergency department	*n* (%)	*n* (%)
From hospital ward	*n* (%)	*n* (%)
From another intensive care unit	*n* (%)	*n* (%)
From another hospital*	*n* (%)	*n* (%)
From operating theatre after elective surgery	*n* (%)	*n* (%)
From operating theatre after emergency surgery	*n* (%)	*n* (%)
Time from admission to randomisation (hours)	xx (SD)	xx (SD)
Physiological and laboratory data		
Peak temperature, previous 24 hours (°C)	xx (SD)	xx (SD)
Mean arterial pressure (mmHg)	xx (SD)	xx (SD)
Heart rate (beats per minute)	xx (SD)	xx (SD)
Minute ventilation (breaths per minute)	xx (SD)	xx (SD)
Most recent creatinine (μmol/L)	xx (SD)	xx (SD)
Baseline pre-illness creatinine (μmol/L)	xx (SD)	xx (SD)
Creatine kinase (U/L)	xx (SD)	xx (SD)
Bilirubin (μmol/L)	xx (SD)	xx (SD)
Prothrombin time (seconds)	xx (SD)	xx (SD)
Aspartate aminotransferase (U/L)	xx (SD)	xx (SD)
Alanine aminotransferase (U/L)	xx (SD)	xx (SD)
C-reactive protein (mg/L)	xx (SD)	xx (SD)
APACHE-II score	xx (SD)	xx (SD)
Receiving physiological support (% yes)		
Inotropes or vasopressors	*n* (%)	*n* (%)
Invasive ventilation	*n* (%)	*n* (%)
Non-invasive ventilation	*n* (%)	*n* (%)
Renal replacement therapy	*n* (%)	*n* (%)
Other extracorporeal therapy	*n* (%)	*n* (%)
Steroid therapy	*n* (%)	*n* (%)
Aspirin therapy	*n* (%)	*n* (%)

APACHE = Acute Physiology and Chronic Health Evaluation. * Except from another intensive care unit.

Secondary end points

The secondary outcome variables are, in order of importance:

Mortality and survival

- All-cause mortality at Day 90.
- All-cause mortality at Day 28.
- Survival time from randomisation to Day 90, with participants still alive after 90 days treated as censored at that time.

ICU and hospital support requirements

- ICU and hospital length-of-stay from time of randomisation censored at death or Day 90 (whichever is sooner).
- Hospital-free days, mechanical ventilation-free days, inotrope and vasopressor-free days and ICU support-free days will be assessed at Day 90. To be deemed ICU support-free, a patient must be free of any ICU support for an entire calendar day and must remain free from such supports until the time of physical discharge from the ICU. For hospital-free days, mechanical ventilation free-days, and inotrope and vasopressor-free days, 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 and biochemical outcome variables

- Mean and maximum axillary temperatures, measured using a Protec BX/144 digital thermometer (Protec Solutions).
- Proportion of patients who stop study treatment due to development of liver dysfunction (as defined in exclusion criteria).
- Mean CRP levels, as measured on Days 1, 4, 5 and 7.
- Proportion of patients with creatine kinase level > 5000 units on Day 1, 3, 5 or 7 will be compared.
- Highest creatinine level measured in the ICU in the first 7 days after randomisation.

Recruitment rate

Average weekly recruitment rate.

Analysis principles

Analyses will be by intention-to-treat. All statistical tests will be two-sided with an α of 0.05, except for the primary outcome variable where a *P* of 0.0379 will be used to allow for appropriate α spending in the two planned interim analyses to preserve the overall α of

Table 3. Microbiological and sepsis data

Variable	Paracetamol *n* (%)	Placebo *n* (%)
Sepsis status		
Sepsis	*n* (%)	*n* (%)
Severe sepsis	*n* (%)	*n* (%)
Septic shock	*n* (%)	*n* (%)
Where sepsis was acquired		
Community	*n* (%)	*n* (%)
Hospital (intensive care unit)	*n* (%)	*n* (%)
Hospital (outside intensive care unit)	*n* (%)	*n* (%)
Primary site of infection		
Lung	*n* (%)	*n* (%)
Abdomen	*n* (%)	*n* (%)
Pleura	*n* (%)	*n* (%)
Other thoracic site	*n* (%)	*n* (%)
Ear, nose, throat, teeth	*n* (%)	*n* (%)
Vascular catheter	*n* (%)	*n* (%)
Bone or joint	*n* (%)	*n* (%)
Skin or soft tissue	*n* (%)	*n* (%)
Urinary tract	*n* (%)	*n* (%)
Gynaecological site	*n* (%)	*n* (%)
Endocardium	*n* (%)	*n* (%)
Blood stream	*n* (%)	*n* (%)
Neutropenic sepsis	*n* (%)	*n* (%)
No clear source	*n* (%)	*n* (%)
Causative organisms		
Infecting organism identified	*n* (%)	*n* (%)
Blood culture positive	*n* (%)	*n* (%)
Gram-positive bacteria	*n* (%)	*n* (%)
Gram-negative bacteria	*n* (%)	*n* (%)
Other (fungi, viruses, etc)	*n* (%)	*n* (%)

0.05 for the primary end point. All analyses will be conducted masked for treatment allocation. We will maintain allocation concealment until all analyses (including any post-hoc analyses) are completed.

Analyses for the primary outcome variable will be unadjusted. We will use sensitivity analysis incorporating adjustment for important prognostic variables (described below) for Day 90 mortality and survival, as described in subsequent sections. Some important participant characteristics will be the subject of possible subgroup analysis (described below). Whether or not the characteristics are associated with a different treatment outcome will be tested by an interaction term between the characteristic and the treatment. We will not impute missing values and, where there are missing values, we will use a complete case analysis. No adjustment of *P* values for multiple comparisons will be undertaken.

Table 4. Intensive care unit admission diagnoses

Diagnosis	Paracetamol *n* (%)	Placebo *n* (%)
Operative admission diagnoses		
Cardiovascular	*n* (%)	*n* (%)
Gastrointestinal	*n* (%)	*n* (%)
Gynaecological	*n* (%)	*n* (%)
Neurological	*n* (%)	*n* (%)
Orthopaedic	*n* (%)	*n* (%)
Renal	*n* (%)	*n* (%)
Respiratory	*n* (%)	*n* (%)
Trauma	*n* (%)	*n* (%)
Other postoperative	*n* (%)	*n* (%)
Non-operative admission diagnoses		
Cardiovascular	*n* (%)	*n* (%)
Gastrointestinal	*n* (%)	*n* (%)
Haematological	*n* (%)	*n* (%)
Metabolic	*n* (%)	*n* (%)
Neurological	*n* (%)	*n* (%)
Other medical diseases	*n* (%)	*n* (%)
Renal	*n* (%)	*n* (%)
Respiratory	*n* (%)	*n* (%)
Sepsis	*n* (%)	*n* (%)
Trauma	*n* (%)	*n* (%)

Design issues

Data collection follow-up

Table 1 shows a summary and time schedule of data to be collected; patient consent before randomisation may not be possible. If subsequent consent to the use of data is not provided, that patient's data (except for data related to consent) will be removed from the analysis. Censoring will only apply when there is no information available beyond a particular time, in which case the date of censoring applied will be the last day of contact with the patient, or the date of hospital discharge if no other information is available. Patients who withdraw consent to continue study treatment but consent to the use of their data will be analysed on an intention-to-treat basis.

Justification of the sample size

Our study is substantially larger than all previous studies of paracetamol in febrile, critically ill patients combined.[7,8] The sample size calculation for ICU-free survival to Day 28 is based on an unpaired *t* test. Based on our pilot work, we estimate that the baseline alive ICU-free days to Day 28 is 16 days (SD, 9.2 days).[9] The consensus of the investigators is that a difference of 2.5 days is likely to represent a

Table 5. Primary outcome and key secondary outcome variables

Variable	Paracetamol	Placebo	Point estimate (95% CI)	Statistical significance
Primary outcome				
ICU-free days, median (IQR)	xx (xx–xx)	xx (xx–xx)	Difference in medians (95% CI)	*P*
Secondary outcomes				
Hospital-free days, median (IQR)	xx (xx–xx)	xx (xx–xx)	Difference in medians (95% CI)	*P*
Mechanical ventilation-free days, median (IQR)	xx (xx–xx)	xx (xx–xx)	Difference in medians (95% CI)	*P*
Inotrope-free or vasopressor-free days, median (IQR)	xx (xx–xx)	xx (xx–xx)	Difference in medians (95% CI)	*P*
RRT-free days, median (IQR)	xx (xx–xx)	xx (xx–xx)	Difference in medians (95% CI)	*P*
ICU support-free days, median (IQR)	xx (xx–xx)	xx (xx–xx)	Difference in medians (95% CI)	*P*
Day 28 mortality	*n* (%)	*n* (%)	Relative risk (unadjusted) (95% CI) Relative risk (adjusted) (95% CI)	*P* (unadjusted) *P* (adjusted)
Day 90 mortality	*n* (%)	*n* (%)	Relative risk (unadjusted) (95% CI) Relative risk (adjusted) (95% CI)	*P* (unadjusted) *P* (adjusted)

ICU = intensive care unit. IQR = interquartile range. RRT = renal replacement therapy.

clinically important difference. We previously identified that the distribution of alive ICU-free days to Day 28 is not Gaussian.[9] To account for this, we inflated our sample size, which is based on a *t* test, by 15% to allow for subsequent use of a Mann–Whitney test for analysis.[10] A sample size of 700 patients thus has 80% power to allow us to detect a difference of 2.2 days, with an α of 0.05, allowing for a 5% dropout rate. In a secondary power calculation, we determined that our sample size will provide 80% power to detect a reduction in 28-day mortality from a baseline mortality of 16% to a mortality of 9% at an α of 0.05.

Interim analyses and the DSMB

The DSMB will review data at interim analyses planned after data collection has been completed for one-third and two-thirds of the enrolled patients. For the planned interim analyses after one-third and two-thirds of the data collection, we will use a *P* of 0.00021 and 0.01189, respectively, to define early stopping criteria. We will use a group sequential α-spending function, calculated using the O'Brien–Fleming method, with two-sided symmetric bounds.

The DSMB will also review summaries of adverse events. There is potential for Type 1 error in examining multiple adverse events, there is considerable existing knowledge about the safety of paracetamol,[11] and paracetamol is commonly used in routine practice.[11] Therefore, the guidelines from the management committee indicate that advice to stop the clinical trial early on the basis of reported adverse events should be given only in exceptional circumstances.

The DSMB consists of three members: Jeff Lipman, Chair (Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital), Michael Bailey (Australian and New Zealand Intensive Care Research Centre), and Brian Anderson (Paediatric Intensive Care Unit, Auckland District Health Board). The members of the DSMB have changed since the study protocol was published,[1] but the current committee was established shortly after the commencement of trial recruitment and met before any interim analyses and before any serious adverse events or protocol deviations had been reported.

Statistical analysis

Trial profile

The flow of patients through the study will be presented in a Consolidated Standards of Reporting Trials (CONSORT) diagram[12] (Figure 1).

Characteristics of patients and baseline comparisons

Baseline characteristics will be presented by treatment group (Table 2). Discrete variables will be presented as numbers and percentages (calculated using the number of patients for whom data are available). When values are missing, the denominator will be stated. Continuous variables will be summarised as a mean (with SD), and a minimum, maximum and median (with interquartile range) will be provided for each variable in a supplementary appendix. Microbiological and sepsis status data will be reported in a separate table from other baseline data, as outlined in Table 3. ICU admission diagnoses will be presented in a supplementary appendix as shown in Table 4.

Concomitant treatments

In this study, open-label paracetamol use is only allowed in patients who have completed the course of study medication. Any use of open-label paracetamol in the ICU will be recorded daily until Day 28 for patients who remain in ICU. Similarly, the use of treatments that alter temperature management will be recorded: physical cooling measures, non-steroidal anti-inflammatory drugs, low-dose aspirin and steroid use. Time until cessation of antibiotics, for paracetamol and placebo groups, will be reported as a process measure in a time-to-event analysis with data truncated at death or ICU discharge.

Consent and permanent discontinuation of study medication

Patient consent type will be recorded and categorised into the following groups, with number and percentage:

- prior informed consent from the patient
- prior informed consent from a legal surrogate
- delayed informed consent from the patient
- delayed informed consent from a legal surrogate
- consent from another legal body before the patient's consent
- no consent obtained; data withdrawn.

The reason for discontinuation of study medication will be documented in all patients and will be categorised into the following groups, with number and percentage:

- discharge from the ICU
- resolution of fever
- cessation of antimicrobials
- reached Day 28
- withdrawal of consent while study drug is indicated
- acute myocardial infarction
- rhabdomyolysis
- liver dysfunction
- accidental administration of non-study paracetamol
- other treatment-related adverse event
- focus changed to palliative care because death imminent
- death
- clinician's decision to withdraw for other reasons
- other reason.

Description of analyses

Primary outcome

A Mann–Whitney test will be used as the primary analysis of the effect of treatment allocation on alive ICU-free days to Day 28. Data will be presented as point estimates of the difference in medians between the treatment groups, with 95% CI, calculated using the Hodges–Lehmann method.[13]

Secondary outcomes

The risks of death at Day 28 and Day 90 will be calculated by logistic regression, estimated as odds ratios with 95% CI. For Day 90 mortality, multivariate logistic regression analysis will be used to adjust for important potential predictors of outcome: age, ICU admission source and Acute Physiology and Chronic Health Evaluation II score. Survival time from randomisation to Day 90 will be analysed using the log-rank test and supplemented by a Cox proportional hazards model to calculate hazard ratios for survival. The proportional hazard assumption across treatment arms will be checked graphically using a log-cumulative hazard plot or the addition of time-dependent covariate to the model. Probability of survival by treatment group will also be presented as Kaplan–Meier curves.

ICU and hospital length-of-stay will be calculated from randomisation until discharge, death, or Day 90 (whichever comes first). In addition to comparing the ICU and hospital length-of-stay between treatment groups for all patients, we will also report ICU and hospital length-of-stay for survivors and non-survivors separately. Data distribution assumptions will be tested for normality. If data are normally distributed, comparisons between groups will be undertaken using an unpaired *t* test. If normality assumptions are not met, we plan to compare groups using the Mann–Whitney test and Hodges–Lehmann confidence intervals.

Hospital-free days, mechanical ventilation-free days, inotrope-free and vasopressor-free days, renal replacement therapy-free days, and ICU support-free days will be compared between treatment groups using the Wilcoxon rank-sum test. The effect of treatment will be represented using point estimates of the difference in medians between the treatment groups, with 95% CI, calculated using the Hodges–Lehmann method.

Peak and mean temperature measurements will be analysed in mixed linear models incorporating the peak temperature in the 24 hours before randomisation as a fixed effect covariate, to account for the repeated measurements. Different possible covariance matrices will be fitted and assessed by the Akaike information criterion to find a suitable structure less complex than a full unstructured matrix. CRP levels will be analysed similarly.

The highest recorded creatinine level during the first 7 days in the ICU will be compared between treatment groups, using a regression approach incorporating baseline creatinine as a covariate. The proportion of patients whose creatine kinase level, measured on Day 1, Day 3, Day 5 and Day 7, exceeds 5000 units will be compared between treatment groups by logistic regression.

Subgroups

The primary outcome for planned subgroup analyses will be 28 day ICU-free survival. Subgroup analyses are exploratory analyses which aim to generate new hypotheses. Four prespecified subgroup analyses will be undertaken, for patients:

- with severe hyperthermia at baseline (temperature $\geqslant 39°C$)
- with ICU-acquired, community-acquired or other hospital-acquired infection
- with septic shock
- taking aspirin.

Presentation of outcome data

We will present principal outcome data as shown in Table 5; daily temperature data in a figure that compares the mean and peak temperatures between treatment groups over time; and survival time up to Day 90, by treatment group, as Kaplan–Meier survival curves.

Conclusion

We propose that this prespecified SAP accords with high quality standards of internal validity and should minimise future analysis bias.

Competing interests

None declared.

Author details

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

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

References

1 Young PJ, Saxena MK, Bellomo R, et al. The HEAT trial: a protocol for a multicentre randomised placebo-controlled trial of IV paracetamol in ICU patients with fever and infection. *Crit Care Resusc* 2012; 14: 290-6.
2 Finfer S, Cass A, Gallagher M, et al. The RENAL (Randomised Evaluation of Normal vs. Augmented Level of Replacement Therapy) study: statistical analysis plan. *Crit Care Resusc* 2009; 11: 58-66.
3 Finfer S, Heritier S. The NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) Study: statistical analysis plan. *Crit Care Resusc* 2009; 11: 46-57.
4 Myburgh J, Li Q, Heritier S, et al. Statistical analysis plan for the Crystalloid Versus Hydroxyethyl Starch Trial (CHEST). *Crit Care Resusc* 2012; 14: 44-52.
5 Finfer S, Bellomo R. Why publish statistical analysis plans? *Crit Care Resusc* 2009; 11: 5-6.
6 Young P, Hodgson C, Dulhunty J, et al. End points for phase II trials in intensive care: recommendations from the Australian and New Zealand Clinical Trials Group consensus panel meeting. *Crit Care Resusc* 2012; 14: 211-5.
7 Niven DJ, Stelfox HT, Laupland KB. Antipyretic therapy in febrile critically ill adults: a systematic review and meta-analysis. *J Crit Care* 2013; 28: 303-10.
8 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.
9 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.
10 Lehmann EL, D'Abrera HJM. Nonparametrics: statistical methods based on ranks. New York: Springer, 2006.
11 Jefferies S, Saxena M, Young P. Paracetamol in critical illness: a review. *Crit Care Resusc* 2012; 14: 74-80.
12 Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med* 2010; 152: 726-32.
13 Lehmann EL. Non parametric confidence intervals for a shift parameter. *Ann Math Statist* 1963; 34: 1507-12. ❑

Oxygen therapy in non-intubated adult intensive care patients: a point prevalence study

Rachael L Parke, Glenn M Eastwood, Shay P McGuinness on behalf of the George Institute for Global Health and the Australian and New Zealand Intensive Care Society Clinical Trials Group

ABSTRACT

Background: Oxygen is commonly administered to intensive care unit patients. Although there is knowledge of how oxygen is administered to mechanically ventilated patients, there are few data about its use in non-intubated ICU patients.

Objective: To describe how oxygen therapy is prescribed, administered and monitored for non-intubated patients in New Zealand and Australian ICUs.

Design, participants and setting: Prospective, observational, binational, multicentre, 1-day point prevalence study of all adult patients in 40 New Zealand and Australian ICUs at 10 am on a study day.

Main outcome measures: We collected patient demographic data, 28-day mortality and details of oxygen therapy (oxygen therapy prescription, oxygen delivery device use and oxygen saturation targets).

Results: We audited 506 patients, of whom 178 (35.2%) were not intubated but receiving oxygen therapy; 59.5% were men. Their mean age was 57.3 years (SD, 18.8 years), mean Acute Physiology and Chronic Health Evaluation (APACHE) II score was 16.2 (SD, 7.3) and 47.2% were admitted after surgery. Most patients (66%) received oxygen via simple nasal cannulae, and patients also received oxygen via open face mask, nasal high-flow and non-invasive ventilation. A documented prescription for oxygen therapy was in place for 24.4% of patients, and we considered 7% to be complete and comprehensive.

Conclusions: Oxygen therapy is commonly administered to non-intubated adult patients in New Zealand and Australian ICUs. Most patients received oxygen by simple nasal cannulae, and oxygen therapy prescriptions were often absent or incomplete. We advise continuing education to ensure that oxygen is prescribed, administered and documented correctly.

Crit Care Resusc 2013; 15: 287–293

Oxygen is one of the most widely available and prescribed therapeutic drugs in medicine.[1] Intensive care unit patients are usually given supplemental oxygen to avoid or treat hypoxaemia or as routine postoperative care. Optimisation of oxygen delivery remains the cornerstone of treatment for common ICU syndromes such as sepsis, multiorgan dysfunction, acute respiratory distress syndrome and acute lung injury.[2] When administered correctly, oxygen may be life-saving, but if given without careful management it can lead to adverse effects and poor patient outcomes.[1]

The risks associated with hypoxaemia are well recognised, but there is growing evidence that prolonged hyperoxia should also be avoided, as high fractions of inspired oxygen may cause damage to the lungs and have other detrimental systemic effects.[3-5] Furthermore, findings from previous intensive care-based studies have shown that oxygen is poorly prescribed, monitored and administered in the critical care setting.[6-8] To optimise the safe and effective administration of oxygen, there should be a prescription detailing the oxygen flow rate, concentration and delivery method, and a method of assessing treatment should be available.[1,7]

There is currently little published evidence to guide ICU clinicians in their selection and use of oxygen delivery devices or the prescription of oxygen therapy for non-intubated patients.[9] In 1999, Mao et al surveyed 52 medical directors of ICUs in 48 institutions via a structured postal questionnaire.[10] All respondents considered oxygen toxicity to be a concern, yet only 71% reported assessing tissue oxygenation on a routine basis, as there was considerable variation in the attitudes, beliefs and self-reported practice of oxygen therapy. Two Australian surveys have been published describing the attitudes of ICU doctors and nurses to oxygen therapy.[11,12] Eastwood et al, in an online survey of intensivists, suggested that variability in oxygen therapy practice is likely to continue until there is evidence from clinical trials to support clinical practice guidelines, and concluded that there is a need to further explore factors that influence clinical decisions about oxygen therapy.[11] A large international study providing information on the characteristics and outcomes in 15 757 adult patients in 20 countries receiving mechanical ventilation was performed in 2002 by Esteban et al.[13] Although this prospective cohort study detailed current practice in intubated patients in the ICU, it does not provide evidence on current oxygen therapy practice in non-intubated patients.

Table 1. Estimated inspired oxygen concentration

Nasal cannulae		Face mask	
Flow rate (L/min)	Estimated FIO_2 (%)	Flow rate (L/min	Estimated FIO_2 (%)
1	24%	5	30%
2	28%	6	35%
3	32%	7	40%
4	36%	8	45%
5	40%	9	50%
6	44%	10	55%

FIO_2 = fraction of inspired oxygen.

There appears to be minimal literature describing oxygen therapy in non-intubated adult ICU patients. In response, we sought to describe how oxygen therapy was prescribed, administered and monitored to non-intubated ICU patients.

Methods

Design and approval

Our observational study was embedded in the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG) point prevalence program (PPP). Infrastructure support for the ANZICS CTG PPP was provided by the George Institute for Global Health. The PPP is a prospective, 1-day, binational research initiative of the ANZICS CTG used by researchers to support avenues of clinical enquiry. Ethics committee approval to conduct the audit and for collection of data related to the study was obtained by all sites. The need for informed patient consent was waived by each committee.

Data collection

Data for this study were collected on 13 November, 21 November or 6 December 2012. A choice of dates allowed flexibility for sites to participate. Trained research staff collected data on all adult patients (aged 16 years or older) in their ICU at 10 am on the study day. General demographic data (eg, age, sex and admission diagnosis) and care and therapeutic intervention data for 24-hour and 28-day mortality were collected. For all non-intubated patients, the oxygen therapy data collected included:

- oxygen prescription (oxygen flow rate or inspired oxygen concentration, oxygen delivery device, level of monitoring and target oxygen saturation)
- method of administration (delivery device use and oxygen flow rate or inspired oxygen concentration)
- monitoring of therapy (presence of arterial or cutaneous oxygen saturation monitoring).

Details of the highest and lowest partial pressure of oxygen (Pao_2) and carbon dioxide ($Paco_2$) in the previous 24 hours were recorded in patients who had had routine arterial blood gas sampling performed. The fraction of inspired oxygen concentration (FIO_2) was measured for high-flow devices and was estimated for low-flow devices, according to Table 1.[14] A survey of ICUs about oxygen therapy protocols and devices available for oxygen therapy within the unit was sent to each site.

Data analysis

Data were entered by the participating sites into a single electronic database managed by The George Institute for Global Health. Data for this study were extracted into Excel (Microsoft) spreadsheets, and then entered into Stata, version 12 (StataCorp) for analysis. Descriptive statistics were used for all clinical and demographic data.

Table 2. Baseline patient characteristics of non-intubated patients receiving oxygen therapy (*N* = 178)

Characteristic	Data (% unless otherwise stated)
Mean age, years (SD)	57.3 (18.8)
Sex (male), number (%)	110 (59.5%)
Mean body weight,* kg (SD)	81.1 (24.3)
Mean APACHE II score (SD)	16.2 (7.3)
ICU admission source, number (%)	
Operating theatre	84 (47.2%)
Emergency department	42 (23.6%)
Hospital ward	33 (18.5%)
Transfer from other hospital	17 (9.6%)
Transfer from other ICU	2 (1.1%)
APACHE II diagnostic categories, number (%) (*N* = 175)	
Cardiovascular	38 (21.7%)
Respiratory	35 (19.7%)
Gastrointestinal	29 (16.3%)
Neurological	15 (8.4%)
Sepsis	18 (10.1%)
Trauma	11 (6.2%)
Renal/genitourinary	7 (3.9%)
Other	22 (12.4%)
Mortality 28 days after study day, number (%)	11 (6.2%)

APACHE = Acute Physiology and Chronic Health Evaluation. ICU = intensive care unit. * Body weight is estimated or measured.

Results

Cohort characteristics

In total, 506 patients were enrolled from 40 New Zealand and Australian ICUs. Of these patients, 178 (35.2%) were not intubated but were receiving oxygen therapy and have been included in the analysis. The mortality of non-intubated patients who received oxygen therapy at Day 28 was 6.2%. Baseline patient characteristics of the non-intubated patients receiving oxygen therapy are shown in Table 2. When compared with the intubated patients, non-intubated patients on the study day were older (mean, 61.2 years [SD, 17.5 years] versus mean, 57.3 years [SD, 18.8 years]; $P = 0.02$) and had lower Acute Physiology and Chronic Health Evaluation II scores (mean, 16.2 [SD, 7.3] versus mean, 21.4 [SD, 7.2]; $P < 0.001$).

Indication for oxygen therapy

The primary indications for oxygen therapy were ($N = 177$):

- hypoxaemia (measured by peripheral oxygen saturation) in 30.5% of patients ($n = 54$)
- routine therapy (not protocolised) in 29.9% of patients ($n = 53$)
- hypoxaemia (measured by arterial blood gas analysis) in 23.7% of patients ($n = 42$).
- protocolised care in 11.9% of patients ($n = 21$).

Figure 1. Oxygen therapy device used at time of survey

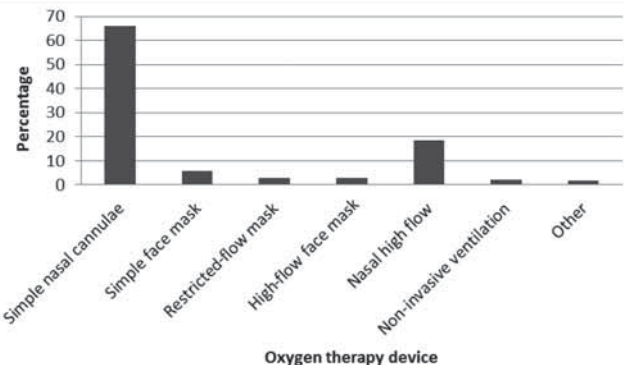


Figure 2. Reasons cited for oxygen therapy device used

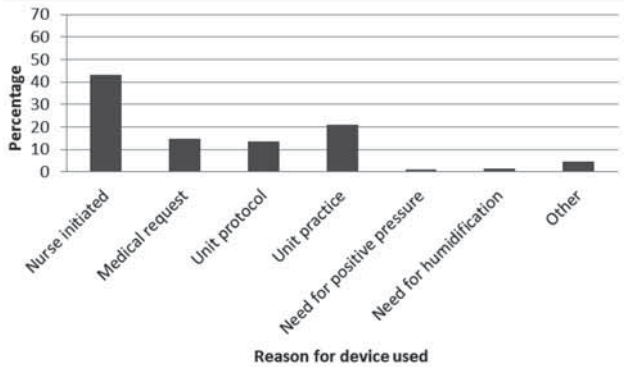


Table 3. Oxygen therapy prescriptions ($N = 43$)

Oxygen therapy prescription	*n (%)*
Oxygen flow rate	22 (51)
Inspired oxygen concentration	16 (37)
Delivery device to be used	31 (72)
Monitoring required	12 (28)
Target oxygen saturation parameters	28 (65)
Patients receiving therapy as prescribed	41 (95)

Oxygen delivery devices

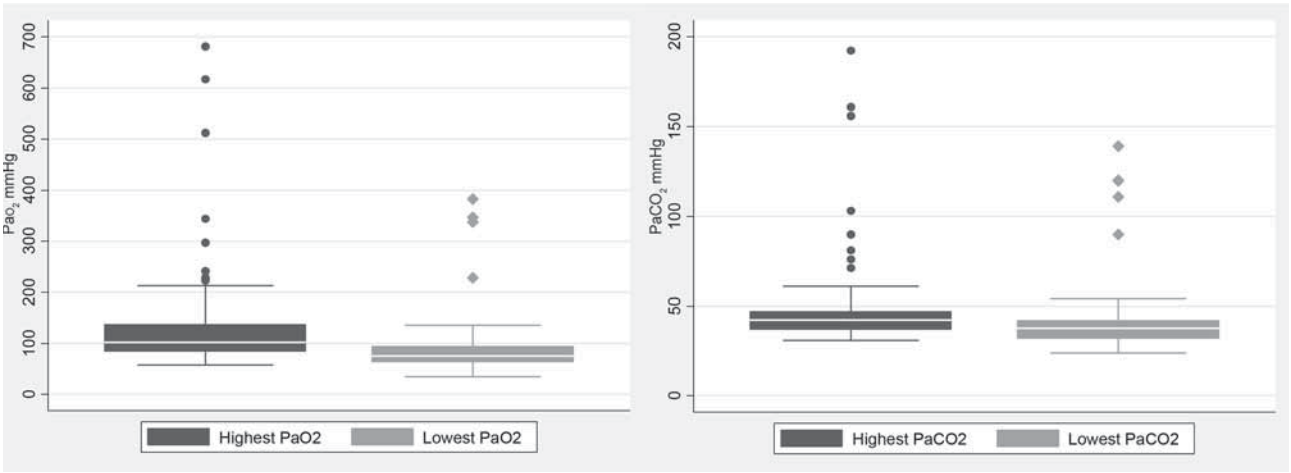
Of the 506 eligible participants 208 patients (41.1%) were not mechanically ventilated. Of these non-ventilated patients, 178 (85.6%) were receiving oxygen therapy at the time of the survey. Of these, 94 patients (52.8%) had been mechanically ventilated previously during this ICU admission. Of the 178 patients receiving supplemental oxygen: 117 (65.7%) received it via simple nasal prongs, 10 (5.6%) via simple face mask, five (2.8%) via restricted-flow mask, five (2.8%) via high-flow mask, 33 (18.5%) via nasal high-flow (NHF), four (2.2%) via non-invasive ventilation (NIV) and four (2.2%) via other devices (Figure 1).

There were no differences in baseline demographics or indications for current oxygen therapy device used between the group receiving oxygen therapy via simple nasal prongs when compared with all others receiving oxygen therapy. There was a significant difference in the mean F_{IO_2} when comparing those using simple nasal prongs to all others (30.5% [SD, 7.9%] versus 43.3% [SD, 14.9]) There was also a significant difference in mean ages of those comparison groups (59.8 years [SD, 19 years] versus 53.7 years [SD, 17.6 years]). The primary reasons the device in use had been employed is shown in Figure 2.

Oxygen therapy prescription

Patients who were receiving supplemental oxygen had a mean estimated F_{IO_2} of 34.2% (SD,11.9%; range, 24%–100%). Forty-five patients (25.4%) were receiving oxygen therapy which was humidified, all by means of an active humidification device, such as a water bath or heated humidifier. Most of these patients (73.3%) were receiving NHF oxygen therapy, and all of those received humidification. Of the patients not receiving humidified oxygen

Figure 3. Comparison of highest and lowest Pao_2 and $Paco_2$ values in study patient



Pao_2 = arterial partial pressure of oxygen. $Paco_2$ = arterial partial pressure of carbon dioxide.

therapy, two were receiving NIV. The remaining patients were using a restrictive flow mask, eg, Venturi mask, simple facemask or simple nasal cannulae.

When we assessed oxygen therapy prescriptions, we found that 43 patients (24.4%; *N* = 176 due to missing data) had a current written therapy order, with only three (7%) covering all suggested parameters for a complete oxygen therapy prescription. Table 3 shows how oxygen therapy prescriptions were detailed.

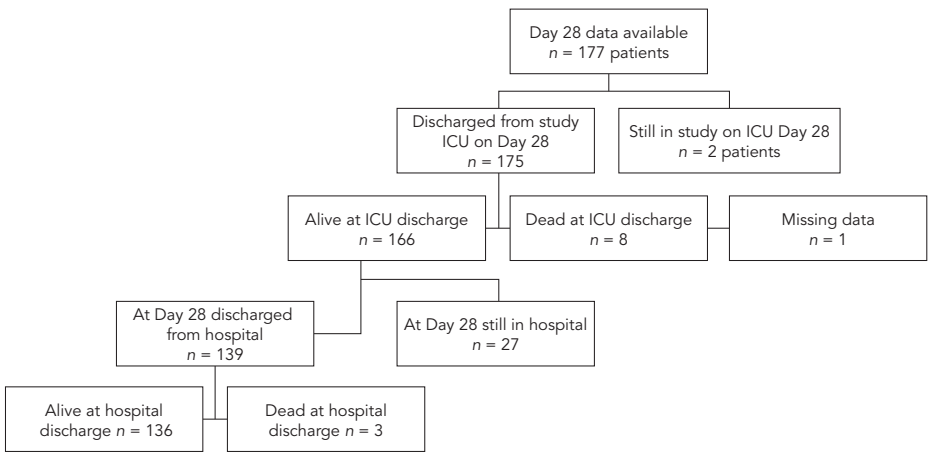
Monitoring oxygen therapy

Overall, 73 patients (41.2%) had an oxygen saturation target documented. The mean lower oxygen saturation target was 92.5% (SD, 2.8%; range 80%–99%), and the mean upper oxygen saturation target was 94.4% (SD, 3.5%; range, 90%–99%).

For patients with arterial lines in situ for at least part of the previous 24 hours, the highest and lowest arterial blood gas measurements of Pao_2 and $Paco_2$ for 108 patients were available for analysis. The mean highest Pao_2 was 129 mmHg (SD, 94 mmHg; range, 58–681 mmHg), the mean lowest Pao_2 was 88 mmHg (SD, 52 mmHg; range, 35–383 mmHg), the mean highest $Paco_2$ was 47 mmHg (SD, 23 mmHg; range, 31–192 mmHg), and the mean lowest $Paco_2$ was 40 mmHg (SD, 16 mmHg; range, 24–139 mmHg). Figure 3 shows the mean and standard deviations for the highest and lowest Pao_2 and $Paco_2$ recorded in the 24 hours before 10 am on the study day.

Of the patients receiving oxygen therapy, 106 (59.9%*) had an arterial line in situ, 161 (91%*) had continuous respiratory rate monitoring available, 176 (99.4%*) had continuous pulse oximetry monitoring in situ and 173 (98.3%*) had continuous electrocardiographic monitoring in place. All patients had one or more of the above monitoring devices in situ. (**N* = 177 due to missing data.)

Figure 4. Patient status at Day 28 of oxygen therapy study



ICU = intensive care unit.

28-day patient outcome

Mortality data at Day 28 were also assessed (see Figure 4). Day 28, data were available for 177 patients. Of these, 175 patients

(98.9%) had been discharged from the study ICU and two patients (1.1%) remained in the ICU. Eleven patients (6.2%) had died by Day 28 in the ICU or between ICU discharge and Day 28.

Data about ICUs

Twenty-six ICUs (65%) submitted data detailing the availability of oxygen therapy protocols and devices available for use within their unit. Only 13 of these ICUs (50%) had a protocol to guide oxygen therapy in the unit. All 26 ICUs used NHF oxygen therapy, with 16 (61.5%) having a protocol to guide use of this therapy. The mean starting flow rate for NHF therapy recommended by these protocols was 38 L/minute (SD, 5 L/minute; range, 30–50 L/minute) and the mean highest flow rate recommended was 57 L/minute (SD, 12 L/minute; range, 35–70 L/minute). NIV was actively humidified by ICUs 100% of the time in 16 units (61.5%), 50%–99% of the time in nine units (34.6%), and never in one unit (3.8%). Some hospital wards (including respiratory, cardiothoracic, neurology, oncology and ear, nose and throat wards and coronary care units) were identified as being able to receive patients receiving humidified oxygen therapy, NHF or non-invasive oxygen therapy.

Discussion

Key findings

In our point prevalence study, describing how oxygen therapy is prescribed, administered and monitored for non-intubated adult patients admitted to New Zealand and Australia ICUs, we made three key findings:

- On the study day, 85.6% of non-intubated adult patients in the ICUs were receiving oxygen therapy, and this sometimes resulted in supraphysiological arterial oxygenation.
- Most patients (66%) received oxygen via simple nasal cannulae, and fewer patients received it via face masks, NHF or NIV.
- Oxygen therapy was poorly prescribed and failed to meet the recommended standards.

Comparison with previous studies

The patient cohort we describe is similar to that described in other ICU studies, internationally and from Australasia.[13,15-17] To the best of our knowledge, no other study has described how oxygen therapy is administered to non-intubated patients in the ICU, therefore comparisons of the range of delivery devices employed and the reasons for oxygen therapy cannot be made. Oxygen therapy has been described in patients on hospital wards and in emergency departments but poorly described in the ICU.[18-21]

Our study confirms that supplemental oxygen administration is almost universal in non-intubated patients in ICUs. Despite the availability of monitoring for oxygenation parameters, including pulse oximetry and arterial blood gas analysis, there is little apparent attempt to titrate oxygen to physiological levels.

In our study, only 24.4% of patients had a prescription for oxygen therapy, meaning that 75.6% were receiving oxygen therapy that was not prescribed. Failure to have a documented oxygen therapy prescription may result in inappropriate administration of oxygen and may contribute to prolongation of therapy that is no longer required. Differing results have been found in other studies, eg, in one study, only 8% of patients receiving oxygen therapy in a medical ward had an oxygen prescription,[7] and in another study 93.4% had a current prescription.[18] The criteria we used to determine if a prescription covered all necessary components is consistent with other studies which have assessed similar points for inclusion.[19]

Our findings support previously identified concerns about the safety of oxygen administration in New Zealand and Australian ICUs.[7,9,19] Although they receive high-level monitoring, ICU patients still need a current prescription for oxygen therapy in order to ensure high-quality care. Further training in oxygen therapy prescription is required, and more frequent surveys of practice should be undertaken, with feedback of results to individual sites. Results could be used as the basis for future quality assurance projects.

A possible reason oxygen therapy may be poorly prescribed is that most ICUs use large-format bedside charts, which may not have a specific area for oxygen therapy, or the allocated space may be small or located on the reverse side of the chart. Oxygen therapy-related variables are also often termed "ventilation orders" and may be better termed "oxygen therapy" to include intubated and non-intubated patients. Many institutions are now moving towards prescribing oxygen therapy on combination drug charts. Two studies have shown that the institution of specific documentation for prescribing oxygen results in improved prescription.[19,22] We were pleased to find (as did a previous audit[19]) that all patients had some form of oxygen monitoring in place and that essentially all had continuous pulse oximetry in situ. However, it was unclear how often these devices were being used to wean patients off oxygen.

Strengths and limitations

Our study has several strengths, including a prospective design, standardised data-collection methods, robust outcomes and the capture of data from multiple sites from two countries. To the best of our knowledge, this is the first study of the use of oxygen in an undifferentiated, non-intubated adult patient population in the ICU.

The actual F_{IO_2} delivered using low-flow systems (or any systems in which a patient's peak inspiratory flow exceeds the flow provided by the device) is difficult to estimate accurately and varies according to patient characteristics (including respiratory rate, peak inspiratory flow and mouth-open breathing versus mouth-closed breathing).[23,24] Despite this, we employed a widely used conversion chart to convert device and flow data into F_{IO_2}.[14] In clinical practice, the actual F_{IO_2} delivered in the range possible for low-flow devices (0.24–0.55) is less important than the ability to titrate oxygen to a measured end point. In our study, there was little evidence that down-titration, in particular, is widely practised.

Our findings should be interpreted with caution as they represent a snapshot of oxygen therapy administered to non-intubated patients in the ICU and cannot be compared with other longitudinal data. Also, depending on the clinical condition of the patients on the study day, the study cohort may not be representative of the broader ICU population on another day. However, because oxygen therapy is essentially given to all ICU patients, our study findings can be generalised to a degree to reflect oxygen therapy practice in other New Zealand and Australian ICUs.

Conclusion

We found that a large proportion of ICU patients were receiving oxygen therapy but that it was rarely titrated to monitored end points. The most commonly used oxygen delivery device were simple nasal cannulae. Generally, oxygen therapy was poorly prescribed and prescriptions did not meet standard recommendations. These findings are important for understanding current oxygen therapy practice in ICUs and will inform future interventional clinical trials of oxygen therapy. We advise continuing education interventions to ensure that oxygen therapy is prescribed, administered and documented correctly.

Competing interests

None declared.

Author details

Rachael L Parke, Research Nurse Coordinator[1,2]
Glenn M Eastwood, Research Manager[3]
Shay P McGuinness, Intensive Care Specialist[1]

1 Cardiothoracic and Vascular Intensive Care Unit, Auckland City Hospital, Auckland, New Zealand.
2 School of Nursing, University of Auckland, Auckland, New Zealand.
3 Department of Intensive Care, Austin Hospital, Melbourne, VIC, Australia.

Correspondence: rparke@adhb.govt.nz

References

1 Bateman NT, Leach RM. ABC of oxygen. Acute oxygen therapy. *BMJ* 1998; 317: 798-801.

2 Blinman T, Maggard M. Rational manipulation of oxygen delivery. *J Surg Res* 2000; 92: 120-41.

3 de Jonge E, Peelen L, Keijzers PJ, et al. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. *Crit Care* 2008; 12: R156.

4 Thomson AJ, Webb DJ, Maxwell SR, Grant IS. Oxygen therapy in acute medical care. *BMJ* 2002; 324: 1406-7.

5 Capellier G, Beuret P, Clement G, et al. Oxygen tolerance in patients with acute respiratory failure. *Intensive Care Med* 1998; 24: 422-8.

6 Dodd ME, Kellet F, Davis A, et al. Audit of oxygen prescribing before and after the introduction of a prescription chart. *BMJ* 2000; 321: 864-5.

7 Boyle M, Wong J. Prescribing oxygen therapy. An audit of oxygen prescribing practices on medical wards at North Shore Hospital, Auckland, New Zealand. *N Z Med J* 2006; 119: U2080.

8 Hickey S. An audit of oxygen therapy on a respiratory ward. *Br J Nurs* 2007; 16: 1132-6.

9 Eastwood GM, O'Connell B, Considine J. Oxygen delivery to patients after cardiac surgery: a medical record audit. *Crit Care Resusc* 2009; 11: 238-43.

10 Mao C, Wong DT, Slutsky AS, Kavanagh BP. A quantitative assessment of how Canadian intensivists believe they utilize oxygen in the intensive care unit. *Crit Care Med* 1999; 27: 2806-11.

11 Eastwood GM, Reade MC, Peck L, et al. Intensivists' opinion and self-reported practice of oxygen therapy. *Anaesth Intensive Care* 2011; 39: 122-6.

12 Eastwood GM, Reade MC, Peck L, et al. Critical care nurses' opinion and self-reported practice of oxygen therapy: a survey. *Aust Crit Care* 2012; 25: 23-30.

13 Esteban A, Anzueto A, Frutos F, et al; Mechanical Ventilation International Study Group. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. *JAMA* 2002; 287: 345-55.

14 Pruitt WC, Jacobs M. Breathing lessons: basics of oxygen therapy. *Nursing* 2003; 33: 43-5.

15 Peake SL, Chapman MJ, Davies AR, et al; George Institute for Global Health; Australian and New Zealand Intensive Care Society Clinical Trials Group. Enteral nutrition in Australian and New Zealand intensive care units: a point-prevalence study of prescription practices. *Crit Care Resusc* 2012; 14: 148-53.

16 NICE-SUGAR Study Investigators; Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009; 360: 1283-97.

17 RENAL Replacement Therapy Study Investigators; Bellomo R, Cass A, Cole L, et al. Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med* 2009; 361: 1627-38.

18 Neves TJ, Lobão MJ; Grupo de trabalho EMO [EMO working group]. Oxygen therapy multicentric study - a nationwide audit to oxygen therapy procedures in internal medicine wards. *Rev Port Pneumol* 2012; 18: 80-5.

19 Wijesinghe M, Shirtcliffe P, Perrin K, et al. An audit of the effect of oxygen prescription charts on clinical practice. *Postgrad Med J* 2010; 86: 89-93.

20 Eastwood GM, Peck L, Young H, et al. Oxygen administration and monitoring for ward adult patients in a teaching hospital. *Intern Med J* 2011; 41: 784-8.

21 Considine J, Botti M, Thomas S. Descriptive analysis of emergency department oxygen use in acute exacerbation of chronic obstructive pulmonary disease. *Intern Med J* 2012; 42: e38-47.

22 Dodd ME, Kellet F, Davis A, et al. Audit of oxygen prescribing before and after the introduction of a prescription chart. *BMJ* 2000; 321: 864-5.

23 Wettstein RB, Shelledy DC, Peters JI. Delivered oxygen concentrations using low-flow and high-flow nasal cannulas. *Respir Care* 2005; 50: 604-9.

24 Casaburi R. Assessing the dose of supplemental oxygen: let us compare methodologies. *Respir Care* 2005; 50: 594-5. ❑

Appendix. Site investigators for study of oxygen therapy in non-intubated adult intensive care patients (sites in Australia unless otherwise stated)

Albury Wodonga Health, Albury, NSW: C Mashonganyika, C Maher, E Brom
Auckland City Hospital, Cardiothoracic and Vascular Intensive Care Unit, Auckland, New Zealand: R Parke, E Gilder, L McCarthy
Auckland City Hospital, Department of Critical Care Medicine, Auckland, New Zealand: C McArthur, L Newby, K Benefield, Y Chen
Austin Hospital, Melbourne, VIC: R Bellomo, L Peck, H Young
Bendigo Hospital, Bendigo, VIC: J Fletcher, J Smith
Calvary Mater Hospital, Newcastle, NSW: K Ellem, S Meaks
Central Gippsland Health Service, VIC: J Dennett, H Connor, T Coles
Christchurch Hospital, Christchurch, New Zealand: S Henderson, D Knight, J Mehrtens
Concord Hospital, Sydney, NSW: D Milliss, H Wong
Flinders Medical Centre, Adelaide, SA: S Verghese, E Ryan, C Hannan, S Clarke
Geelong Hospital, Geelong, VIC: C Cattigan, T Elderkin, A Bone, T Salerno, M Fraser
Gold Coast Hospital, Southport, QLD: B Richards, M Tallott
John Hunter Hospital, Newcastle, NSW: P Harrigan, M Hardie, E Pollock
Lyell McEwin Hospital, Adelaide, SA: R Ramadoss, J Wood
Mater Health Services, Brisbane, QLD: A Schibler, C Stocker, S Mayfield
Middlemore Hospital, Auckland, New Zealand: A Williams, A Tilsley, R Song, L Rust
Nepean Hospital, Penrith, NSW: I Seppelt, L Weisbrodt
North Shore Hospital, Auckland, New Zealand: J Liang, J Bell
North Shore Private Hospital, Sydney, NSW: A Delaney, S Ash, D Hogben
Princess Margaret Hospital for Children, Perth, WA: S Erickson, J Abe
Royal Adelaide Hospital, Adelaide, SA: H Mcbeth, J Rivett, S O'Connor
Royal Children's Hospital, Brisbane, QLD: A Slater, D Long, S Kendall
Royal Children's Hospital, Melbourne, VIC: W Butt, C Delzoppo
Royal Hobart Hospital, Hobart, TAS: A Turner, D Cooper, R McAllister
Royal Melbourne Hospital, Melbourne, VIC: C MacIsaac, D Barge
Royal North Shore Hospital, Sydney, NSW: S Bird, A O'Conner
Royal Perth Hospital, Perth, WA: S Webb, J Chamberlain
Royal Prince Alfred Hospital, Sydney, NSW: D Gattas, H Buhr, M Keir
Sir Charles Gairdner Hospital, Perth, WA: S Baker, B Roberts
St George Hospital, Sydney, NSW: J Myburgh, J Miller, R Sidoli, D Inskip
St Vincent's Hospital, Melbourne, VIC: J Santamaria, R Smith, J Holmes
Starship Children's Health, Auckland, New Zealand: J Beca, E Segedin, C Sherring, M Rea, T Bushell
Sydney Children's Hospital, Sydney, NSW: M Morritt, G Williams, J Young
Tauranga Hospital, Tauranga, New Zealand: T Browne, R Atkin, J Goodson
The Alfred Hospital, Melbourne, VIC: A Davies, S Vallance, J Board
The Canberra Hospital, Canberra, ACT: I Mitchell, H Rodgers, E Taylor, E Fulton
The Northern Hospital, Melbourne, VIC: G Duke, J Green, A Casamento, M Park, O Burgess
The Queen Elizabeth Hospital, Adelaide, SA: S Peake, T Williams, K Kurenda
Waikato Hospital, Hamilton, New Zealand: A Forrest, J Durning, M La Pine
Wellington Hospital, Wellington, New Zealand: D Dinsdale, L Andrews, D Mackle, J Ongley, J Tang-Hickey
Western Health, Melbourne, VIC: C French, S Bates
Westmead Hospital, Sydney, NSW: V Nayyar, C Skelly, J Kong
Wollongong Hospital, Wollongong, NSW: M Sterba, B Johnson

Sodium administration in critically ill patients in Australia and New Zealand: a multicentre point prevalence study

Shailesh Bihari, Sandra L Peake, Ian Seppelt, Patricia Williams, Andrew Bersten, for the George Institute for Global Health and the Australian and New Zealand Intensive Care Society Clinical Trials Group

ABSTRACT

Background: Inadvertent sodium administration in excess of recommended daily requirements has been reported during routine care of critically ill patients.

Aim: To determine the amount and sources of sodium administered in Australian and New Zealand intensive care units.

Design, setting and participants: Prospective, observational, single-day, point prevalence survey conducted in 46 Australian and New Zealand ICUs on 21 September 2011. All patients present in ICU at 10 am and not receiving an oral diet on the study day were evaluated. Demographic data, ICU admission diagnosis, Acute Physiology and Chronic Health Evaluation (APACHE) II score and sources of sodium administration over the study day were recorded.

Results: 356 patients (64% male) were enrolled. Mean (SD) age and weight were 58.5 years (18.0 years) and 81.6 kg (24.0 kg), respectively. Mean ICU admission APACHE II score was 20 (SD, 8). Overall median (interquartile range [IQR]) sodium administration was 224.5 mmol (IQR, 144.9–367.6 mmol), or 2.8 mmol/kg (IQR, 1.6–4.7 mmol/kg). Among patients who were on Day 2–10 of their ICU admission on the study day, sodium sources and amounts administered were: i) maintenance or replacement intravenous (IV) infusions, 69.3 mmol; 30.9% of all sodium sources; ii) IV fluid boluses, 36.5 mmol; 16.3%; iii) IV drug boluses, 27.6 mmol; 12.3%; iv) enteral nutrition, 26.5 mmol; 11.8%; v) IV drug infusions, 19.3 mmol; 8.6%; vi) IV flushes, 16.6 mmol; 7.4%; vii) blood products, 13.5 mmol; 6%; viii) IV antimicrobials, 11.2 mmol; 5%; and ix) parenteral nutrition, 4.3 mmol; 1.9%. Factors associated with sodium administration were site ($P = 0.04$), age ($P < 0.001$), administered fluid ($P = 0.03$) and day of ICU stay ($P = 0.01$) (multiple linear regression).

Conclusion: This point prevalence study suggests that sodium administration in excess of recommended daily requirements may be common in Australia and New Zealand ICUs. The main sodium source was IV maintenance fluids, followed by fluid boluses and drug boluses.

Crit Care Resusc 2013; 15: 294–300

Critically ill patients are at risk of sodium retention due to activation of the renin–angiotensin–aldosterone system[1] and impaired activity of dopamine in the proximal tubule of the kidney[2] where dopamine normally inhibits sodium reabsorption.[3] Depending upon concomitant water balance, the administration of large amounts of sodium, combined with the propensity for sodium retention, may have important clinical implications such as hypernatraemia,[4] which has been associated with poor outcomes,[5,6] and changes in extracellular and intracellular fluid volumes.

Two of us (S B and A B) were involved in running a single-centre study[7] that reported that the amount of sodium administered to intensive care patients receiving invasive mechanical ventilation for more than 5 days was over twice the recommended daily intake of 100 mmol.[8] We also found that the main sources of sodium administration were intravenous (IV) maintenance fluids, flushes and drugs.[7] However, the results of a single-centre study reflect local practice and are not generalisable to other centres. To confirm these results, a multicentre, single-day point prevalence study was undertaken in conjunction with the Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group (CTG) and the George Institute for Global Health.

The primary aim of the study was to determine the total amount of sodium administered in critically ill patients in Australian and New Zealand intensive care units and to determine the most common sources of administration.

Methods

All Australian and New Zealand CTG-affiliated ICUs were invited to participate. Approval was obtained, when required, from the individual research ethics committees of participating sites. The study was a prospective, cross-sectional, observational audit and, as such, the requirement for individual patient consent was waived at all sites.

All adult patients ($\geq$ 16 years) present in participating ICUs at 10 am on the study day (Wednesday 21 September 2011, with a back-up day, 19 October 2011) were enrolled. Routine survey data for all patients included age, sex, weight (estimated or measured), Acute Physiology and Chronic Health Evaluation (APACHE) II score on ICU admis-

Table 1. Patient characteristics ($n = 356$)

Characteristic	No. of patients (%)*
Age, years†	58.5 (18)
Male sex	229 (64.3%)
Weight, kg†‡	81.6 (24)
APACHE II score†	20 (8)
Intensive care unit admission source	
Emergency department	110 (30.8%)
Hospital ward	75 (21.1%)
Operating theatre	109 (30.6%)
Other	62 (17.4%)
APACHE III diagnosis categories	
Cardiovascular	40/247 (16.2%)
Respiratory	65/247 (26.3%)
Gastrointestinal	15/247 (6.0%)
Neurological	39/247 (15.8%)
Sepsis	35/247 (14.2%)
Trauma	22/247 (8.9%)
Other	29/247 (11.7%)
SOFA score on study day§	7 (4–11)
Respiratory SOFA score on study day§	2 (1–3)
Sepsis on study day	127 (35.6%)
ALI/ARDS on study day	38 (10.6%)
Renal replacement therapy	41 (11.5%)
Hospital length of stay, days§	5.0 (2.0–13.0)
28-day mortality	45 (12.6%)

APACHE = Acute Physiology and Chronic Health Evaluation. SOFA = Sequential Organ Failure Assessment. ALI = acute lung injury. ARDS = acute respiratory distress syndrome. * Unless otherwise specified. † Mean (SD). ‡ Weight estimated or actual. § Median (interquartile range).

sion, Sequential Organ Failure Assessment (SOFA) score within the 24 hours preceding the study day, and ICU admission source. Data related to ICU admission diagnoses (operative v non-operative, burns, trauma) and specific diagnoses on the study day (acute lung injury [ALI], acute respiratory distress syndrome [ARDS], sepsis) were collected. Requirement for renal replacement therapy (RRT) on study day was also collected. The highest serum sodium level on the study day was recorded, and patients were defined as having hypernatraemia ($\geqslant 150$ mmol/L[6]) or hyponatraemia (< 130 mmol/L[9]). Vital status 28 days after study day was ascertained using hospital administrative databases.

Patients receiving an oral diet (at least 50% of dietary requirements met by oral intake, and enteral and/or parenteral nutrition not administered on the study day) were excluded for the purposes of ascertaining the sources of sodium administration.

Table 2: Sodium administration according to diagnostic category

Diagnostic category*	No. (%)	Sodium administered, mmol†
Postoperative	109 (30.6%)	224.3 (142.0–368.5)
Trauma	61 (17.0%)	256.7 (165.1–445.0)
Burns	3 (0.8%)	464.9 (168.6–686.5)
Sepsis	127 (35.6%)	224.3 (142.0–368.5)
ALI or ARDS	38 (10.6%)	200.8 (140.9–367.7)

* Postoperative, trauma (operative and non-operative) and burns diagnostic categories were at intensive care unit admission. Sepsis and ALI/ARDS diagnoses were on study day. † Data expressed as median (interquartile range). ALI = acute lung injury. ARDS = acute respiratory distress syndrome.

Data on all remaining patients included:

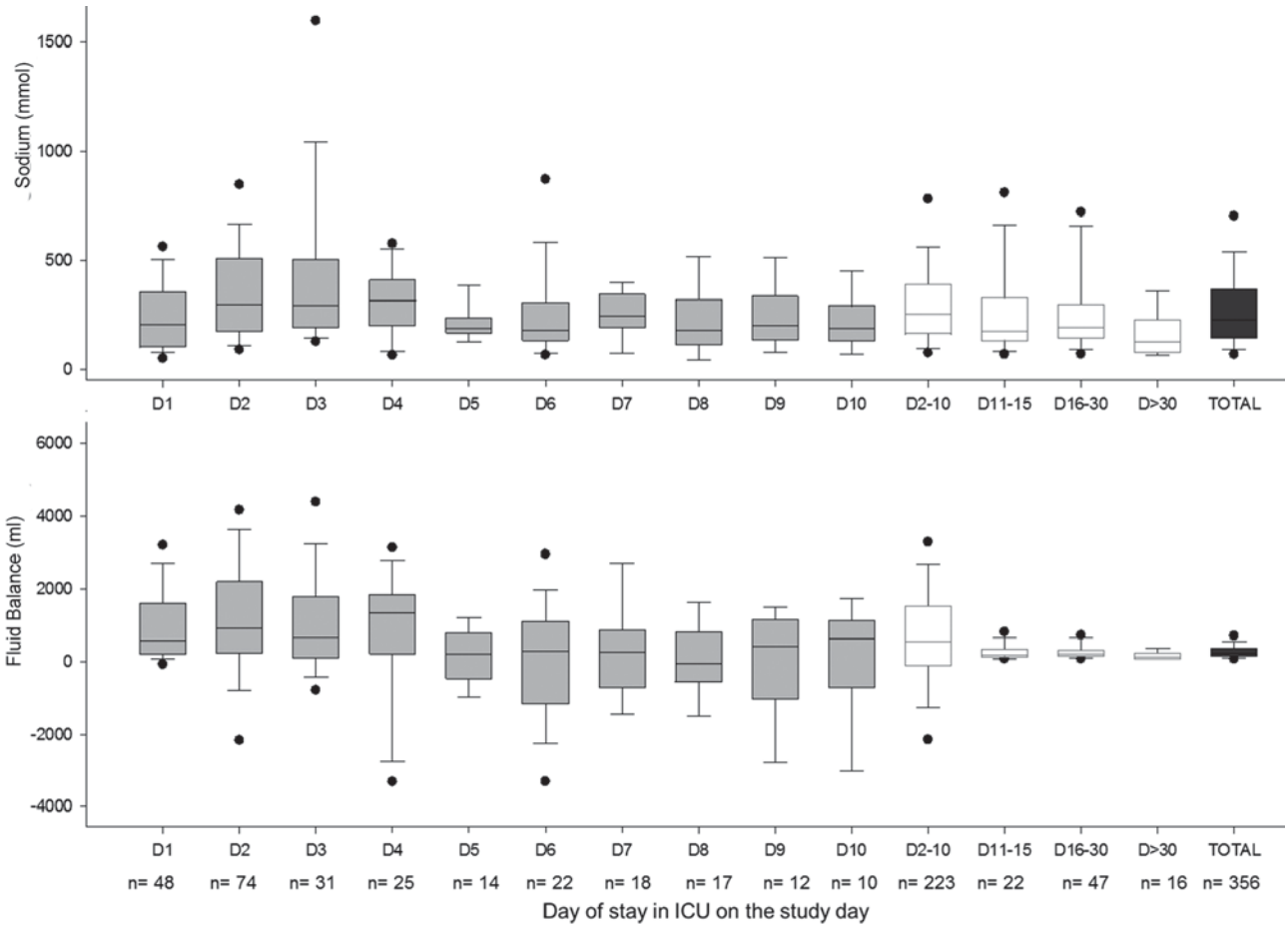
- IV bolus fluids administered for volume expansion or "fluid resuscitation" (ie, crystalloid infusion $\geqslant 5$ mL/kg/h or $\geqslant 400$ mL/h or any colloid bolus or infusion);
- blood products (ie, red blood cells, platelets, fresh frozen plasma);
- IV maintenance or replacement fluids (ie, crystalloids given by continuous infusion);
- IV drug infusions (ie, drugs administered by continuous infusion) together with their vehicles;
- IV drug boluses together with their vehicles;
- IV flushes associated with haemodynamic monitoring (eg, intra-arterial or central venous catheter);
- enteral nutrition;
- parenteral nutrition.

For all IV fluids and blood products, the type and volume administered over the 24-hour study day were recorded and the amount of sodium administered was calculated based on published sodium concentrations.[7] For drug infusions and boluses, sodium content was calculated from both the sodium content of the drug and the type and volume of carrier fluid or diluent. For enteral and parenteral nutrition, information on the type and volume of feed was recorded and the sodium content was calculated accordingly. For custom parenteral nutrition, the sodium content was recorded. No data on oral sodium intake were collected.

Statistical analysis

Variables are reported as mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate. Sources

Figure 1: Sodium and fluid balance on study day according to day of stay in the intensive care unit after ICU admission*



* Data presented as box plot representing median, upper and lower quartile with the 10th and 90th percentile either side, dots are 95th and 5th percentiles. Day 1 has 14 h (median; IQR 11–18 h) of data. "n =" represents the total number of patients according to the day of stay in ICU on study day.

of sodium administration are reported as percentages with 95% CI. Antimicrobials were analysed separately to other IV drugs due to the high sodium load of some agents.[7]

Pearson correlation was used to test for the association between sodium administered (log transformed for normal distribution) and the following factors: age, weight, APACHE II score and day of ICU stay, SOFA score, serum sodium, fluid administered and 24-hour fluid balance on study day. Predictor variables for sodium administration (age, sex, APACHE II score, site, and variables significant at $\alpha \leqslant 0.10$) were analysed using multiple linear regression (SPSS version 2.0). Day 1 data were not included in the model as 24-hour data were incomplete (median [IQR] ICU length of stay, 14 [11–18] hours). In addition, the amount of sodium administered during routine care as opposed to the initial resuscitation phase that occurs at ICU admission is potentially different.

For all analyses, a *P* value of less than 0.05 was considered significant.

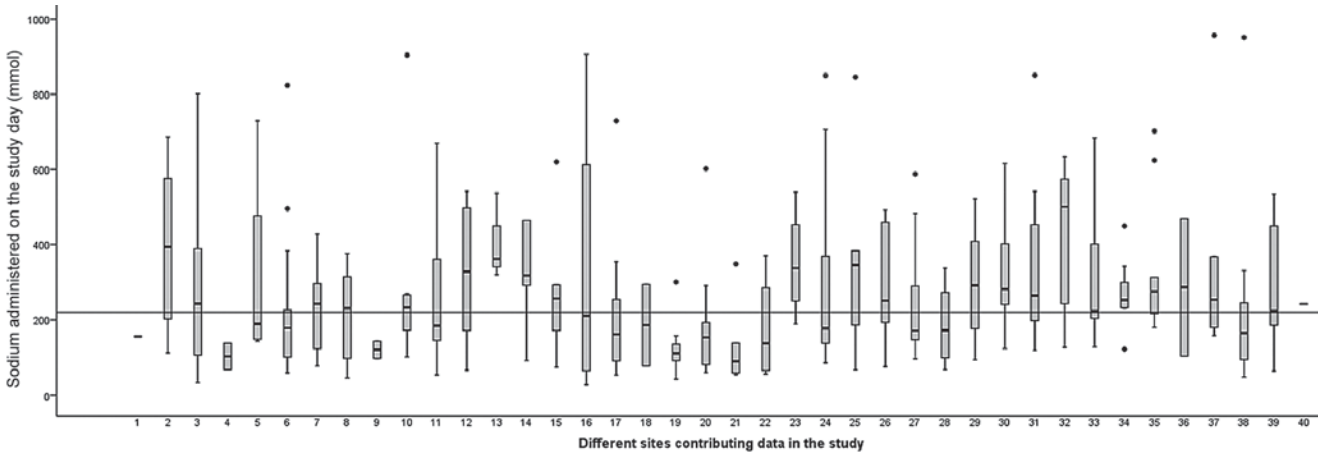
Results

Patient characteristics

Five hundred and eleven patients from 46 tertiary referral, metropolitan and rural hospital ICUs were enrolled in the point prevalence survey (Appendix). One hundred and fifty-five patients (30.3%) were excluded, either because of oral intake (148; 28.9%) or missing data (7; 1.4%).

Of the remaining 356 patients (40 sites), 64.3% (229) were men and the mean (SD) age and estimated body weight (on study day) were 58.5 years (18.0 years) and 81.6 kg (24.0 kg), respectively. Twenty-eight-day mortality was 12.6%. Other patient characteristics are shown in Table 1.

Figure 2: Sodium administration on study day at different sites*



* Box plot representing median, upper and lower quartile with the 95 and 5 percentile either side; dots are outliers. Horizontal line represents the median level of administered sodium, 224.5 mmol.

Serum sodium

Mean (SD) serum sodium level on study day was 140.5 mmol/L (5.0 mmol/L). Sixty-nine patients (19.3%) had a serum sodium ⩾ 145 mmol/L and 18 (5.1%) were hypernatraemic (serum sodium, ⩾ 150 mmol/L). Fifty-seven patients (16.0%) had a serum sodium < 135 mmol/L and 6 (1.7%) were hyponatraemic (serum sodium, ⩽ 130 mmol/L) on study day.

Sodium and fluid administration

The median (IQR) total amount of sodium administered at individual study sites ranged from 90.0 mmol (56.5–243.3 mmol) to 500.1 mmol (199.5–604.1 mmol). Overall sodium administration across all the sites was 224.5 mmol (144.9–367.6 mmol) or 2.8 mmol/kg (1.6–4.7 mmol/kg). Twenty-four hour fluid balance was +503.5 mL (+2.5 to +1345 mL). Sodium administration according to diagnostic category is shown in Table 2. Sodium administration and fluid balance according to the day of stay in ICU is shown in Figure 1.

Among patients for whom the study day was Day 1 (median [IQR] ICU length of stay 14 h [11–18 h]) of their ICU admission (48/356; 13.4%), 202.9 mmol (101.5–352.9 mmol) of sodium was administered. The main sodium source was IV maintenance or replacement fluids (77.5 mmol; 38.2% [95% CI, 37.3%–39.0%] of all sodium administered). Other sources included IV fluid boluses (44.4 mmol; 22.0% [95% CI, 21.3%–22.7%]), IV drug boluses other than antimicrobials (22.9 mmol; 11.3% [95% CI, 10.7%–11.8%]), IV drug infusions (19.1 mmol; 9.4% [95% CI, 8.9%–9.9%]), IV flushes (12.6 mmol; 6.2% [95% CI, 5.8%–6.6%]), blood products (12.4 mmol; 6.1% [95% CI, 5.6%–6.5%]), IV antimicrobials (7.2 mmol; 3.5% [95% CI, 3.2%–3.8%]), enteral nutrition (6.2 mmol; 3.1% [95% CI, 2.7%–3.3%]), and parenteral nutrition (0.3 mmol; 0.1% [95% CI, 0.0–0.1%]). The total amount of fluid administered as a bolus on Day 1 was 800 mL (467–1048 mL).

Among patients for whom the study day was Day 2–10 of their ICU admission (223/356; 62.6%), 255.1 mmol (163.2–390.5 mmol) of sodium was administered. Twenty-four hour fluid balance was +550 mL (– 126 to +1515 mL) (Figure 1). The main source of sodium administration was IV maintenance or replacement fluids (69.3/224.5 mmol; 30.9% [95% CI, 30.6%–31.2%] of all sodium administered). Of the 225 patients receiving IV maintenance or replacement fluids, 33.7% (76/225) received 0.9% saline. The four other most common fluids infused were Hartmann's solution (in 55/225 patients; 24.4%), 5% dextrose (34/225; 15.1%) and 4% dextrose and 0.18% saline (21/225; 9.3%).

Other sodium sources included IV fluid boluses (36.5 mmol; 16.3% [95% CI, 16.0%–16.4%]), IV drug boluses other than antimicrobials (27.6 mmol; 12.3% [95% CI, 12.1%–12.5%]), enteral nutrition (26.5 mmol; 11.8% [95% CI, 11.5%–12.0%]), IV drug infusions (19.3 mmol; 8.6% [95% CI, 8.4%–8.8%]), IV flushes (16.6 mmol; 7.4% [95% CI, 7.2%–7.5%]), blood products (13.5 mmol; 6% [95% CI, 5.8%–6.4%]), IV antimicrobials (11.2 mmol; 5% [95% CI, 4.8%–5.1%]) and parenteral nutrition (4.3 mmol; 1.9% [95% CI, 1.8%–2.0%]). Saline 0.9% was the most commonly used vehicle for IV drug boluses (177/234; 75.6%) and IV drug infusions (152/236; 64.4%). Heparinised saline was the most commonly used IV flush fluid (214/218; 98.1%).

The highest proportion of sodium administered from IV fluid boluses occurred on Days 2 and 3 of ICU admission. Seventy-four patients (20.8%) received a fluid bolus on Day 2 (513 mL [332–1637 mL]) that delivered 66.0 mmol of sodium (22.3% [95% CI, 21.8%–22.8%]) of all sodium administered). Patients for whom the study day was Day 3 of their ICU admission (31/356; 20.8%), received 467 mL (257–1971 mL) as fluid boluses, amounting to 55.2 mmol (18.8% [95% CI, 18.1%–19.4%]) of administered sodium. Overall, albumin (4% or 5%) was the most commonly administered bolus fluid (46/125 fluid boluses; 36.8%), followed by 0.9% saline (30/125; 24%) and Hartmann solution (16/125; 12.8%).

Sodium administration was weakly correlated with study day total SOFA score ($P = 0.001$; $r = 0.19$), the respiratory component of the SOFA score ($P = 0.032$; $r = 0.14$), 24-hour administered fluid ($P = 0.038$; $r = 0.11$) and fluid balance ($P < 0.001$; $r = 0.45$). Using multiple linear regression modelling ($R^2 = 0.115$), factors associated with administered sodium were site (standardised β coefficient, 0.105; $P = 0.044$) (Figure 2), age (–0.227; $P < 0.001$), administered fluid on study day (0.121; $P = 0.03$) and day of stay in ICU (–0.167; $P = 0.01$) (Figure 1).

Discussion

In this multicentre point prevalence study of Australian and New Zealand ICUs, the median sodium administration was greater than 220 mmol on the study day. In contrast, fluid balance on the study day was only 500 mL positive, suggesting that ICU patients, despite a small positive fluid balance, receive a high sodium load in excess of recommended daily requirements for a healthy population[8] (albeit there is no recommended daily intake for critically ill patients in ICU).

The principal source of sodium administration was not IV fluid resuscitation as one may have presupposed, but was IV infusions — in particular, maintenance fluids — as well as IV drug infusions, boluses and flushes. These sources of sodium are inadvertent and potentially modifiable, depending on clinician choice for "routine" IV fluid administration. These findings are also similar to the results of our single-centre study.[7] A high level of non-dietary sodium administration has been similarly reported in cardiac patients.[10] Furthermore, although the selection of fluid type varied between participating sites, 0.9% saline was the most common IV fluid, contributing to 59.2% of all sodium administered. While the reason(s) for choosing 0.9% saline cannot be ascertained from this point prevalence survey, it is noteworthy that recent studies have indicated that after a bolus of 0.9% saline, excretion of both water and sodium is slower[11] and may result in reductions in renal blood flow velocity and renal cortical tissue perfusion.[12]

Sodium retention might be more relevant in critically ill patients owing to activation of the renin–angiotensin–aldosterone system.[1] This is especially so in mechanically ventilated patients, where positive pressure ventilation and positive end-expiratory pressure both raise intrathoracic pressure, which results in reduced venous return and consequent complex neurohumoral responses[13,14] leading to sodium[15] and water retention. As seen in this current study, sodium administration on the study day had a weak correlation with the SOFA score and with a net positive fluid balance. Importantly, a positive fluid balance has been shown to be associated with poor lung and kidney function,[16,17] delayed return of gastrointestinal function after surgery[18] and an increased risk of mortality.[19] The adverse effects of positive fluid balance are probably due to extracellular fluid expansion. Therefore, both water and sodium may be important because water distributes to both intracellular and extracellular spaces. In contrast, sodium distributes into the extracellular spaces leading to cellular dehydration and interstitial oedema in both the lungs[15] and the systemic circulation. Current strategies using conservative fluid balance therapy without attention to concomitant sodium balance could potentially lead to intracellular dehydration, and it could have been one of the mechanisms contributing to abnormal neurocognitive effects in patients with lung injury managed with conservative fluid balance.[20]

Sodium administration is often coupled with chloride, usually as a 1 : 1 ratio except for fluids such as Hartmann solution, where the ratio is 1.2 : 1. Although chloride administration was not directly measured in our study, it can be hypothesised that high sodium administration would have accompanying high chloride administration, which may have adverse effects; effects of chloride restriction on the acid–base status of ICU patients has recently been investigated,[21] and implementation of a chloride-restrictive strategy in a tertiary ICU was associated with a significant decrease in the incidence of kidney injury and the requirement for dialysis in ICU.[22] Irrespective of these considerations, the issue of sodium restriction is increasingly recognised as important in ICU patients.[23]

Large amounts of administered sodium, together with the propensity for sodium retention and a conservative fluid balance, can lead to hypernatraemia. Hypernatraemia is not uncommon in the critically ill;[4] in our study, 19.3% of patients had a serum sodium ⩾ 145 mmol/L and 5% had hypernatraemia (⩾ 150 mmol/L). This rate of hypernatraemia is consistent with the literature[6] and has previously been associated with poor outcomes.[5,6]

Limitations

Our single-day point prevalence study conducted across multiple ICUs in Australia and New Zealand represents a snapshot of current practices for critically ill patients not receiving oral nutrition on study day. Despite our best efforts to record all IV and enteral fluids administered, it is possible that other sources of sodium were not included. Formal sodium balance and the indications for the prescription of high-sodium fluids such as 0.9% saline were also not collected. Finally, inferences regarding sodium administration on Day 1 are limited, as data collection covered less than 24 hours.

Future directions

Inadvertent high levels of sodium administration are potentially modifiable as IV sodium sources are primarily maintenance fluids, vehicles for infusions and drug boluses, and flushes. Future studies should include both prospective observational studies examining the relationship between sodium administration, sodium balance and important clinical outcomes (eg, mortality) and interventional trials to assess whether it is desirable and/or safe to modify daily sodium administration in critically ill patients, and can be coupled with simultaneous measurement of chloride administration and balance.

Conclusion

We have shown high levels of sodium administration in multiple ICUs across Australia and New Zealand in a large cohort of patients. Most administered sodium is from inadvertent sources. However, there is wide variability in the use of infusions and vehicles for drug infusions and boluses.

Competing interests

None declared.

Author details

Shailesh Bihari, Lecturer,[1] and Fellow[2]
Sandra L Peake, Associate Professor,[3] Adjunct Associate Professor,[4] and Senior Staff Specialist[5]
Ian Seppelt, Senior Staff Specialist in Intensive Care Medicine,[6] Clinical Lecturer,[7] and Senior Research Fellow[8]
Patricia Williams, Affiliate Lecturer, Discipline of Acute Care,[3] Adjunct Research Fellow,[4] and Research Manager[5]
Andrew Bersten, Professor,[1] and Head of Department[2]

1 Department of Critical Care Medicine, Flinders University, Adelaide, SA, Australia.
2 Department of Intensive Care Medicine, Flinders Medical Centre, Adelaide, SA, Australia.
3 School of Medicine, University of Adelaide, Adelaide, SA, Australia.
4 Australian and New Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, VIC, Australia.
5 Department of Intensive Care Medicine, The Queen Elizabeth Hospital, Adelaide, SA, Australia.
6 Department of Intensive Care Medicine, Nepean Hospital, Sydney, NSW, Australia.
7 Sydney Medical School — Nepean, University of Sydney, Sydney, NSW, Australia.
8 George Institute for Global Health, Sydney, NSW, Australia.
Correspondence: biharishailesh@gmail.com

References

1 Jungmann E, Schifferdecker E, Rümelin A, et al. [Plasma renin activity and aldosterone behavior in critically ill patients] [German]. *Klin Wochenschr* 1987; 65: 87-91.
2 Seri I, Kone BC, Gullans SR, et al. Locally formed dopamine inhibits Na+-K+-ATPase activity in rat renal cortical tubule cells. *Am J Physiol* 1988; 255 (4 Pt 2): F666-73.
3 Seri I, Kone BC, Gullans SR, et al. Influence of Na+ intake on dopamine-induced inhibition of renal cortical Na(+)-K(+)-ATPase. *Am J Physiol* 1990; 258 (1 Pt 2): F52-60.
4 Palevsky PM, Bhagrath R, Greenberg A. Hypernatremia in hospitalized patients. *Ann Intern Med* 1996; 124: 197-203.
5 Hoorn EJ, Betjes MG, Weigel J, Zietse R. Hypernatraemia in critically ill patients: too little water and too much salt. *Nephrol Dial Transplant* 2008; 23: 1562-8.
6 Lindner G, Kneidinger N, Holzinger U, et al. Tonicity balance in patients with hypernatremia acquired in the intensive care unit. *Am J Kidney Dis* 2009; 54: 674-9.
7 Bihari S, Ou J, Holt AW, Bersten AD. Inadvertent sodium loading in critically ill patients. *Crit Care Resusc* 2012; 14: 33-7.
8 Australian Government National Health and Medical Research Council, New Zealand Ministry of Health. Sodium. Nutrient reference values for Australia and New Zealand including recommended dietary intakes. http://www.nrv.gov.au/resources/_files/n35-sodium.pdf (accessed Apr 2013).
9 Asadollahi K, Beeching N, Gill G. Hyponatraemia as a risk factor for hospital mortality. *QJM* 2006; 99: 877-80.
10 Tafreshi J, Hoang TM, Grigorian T, et al. Impact of iatrogenic, excessive, nondietary sodium administration in patients with acute heart failure exacerbation on hospital length of stay. *Pharmacotherapy* 2011; 31: 58-61.
11 Reid F, Lobo DN, Williams RN, et al. (Ab)normal saline and physiological Hartmann's solution: a randomized double-blind crossover study. *Clin Sci (Lond)* 2003; 104: 17-24.
12 Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and Plasma-Lyte 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. *Ann Surg* 2012; 256: 18-24.
13 Bersten AD. Fluid management in the ventilated patient. In: Tobin MJ, editor. Principles and practice of mechanical ventilation. 2nd ed. New York: McGraw Hill, 2006: 1323.
14 Frazier SK. Neurohormonal responses during positive pressure mechanical ventilation. *Heart Lung* 1999; 28: 149-65.
15 Bihari S, Baldwin CE, Bersten AD. Fluid balance does not predict estimated sodium balance in critically ill mechanically ventilated patients. *Crit Care Resusc* 2013; 15: 89-96.

16 National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network; Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; 354: 2564-75.

17 Bouchard J, Soroko SB, Chertow GM, et al; Program to Improve Care in Acute Renal Disease (PICARD) Study Group. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney Int* 2009; 76: 422-7.

18 Lobo DN, Bostock KA, Neal KR, et al. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial. *Lancet* 2002; 359: 1812-8.

19 Boyd JH, Forbes J, Nakada TA, et al. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. *Crit Care Med* 2011; 39: 259-65.

20 Mikkelsen ME, Christie JD, Lanken PN, et al. The adult respiratory distress syndrome cognitive outcomes study long-term neuropsychological function in survivors of acute lung injury. *Am J Respir Crit Care Med* 2012; 185: 1307-15.

21 Yunos NM, Kim IB, Bellomo R, et al. The biochemical effects of restricting chloride-rich fluids in intensive care. *Crit Care Med* 2011; 39: 2419-24.

22 Yunos NM, Bellomo R, Hegarty C, et al. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA* 2012; 308: 1566-72.

23 Saxena MK. Should sodium be the real target of fluid restriction? *Crit Care Resusc* 2013; 15: 75-6. ❑

Appendix List of participating sites and investigators

Albury Base Hospital, Albury, NSW, Australia: P Harrigan, C Mashonganyika

Alfred Hospital, Melbourne, VIC, Australia: A Davies, S Vallance, V Bennett

Auckland City Hospital, Auckland, New Zealand: S McGuiness, R Parke, V Cochrane

Auckland DCCM Hospital, Auckland, New Zealand: C McArthur, L Newby, C Simmonds

Austin Hospital, Melbourne, VIC, Australia: R Bellomo, G Eastwood

Box Hill Hospital, Melbourne, VIC, Australia

Calvary Mater Hospital, Newcastle, NSW, Australia: K Ellem

Canberra Hospital, Canberra, ACT, Australia: I Mitchell, E Crawford, R Ashley

Central Gippsland Health Service, Gippsland, VIC, Australia: J Dennett, H Connor

Christchurch Hospital, Christchurch, New Zealand: S Henderson, J Mehrtens

Concord Hospital, Sydney, NSW, Australia: D Milliss, H Wong

Dandenong Hospital, Melbourne, VIC, Australia: S Vij, B O'Bree, K Shepherd

Flinders Medical Centre, Adelaide, SA, Australia: S Verghese, E Ryan, A Waters

Geelong Hospital, Geelong, VIC, Australia: C Carrington, M Fraser, T Elderkin

Gold Coast Hospital, Southport, QLD, Australia: B Richards, M Tallot

Gosford Hospital, Gosford, NSW, Australia: R Cameron, S Hatter

Hawke's Bay Hospital, Hastings, New Zealand: R Freebairn, L Chadwick

John Hunter Hospital, Newcastle, NSW, Australia: Peter Harrigan

Liverpool Hospital, Sydney, NSW, Australia: M Parr, S Micallef

Macquarie Hospital, Sydney, NSW, Australia: M Parr, D Bhonagiri

Middlemore Hospital, Auckland, New Zealand: T Williams, J Tai, A Tilsley

Maroondah Hospital, Melbourne, VIC, Australia: D Charlesworth

Nambour General Hospital, Nambour, QLD, Australia: P Garrett

Nepean Hospital, Sydney, NSW, Australia: I Seppelt, L Weisbrodt

North Shore Private Hospital, Sydney, NSW, Australia: A Delaney, S Ash, DL Hogben

North Shore Hospital, Takapuna, New Zealand: J Liang

Princess Alexandra Hospital, Brisbane, QLD, Australia: C Joyce

Royal Adelaide Hospital, Adelaide, SA, Australia: M Chapman, S O'Connor

Royal Darwin Hospital, Darwin, NT, Australia: D Stephens, J Thomas

Royal Hobart Hospital, Hobart, TAS, Australia: A Turner, D Cooper

Royal Melbourne Hospital, Melbourne, VIC, Australia: C Macisaac, T Caf

Royal Perth Hospital, Perth, WA, Australia: S Webb, G McEntaggart, J Chamberlain

Royal Prince Alfred Hospital, Sydney, NSW, Australia: D Gattas, D Rajbhandari, H Buhr

Sir Charles Gairdner Hospital, Perth, WA, Australia: S Baker, B Roberts

St George Hospital, Sydney, NSW, Australia: J Myburgh, V Dhiacou

St Vincent's Hospital, Melbourne, VIC, Australia: J Santamaria, R Smith

St Vincent's Hospital, Sydney, NSW, Australia: P Nair, C Burns, C Reynolds

Tauranga Hospital, Tauranga, New Zealand: T Browne, J Goodson

The Queen Elizabeth Hospital, Adelaide, SA, Australia: S Peake, P Williams, C Kurenda

Toowoomba Hospital, Toowoomba, QLD, Australia: I Chatterjee

Townsville Hospital, Townsville, QLD, Australia: G Gordon, L Jones

Waikato Hospital, Hamilton, New Zealand: M La Pine

Wellington Regional Hospital, Wellington, New Zealand: D Dinsdale, D Mackle, L Andrews

Western Health, Melbourne, VIC, Australia: C French

Westmead Hospital, Sydney, NSW, Australia: A Bannerjee, C Skelly

Wollongong Hospital, Wollongong, NSW, Australia: M Sterba, B Johnson

Protocolized Care for Early Septic Shock (ProCESS) statistical analysis plan

Francis Pike, Donald M Yealy, John A Kellum, David T Huang, Amber E Barnato, Tammy L Eaton, Derek C Angus and Lisa A Weissfeld on behalf of the ProCESS Investigators

ABSTRACT

Background: The Protocolized Care for Early Septic Shock study is a randomised, multicentre, prospective, three-arm, parallel-group trial of alternative resuscitation strategies for early septic shock.

Objective: To state our analysis plan for trial data.

Methods: Our plan is to guide data collection and analysis using pre-existing definitions and testing, with local consensus-based efforts where needed. We examine protocolised care (two experimental approaches) and compare this to usual "wild type" care.

Results: Our plan is to address three aims (clinical efficacy, biology of illness and recovery, and costs and cost-effectiveness) and four hypotheses, and we specify rules for handling data and determining outcomes.

Conclusion: By using measures to maintain study conduct and analysis rigour, we hope to improve understanding of early septic shock resuscitation and care of patients.

Crit Care Resusc 2013; 15: 301–308

Overview

Background and goals

In 2001, Rivers and colleagues published a seminal manuscript on the early resuscitation of patients with septic shock.[1] They observed a marked improvement in short-term mortality when using a structured, physiological approach to resuscitation in the first 6 hours of care, delivered via a protocol of fluids, vasopressors, blood or inotropes. The absolute change in mortality was high (46.5% in control patients, compared with 30% in protocol patients), but use of the approach and protocol specified by Rivers and colleagues is hampered by concerns about its generalisability and the contribution of individual components.[2]

The Protocolized Care for Early Septic Shock (ProCESS) study is a randomised, multicentre, prospective, three-arm, parallel-group trial of alternative resuscitation strategies for early septic shock. Institutional review board (IRB) approval was obtained from the University of Pittsburgh and all participating sites, and the trial is registered with Clinical Trials.gov (NCT00510835).

Our primary goal is to determine the clinical efficacy of two protocolised resuscitation strategies, compared with usual care. We will also assess the effect of these resuscitation strategies on markers of biological pathways and on cost and resource use. Our design randomises patients to receive one of two resuscitation strategies or usual care ("wild type", without any structured care). The experimental resuscitation strategies are:

- early goal-directed therapy (EGDT), based on the Rivers protocol and guided by systolic blood pressure, central venous pressure and central venous oximetry;[1] and
- protocolised standard care (PSC), an approach that delivers fluids and vasopressors based on simple bedside criteria without the use of invasive monitoring.

Our trial is harmonised with but independent from similar studies in Australia and the United Kingdom.[3] The three studies target the same group and use the same basic approach — resuscitation in the first 6 hours of recognition of septic shock, testing the River's approach in one arm, and using a randomised, controlled design. The leaders of the three trials are maximising the consistency of their data collection to allow a future patient-level meta-analysis, allowing more insight into early septic shock care. A separate study group drawn from the parent trials will define research questions and an analysis plan before the data merge.

Here we report our statistical analysis plan for the ProCESS study, before unblinding of researchers and per-arm outcome assessments.

Patient population

Based on census data from the emergency departments (EDs) of participating sites and United States federal claims data, we are enrolling a population that we expect to be 56% men, 68% white, 25% African American and 7% other races. We expect this distribution but are enrolling patients without regard to sex, race or age. The trial is not designed to make inferences about non-black minority groups.

Inclusion criteria

Our study is using similar inclusion criteria to that of Rivers and colleagues.[1] Patients must:

- be ⩾ 18 years of age
- have a suspected infection
- meet two or more of the criteria for systemic inflammatory response syndrome, and
- have refractory hypotension (systolic blood pressure < 90 mmHg despite an intravenous [IV] fluid challenge of ⩾ 1000 mL over a 30-minute period), or evidence of hypoperfusion (blood lactate concentration > 4 mmol/L). To identify refractory hypotension, we initially required a 20 mL/kg minimum crystalloid bolus over 30 minutes (identical to that of Rivers and colleagues[1]) but modified this to the simpler 1000 mL bolus in April 2010 to ease logistics.

Exclusion criteria

We are excluding patients who:

- are currently pregnant
- have a primary diagnosis of acute cerebral vascular event, acute coronary syndrome, acute pulmonary oedema, status asthmaticus, major cardiac arrhythmia, active gastrointestinal haemorrhage, seizure, drug overdose, burn or trauma
- need immediate surgery
- have a CD4 count < 50/μL
- have an absolute neutrophil count < 500/μL
- have a "do not resuscitate" code status or an advance directive restricting implementation of the protocol
- have a contraindication to central venous catheterisation
- are likely to refuse a blood transfusion (eg, Jehovah's Witnesses)
- have a treating doctor who deems aggressive care unsuitable
- are participating in another interventional study
- have been transferred from another inhospital setting.

Objectives and aims

Aim 1

To compare the clinical efficacy of alternative resuscitation strategies for patients with septic shock, using sequential hypothesis testing, we are testing the following:

- Hypothesis Ia: structured care (EGDT and PSC) will produce superior short-term mortality outcomes compared with usual care.
- Hypothesis Ib: if Ia is true, EGDT will produce superior outcomes to PSC.

Aim 2

To understand the mechanisms of illness and recovery and how resuscitation strategies affect them, and affect clinical outcomes, we are testing the following:

- Hypothesis IIa: protocolised resuscitation changes the expression of markers of illness and recovery.
- Hypothesis IIb: the clinical efficacy of protocolised resuscitation changes markers of illness and recovery.

Aim 3

We aim to assess the costs and cost-effectiveness of the alternative resuscitation strategies.

Variable definitions

Primary outcome

The primary outcome is all-cause hospital mortality, truncated at 60 days, which is parallel to the approach of the Acute Respiratory Distress Syndrome Network trials of the National Heart, Lung, and Blood Institute. We will unblind researchers and begin analyses only after all data collection forms are complete, to the best of the abilities of the sites, and at least 120 days have passed from the last enrollee entering the trial.

Secondary outcomes

We will assess survival at 90 days and 1 year, clinical evidence of organ dysfunction and, in subsets of patients, absolute values and changes in markers of inflammation, oxidative stress, cellular hypoxia, coagulation and thrombosis. As part of Aim 3, we will also assess inpatient resource use, up to 60 days, including duration of mechanical ventilation, acute dialysis, hospital stay, intensive care unit stay and, in subsets of patients, total hospital charges. We will assess return-to-work, usual activities and health utility using EuroQol-5D scores at 90 days.

Safety

At trial design and start, we expected this study population to have an inhospital mortality rate in the control arm of 30%–46%, based on existing data.[4] To ensure optimal patient exposure and safety, the granting agency, independent safety board and coordinating centre is tracking overall mortality throughout the trial. Only the data and safety monitoring board has seen any per-arm outcome data.

Our reporting plan maximises the ability to detect any signal of differential treatment-related event rates across study arms without being encumbered by large numbers of reported events that accompany the illness (eg, background events). Therefore, our plan is to collect:

- detailed information regarding all serious adverse events occurring until Hour 72
- central venous oximetry catheter serious adverse events for the duration of hospitalisation or until Day 60, whichever period is the shorter
- all late-occurring (after Hour 72) serious adverse events detected by sites and potentially related to the study intervention (including late infections).

Analysis principles

- All primary analyses will be conducted on an intention-to-treat basis.
- Only patients who decline use of outcome data will be excluded from analysis. Exclusions will be reported per arm (see below). Patients who have protocol violations are analysed per the assigned treatment arm.
- All hypothesis tests will be two sided, with an α of 0.0494 unless otherwise specified.
- All analyses are unadjusted unless otherwise specified.
- Subgroup analyses are performed irrespective of treatment efficacy.

Design

Data collection and follow-up

There is the potential for two separate datasets: one for all randomised patients, and one with only randomised patients for whom data are available. For patients who decline participation by withholding consent, we will collect a limited set of demographic data (to the extent allowed by each site IRB) to compare patients who did and did not enrol in the study.

The stages of data collection and follow-up are randomisation, baseline, intervention (Hour 0–Hour 6), postintervention (Hour 7–Hour 72), other hospital follow-up (Day 2–Day 60 or at discharge), postdischarge survival, and data collection supporting Aims 2 and 3. The data collected at each of these stages are as follows.

Randomisation

- Patient demographics and inclusion and exclusion criteria.

Baseline

- Sociodemographics: age, sex, race, ethnicity, residence before admission and employment status.
- Comorbid conditions and medications: Charlson comorbidity index score, chronic illness components of the Acute Physiology and Chronic Health Evaluation (APACHE) III score and exposure in the preceding 7 days to antibiotics and other selected medications.
- Site and aetiology of infection: assignments will be made retrospectively, based on the criteria of the Centers for Disease Control and Prevention, and the Interscience Conference on Antimicrobial Agents and Chemotherapy, and using the schema adopted previously in several multicentre trials on severe sepsis.[5,6]
- Severity of illness: APACHE III, sequential organ failure assessment (SOFA) scoring systems.[6-9]

Intervention period (Hour 0–Hour 6)

- Time of randomisation: the time of randomisation is "time zero" for data collection, although data are collected before randomisation, to assess care.
- Measurements and therapies (all patients): we measure vital signs initially and hourly, until the end of Hour 6. Therapy data include IV fluid volumes, packed red blood cell transfusions, vasoactive agents and inotropic agents. Data are also collected on central line placement and mechanical ventilation before and during the protocol period. We are also recording data on all prehospital and prerandomisation IV fluid administration.
- Additional measurements (EGDT arm only): central venous pressure and central venous oxygen saturation hourly until the end of Hour 6.

Postintervention period (Hour 7–Hour 72)

- Haemodynamics and therapies: vital signs are recorded at Hour 12, Hour 24, Hour 48 and Hour 72.
- Organ dysfunction: we are collecting daily SOFA scores and will use the worst level recorded for each organ system over the time.

Other hospital follow-up data (Day 2–Day 60 or at discharge)

- Daily SOFA scores while in the ICU (data collection resumes for patients who are discharged from the ICU and readmitted within 48 hours of initial admission; any subsequent ICU discharge and readmission will not be collected).
- Hospital location (hospital floor or ICU), timing and type of cointerventions (eg, steroid supplementation and activated protein C) and adverse events.
- At hospital discharge, we are assessing and recording ongoing renal and respiratory support, and discharge disposition (to home, nursing home or rehabilitation facility, etc.). Site investigators will assign the source of original infection.

Postdischarge survival

- We are collecting 90-day mortality data, through a National Death Index (NDI) search or, for more recently

enrolled subjects, by direct contact with the patient or their listed contacts.
- Survivors enrolled after the protocol modification approved in May 2011 by the local IRB will be asked (by direct contact) to complete the EuroQol-5D[10] and questions about their return to work and usual activities at 90 days.
- We are collecting long-term survival status (through to 1 year after discharge) through the NDI. There is a 2-year time lag before these data are available, so for patients enrolled near the end of the trial, we will perform primary analyses before their 1-year follow-up data are available, and a shorter follow-up will be handled with censoring.

Data collection for Aim 2 and Aim 3
- Aim 2: we are collecting blood and urine samples to analyse selected biomarkers. For blood sampling, we are collecting 30–35 mL of blood at four times (Hour 0, Hour 6, Hour 24 and Hour 72) with maximum of 140 mL of blood drawn over the study. For urine sampling, the ProCESS biorepository is also collecting urine samples from the ProCESS lab cohort at Hour 0, Hour 6, Hour 24 and Hour 72.
- Aim 3: we are collecting resource-use data to analyse costs and cost-effectiveness. The primary source of this information is the patient's data collection form and, for a subset of patients, the patient's UB-04 form (the National Uniform Billing Committee institutional provider bill).

Treatment allocation

Assuming entry criteria are met, each patient receives a study identification number and treatment allocation at enrolment. We randomise at a 1:1:1 ratio in variable blocks at each institution.

Power and sample size

We initially designed the study to have 80% power to detect an absolute risk reduction of 6%–7%, at a nominal significance level of 0.05, based on an expected overall event rate of 30%–46%. This required an equal allocation of 650 patients into each of the three study arms for a total sample size of 1950. We planned two interim analyses, when one-third and two-thirds of total enrolment were reached. We completed the first interim analysis with no recommendations for change in data or safety monitoring.

During the trial, we observed an overall blinded event rate of about 20%, the same as occurred in a recent trial with a similar design.[11] After consultation with the DSMB and the federal funding agency in February 2013, we resized the trial to a new total target of 1350 patients, to account for the lower observed overall event rate. The resizing retained the same pretrial targeted 80% power to detect an absolute risk reduction of 6%–7%. After "spending" about 0.0005 α during the first interim analysis at 650 patients, and after resizing to 1350 (which removed the requirement for a second interim analysis), the α required for our hypothesis tests at the close of enrolment will be 0.0494.

For the Aim 2 hypotheses, group sample sizes of 400 and 200 for the combined protocolised arms and control arms, respectively, allow 80% power to detect mean cytokine differences in the range 0.12–2.5 units. This assumes an exchangeable correlation structure, autocorrelation varying from –0.8 to 0.8, an SD of a single measurement varying from 1–10 units, four time points and a significance level of 0.05.

Consent

All patients or their legally authorised representatives provided consent for trial participation, with each site following the local regulations. We considered but did not use alternative consent strategies, including an exception or waiver process.

Permanent discontinuation

Patients who initially consent but later withdraw consent will be asked to agree to allow current data to be used for analysis. If they agree for their existing data to be used, they will be included and analysed on an intention-to-treat basis.

Statistical analysis

Trial profile

We plan a Consolidated Standards of Reporting Trials diagram to detail the movement of patients through the study. This diagram will include total patients screened, number who met inclusion and exclusion criteria, and number included in the study.

Baseline comparisons and assessment of randomisation

To assess randomisation success, we plan to tabulate the distribution of baseline variables across the study arms, and to summarise discrete variables by frequencies and percentages. We will report continuous variables as either means with SDs or as medians with interquartile ranges.

Process measures and concomitant treatments

Process measures

We will assess adherence to the experimental protocols at Hour 2, Hour 4 and Hour 6, based on prespecified actions and goal achievements. Hour 6 will be used for overall adherence analysis, but we will evaluate earlier and sus-

tained adherence and the relationship to outcomes as a secondary effort.

Concomitant treatments

We will track ancillary care during Hour 0–Hour 72, including delivery and timing of antibiotics, activated protein C, steroids and other vasoactive agents.

Treatment limitation

Only counts and percentages will be reported for patients for whom there was a limitation or withholding of treatment. This refers to a bedside doctor withdrawing or withholding treatment that might otherwise prolong life if the treatment is no longer considered appropriate for that patient.

Consent and discontinuation of study treatment

Only counts and percentages will be reported for patient consent and permanent discontinuation of treatment.

Primary outcome: analysis of Hypothesis Ia and Hypothesis Ib

Unadjusted test of treatment effect

We will test the hypothesis that protocolised resuscitation is superior to usual care by comparing the difference in mortality proportions in the combined EGDT and PSC arms versus usual care. We will use an unadjusted two-sample test of proportions with an interim analysis adjusted *P* of 0.0494. If the null hypothesis is rejected, we will test the difference in mortality proportions between experimental arms using the same method. We will test all other treatment arm comparisons as secondary analyses. We also plan exploratory subanalyses in which the first patients at each site and arm are excluded to examine if a "warm-up" effect exists.

Modelling to examine potentially confounding factors

We will also fit logistic regression models to adjust for independent variables that were deemed to be imbalanced after randomisation or of clinical importance. We will explore the main effects and interaction models via stepwise selection or penalised regression approach to arrive at the most parsimonious model with the best fit, as determined by the Hosmer–Lemeshow test.[12] Treatment effect will be expressed as an odds ratio with 95% confidence intervals.

Modelling to adjust for potential institution effects

To address site variation, we will fit generalised linear mixed models[13] with a site-specific random effect to capture this heterogeneity and to adjust for potential confounders as described above.

Secondary and tertiary outcomes analyses

We will test the hypothesis that protocolised care changes long-term survival, compared with usual care. If this hypothesis is affirmed, we will then test whether the EGDT arm is different from the PSC arm. We will plot Kaplan–Meier curves for aggregated and individual experimental arms, testing the equality of survival curves using a log-rank test with a *P* of 0.0494.Long-term survival data from the NDI

We will also construct multivariable Cox proportional hazards models,[14] include treatment assignment as an independent predictor, and adjust for baseline covariates using selection models similar to those described under Primary outcome: analysis of Hypothesis Ia and Hypothesis Ib (above). We will assess the goodness of fit for this model via residual analysis and tests of proportionality. If the proportional hazards assumption is not met, we will use Gray's[15] spline-based extension of the Cox model. This provides time-varying estimates of regression coefficients, allowing the hazard associated with a particular covariate to vary during follow-up. Once we have selected the most parsimonious model, the magnitude and significance of the hazard associated with the treatment covariate will be our estimate of treatment effect.

Non-mortal end points

We will examine non-mortal end points (eg, SOFA and other scores) with descriptive statistics and generalised linear or linear mixed models to account for the different nature of the outcomes and possible repeated measures. The descriptive statistics will include means and frequency distributions, followed by corresponding statistical tests (analysis of variance [ANOVA] for three-group tests, *t* tests for two-group tests, and non-parametric exact tests for categorical outcomes).

Markers of inflammation, oxidative stress, cellular hypoxia, and coagulation and thrombosis

In a subset of 600 patients (200 per arm), we will analyse markers of inflammation (tumour necrosis factor, interleukin [IL]-6, IL-10), oxidative stress (urine isoprostane), cellular hypoxia (lactate), and coagulation and thrombosis (D-dimer and thrombin–antithrombin III complexes). This subset will consist of 600 randomly chosen patients, 300 from the first half of the trial and 300 from the second half of the trial. We will also study biomarkers related to these mechanisms and to organ injury attributable to sepsis.

Analysis of Hypothesis IIa

We plan a descriptive analysis, a primary analysis and exploratory techniques to identify potential clusters of interest within Aim 2.

- Descriptive analyses include computation of mean values and SD at each time point. Correlation matrices of the behaviour of each marker over time will be computed. The validity of the sample will be examined through comparisons of the three treatment arms using ANOVA for continuous outcomes and χ^2 tests for categorical outcomes.
- Primary analysis consists of an application of statistical methods for the analysis of repeated measures using a mixed model or a generalised estimating equations[16] approach. These models include the marker as the outcome, and time, treatment group assignment, and a time-by-treatment group assignment term in the model. We will assume an exchangeable correlation structure for the analyses of these data. The test of the significance of the interaction terms in these models will provide a test of differences across time for the three treatment arms. Should missing data prove problematic, we will use methods that address this issue directly, such as a pattern mixture model[17] approach.
- Exploratory techniques to identify potential clusters of interest will be done by clustering trajectories into groups. This method, implemented using PROC TRAJ (SAS Institute), allows the number of desired clusters to be user-selected or analysis-selected. This procedure is quite general and includes continuous outcome data as well as truncated outcome data. A common problem when analysing changes in markers is truncation of values at the lower limit of detection. However, methods such as a normal model for truncated outcome data can be applied using PROC QLIM) (SAS Institute). This approach can be used for repeated-measures outcomes and for trajectory analyses.

Analysis of Hypothesis IIb

The analysis plan for this hypothesis is similar to the analysis plan for Hypothesis IIa, with one major difference: modelling includes clinical outcome (mortality or morbidity, such as SOFA score) as a predictor. Initially, models will include time, clinical outcome, and time-by-clinical outcome interactions. A test of the significance of the time-by-clinical outcome interaction term will indicate if the behaviour of the marker differs by clinical outcome over time. To explore how these changes occur with treatment, a series of models will be fitted, including as potential variables: time, treatment, clinical outcome, time-by-treatment interaction, clinical outcome-by-time interaction and clinical outcome-by-treatment interaction. Terms will be retained based on statistical significance and validity. The significance of the clinical outcome-by-treatment interaction term will indicate a difference in profiles across the treatment and mortality groups. To test this effect over time, a time-by-treatment-by-clinical outcome term can be included in the model.

Secondary analyses and analytical issues related to Aim 2

For some analyses, we will treat the marker as a covariate. For example, we can summarise the trajectory of a marker through an estimated slope, a maximal value across time points, a mean value across time points, or by growth curve modelling. Using any of these approaches, the summary variable can then be included in a linear, logistic or survival regression model. As a further refinement, errors-in-variables models[18] can be used to account for measurement errors. Alternatively, a joint modelling approach can be used.

Analyses and analytical issues related to Aim 3

We will conduct this analysis following the principles and recommendations of the US Panel on Cost-Effectiveness in Health and Medicine[19] and a position statement of the American Thoracic Society.[20] We will use methods developed as part of our prior cost-effectiveness assessments of other interventions and monitoring tools for sepsis, shock and organ dysfunction.[21,22] We will measure "base case" incremental cost–effectiveness ratios (ICERs), expressed as hospital costs per hospital survivor, from the US hospital perspective, and ICER from the US societal perspective ("reference case"), expressed as lifetime costs per survivor, costs per life-year and costs per quality-adjusted life-year. Hospital costs will be determined by collecting information on resource use in the data collection form, and multiplying resources consumed by cost weights derived from a detailed external cost database. Quality of life will be determined, for a subset of patients, using 90-day EQ-5D data. Estimates of longer term costs and quality of life will be derived from published sources. These measures will be incorporated in a simulation model to produce the reference case.

The effect of adherence on the estimates of treatment effect

We will assess and report adherence measures that include several approaches: intention-to-treat (ITT), as-treated (AT), per-protocol (PP), and instrumental-variables approaches.[23]

The standard approach to assessing the treatment effect in the presence of potential non-adherence is the ITT approach, in which all patients are analysed as if they received the treatment as intended. The limitation of this approach is that the estimates of treatment effect are

biased toward the null hypothesis, resulting in a potential underestimation of the treatment effect.

The AT approach can provide an upper boundary on the treatment effect when non-adherence is random. As it is likely that non-adherence in our trial will not be random, this approach will not be the focus of the analyses.[24]

The PP approach focuses on the analysis of patients who received the treatment as specified in the protocol. These estimates will be computed as a comparison with the estimates obtained using the ITT approach. The instrumental-variables approach will also be considered when estimating the treatment effect in the presence of potential non-adherence. This method is based on the computation of the complier-average causal effect, which measures the causal effect of the intervention on the patients who received it as intended by the original group allocation.[25,26]

Subgroup analyses

We will conduct prespecified subgroup analyses to understand the treatment effect, and to identify subgroups of patients for whom the treatment was particularly beneficial and/or harmful. These also allow future hypothesis generation. The subgroups are predefined to limit biases after unblinding.

We will first use descriptive testing for differences in treatment effects across the groups, through ANOVA techniques and through testing of interaction terms in statistical modelling. These interaction terms will consist of the interaction between the subgroup and treatment assignment. The subgroups of interest include (but are not limited to) the following variables: type of shock, source of infection, race, sex, age, anaemia status, timing of resuscitative actions and goal achievement, and level of adherence.

We will also apply newer methods to address bias when testing for treatment effects in subsets in clinical trials. One of these approaches, subpopulation treatment effect pattern plots, as outlined by Bonetti and Gelber,[27] creates plots of overlapping regions of potential covariates of interest. These plots provide a visual picture of the treatment effect over the full range of the covariate, and are easy to interpret, since they rely on traditional analysis methods for the plot presentation. Another approach is that outlined by Tibshirani and colleagues,[28,29] which relies heavily on the use of the least absolute shrinkage and selection operator for meaningful variable selection in interaction models.

Missing data

Missing data (due to incomplete forms or withdrawal from the study) are handled by the use of weighted estimating equations (in which the weights are functions of the probability of missing data) or by multiple imputation methods.[30-32] These are standard statistical approaches for the handling of missing data, that can be readily implemented in statistical software packages.

Conclusion

We describe, before any data unblinding, our approach to analysing the data from the ProCESS early resuscitation trial. We anticipate that this framework will enhance the utility of the reported result and allow readers to better judge the impact.

Funding

Our trial is supported by grants NIH/NIGMS P50 GM076659 and NIH/NHLBI K12 HL109068. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, the National Institute of General Medical Sciences or the National Heart, Lung, and Blood Institute.

Competing interests

None declared.

Author details

Francis Pike, Assistant Professor,[1] and Director of Biostatistics and Data Management Core[2]
Donald M Yealy, Professor and Chair[3]
John A Kellum, Professor and Vice Chair for Research[2]
David T Huang, Associate Professor[2,3]
Amber E Barnato, Associate Professor of Medicine, Clinical and Translational Science, and Health Policy[4]
Tammy L Eaton, Project Manager[2]
Derek C Angus, Professor and Chair, and Director[2]
Lisa A Weissfeld, Professor[1,2]

1 Department of Biostatistics, Pitt Public Health, University of Pittsburgh, Pittsburgh, Pa, United States.
2 Department of Critical Care Medicine, Clinical Research, Investigation, and Systems Modeling of Acute Illness (CRISMA) Center, University of Pittsburgh, Pittsburgh, Pa, United States.
3 Department of Emergency Medicine, University of Pittsburgh, Pittsburgh, Pa, United States.
4 Department of Medicine, University of Pittsburgh, Pittsburgh, Pa, United States.

Correspondence: lweis@pitt.edu

References

1 Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345: 1368-77.
2 Reade MC, Huang DT, Bell D, et al. Variability in management of early severe sepsis. *Emerg Med J* 2010; 27: 110-5.

3 ProCESS/ARISE/ProMISe Methodology Writing Committee. Harmonizing international trials of early goal-directed resuscitation for severe sepsis and septic shock: methodology of ProCESS, ARISE, and ProMISe. *Intensive Care Med* 2013; Aug 20 [Epub ahead of print].

4 Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; 344: 699-709.

5 Abraham E, Reinhart K, Opal S, et al. Efficacy and safety of tifacogin (recombinant tissue factor pathway inhibitor) in severe sepsis: a randomized controlled trial. *JAMA* 2003; 290: 238-47.

6 Warren BL, Eid A, Singer P, et al. Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: a randomized controlled trial. *JAMA* 2001; 286: 1869-78.

7 Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* 1991; 100: 1619-36.

8 Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; 22: 707-10.

9 Shapiro NI, Wolfe RE, Moore RB, et al. Mortality in Emergency Department Sepsis (MEDS) score: a prospectively derived and validated clinical prediction rule. *Crit Care Med* 2003; 31: 670-5.

10 Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. *Med Care* 2005; 43: 203-20.

11 Jones AE, Shapiro NI, Trzeciak S, et al. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA* 2010; 303: 739-46.

12 Hosmer DW, Lemeshow S. Applied logistic regression. 2nd ed. New York: John Wiley & Sons, 2000.

13 Fitzmaurice GM, Laird NM, Ware JH. Applied longitudinal analysis. Hoboken, NJ: John Wiley & Sons, 2004.

14 Cox DR. Regression models and life-tables. *J Royal Stat Soc B* 1972; 34: 187-220.

15 Gray RJ. Flexible methods for analyzing survival data using splines, with applications to breast cancer prognosis. *J Am Stat Assoc* 1992; 87: 942-51.

16 Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika* 1986; 73: 13-22.

17 Hedeker D, Gibbons RD. Application of random-effects pattern-mixture models for missing data in longitudinal studies. *Psychological Methods* 1997; 2: 64-78.

18 Bekker PA. Comment on identification in the linear errors in variables model. *Econometrica* 1986; 54: 215-7.

19 Weinstein MC, Siegel JE, Gold MR, et al. Recommendations of the panel on cost-effectiveness in health and medicine. *JAMA* 1996; 276: 1253-8.

20 American Thoracic Society. Understanding costs and cost-effectiveness in critical care: report from the second American Thoracic Society Workshop on outcomes research. *Am J Respir Crit Care Med* 2002; 165: 540-50.

21 Angus DC, Linde-Zwirble WT, Clermont G, et al; PROWESS Investigators. Cost-effectiveness of drotrecogin alfa (activated) in the treatment of severe sepsis. *Crit Care Med* 2003; 31: 1-11.

22 Angus DC, Clermont G, Watson RS, et al. Cost-effectiveness of inhaled nitric oxide in the treatment of neonatal respiratory failure in the United States. *Pediatrics* 2003; 112 (6 Pt 1): 1351-60.

23 McNamee R. Intention to treat, per protocol, as treated and instrumental variable estimators given non-compliance and effect heterogeneity. *Stat Med* 2009; 28: 2639-52.

24 Bang H, Davis CE. On estimating treatment effects under non-compliance in randomized clinical trials: are intent-to-treat or instrumental variables analyses perfect solutions? *Stat Med* 2007; 26: 954-64.

25 Lui KJ. Comments on 'On estimating treatment effects under non-compliance in randomized clinical trials: are intent-to-treat or instrumental variables analyses perfect solutions?' *Stat Med* 2009; 28: 531-4.

26 Hewitt CE, Torgeson DJ, Miles JN. Is there another way to take account of noncompliance in randomized controlled trials? *CMAJ* 2006; 175: 347.

27 Bonetti M, Gelber RD. Patterns of treatment effects in subsets of patients in clinical trials. *Biostatistics* 2004; 5: 465-81.

28 Tibshirani R. Regression shrinkage and selection via the lasso. *J Royal Stat Soc B* 1996; 58: 267-88.

29 Bien J, Taylor J, Tibshirani R. A lasso for hierarchical interactions. *Ann Statist* 2013; 41: 1111-41.

30 Rubin DB. Multiple imputation after 18+ years. *J Am Stat Assoc* 1996; 91: 473-89.

31 Sattar A, Weissfeld LA, Molenberghs G. Analysis of non-ignorable missing and left-censored longitudinal data using weighted random effects tobit model. *Stat Med* 2011; 30: 3167-80.

32 Lee M, Kong L, Weissfeld L. Multiple imputation for left-censored biomarker data based on Gibbs sampling method. *Stat Med* 2012; 31: 1838-48.

33 Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int* 2012; 2 Suppl: 1-138. ❑

Appendix 1. Secondary clinical outcome definitions and rules for the Protocolised Care for Early Septic Shock study

Rules for resolution of shock

- Shock is resolved when all four criteria for resolution of shock (below) are met for 72 hours. The following provisions also apply:
  - Because of data collection limitations, eligibility for shock resolution will be within the first 7 days of study randomisation. Patients who do not meet shock resolution criteria by Day 7 will be classified as unresolved at Day 7.
  - The assessment for the resolution of shock begins at the first time point that the patient meets all four criteria simultaneously. Assessment can also begin when data are not obtained (see below).
  - The resolution of shock is not achieved if the patient dies within the 72-hour assessment period.
  - If a patient was discharged alive from the hospital, having met criteria for resolution but before completing the entire 72-hour assessment period for resolution of shock, the criterion is met at hospital discharge.
  - Resetting the clock: if a patient, having met the criteria for shock resolution, fails to meet criteria at any time during the 72-hour assessment period, the clock (72-hour assessment) will restart once the patient meets all four criteria again.

1. Resolution of vasopressors, defined as:

- Dose of vasopressors is zero.
- No vasopressor information is entered (information is missing).
- None of the following is administered: dopamine, adrenaline, noradrenaline, vasopressin, phenylephrine.
- Dobutamine is not a vasopressor for this determination.
- Stand-alone analysis of resolution of vasopressors only (not to be used within criteria for resolution of shock):
  - Because of data collection limitations, eligibility for vasopressor resolution will be within the first 7 days of study randomisation. Patients who do not meet vasopressor resolution criteria by Day 7 will be classified as unresolved at Day 7.
  - A patient must survive for at least 24 hours after vasopressor use is not reported.
  - If the patient is discharged from the intensive care unit and survives ⩾ 24 hours, the patient is to be free from vasopressor use.

2. Systolic blood pressure (SBP) ⩾ 90 mmHg.

- Defined as: all SBP values entered are ⩾ 90 mmHg, or no SBP is entered (information is missing).

3. Serum lactate < 4 mmol/L, defined as: all recorded values < 4 mmol/L or no values recorded.If SBP is < 90, the SBP criteria will be considered met if the patient has been discharged from the ICU (with no readmissions within 48 hours) and death has not occurred.

4. Patient has not received > 4 L intravenous (IV) fluid within a 24-hour period, defined as: total IV fluids received in a 24-hour period is not > 4 L. Do not use multiplier (for colloids) and do not use any blood product volumes for these criteria. IV fluid totals are only recorded in the electronic data collection form until Hour 72 only. Therefore, after the initial 72 hours, this criterion is always presumed to be met.

Rules for duration of mechanical ventilation (MV)

- We define MV as invasive ventilation only; it does not include non-invasive techniques such as continuous positive airway pressure or bi-level positive airway pressure mask ventilation.
- Duration of MV is the number of consecutive* days that a patient requires invasive MV. *If a patient is free of MV for < 48 hours (or 2 days when hours are not recorded), these days are counted as part of the duration of MV.
- Patients known to require chronic invasive MV before hospital admission are not included in this category.
- Duration of MV is calculated for patients who start invasive MV within the first 7 days of study randomisation.
- To be considered free of MV, the patient must survive for at least 48 hours (or 2 days when hours are not recorded) after the last recorded use of MV.

Rules for renal replacement therapy (RRT)

- Types of RRT in this measurement include peritoneal RRT, continuous renal replacement therapy and haemodialysis.
- Duration of RRT is defined as the number of consecutive* days that a patient requires RRT. *If a patient is free of RRT for < 72 hours (or 3 days when hours are not recorded), these days are counted as part of the duration of RRT.
- Patients with a history of chronic dialysis prior to hospital admission are not to be included in this category.
- Duration of RRT is calculated for patients for whom RRT started within the first 7 days of study randomisation.
- Manual adjudication of RRT duration will be used for all patients who:
  - die in hospital after completing RRT therapy (ie, all patients who are free of RRT but do not survive to hospital discharge)
  - are discharged from the hospital alive within 72 hours (3 days) of last recorded RRT.

Rules for acute kidney injury (AKI) recovery

- We define AKI as any of the following (see modified risk, injury, failure; loss, end-stage renal disease [RIFLE] and Kidney Disease: Improving Global Outcomes [KDIGO][7] criteria for additional staging in Appendix B):
  - increase in serum creatinine (SCr) level by > 0.3 mg/dL within any 48-hour period
  - increase in SCr level to > 1.5 times baseline level
  - urine volume < 0.5 mL/kg/hour for any 6-hour period.
- Full AKI recovery: all AKI patients; return to < 1.5 times baseline SCr level (no RIFLE criteria met)
- Partial AKI recovery: all AKI patients; return to a lower RIFLE criterion (eg, 3 to 2 or 1, or 2 to 1)
- Full AKI recovery after RRT, meets all of the following:
  - independence from RRT for > 72 hours (or 3 days when hours are not recorded)
  - documentation of at least one estimated glomerular filtration rate (eGFR) level > 30 mL/minute/1.73 m^2 (or no less than baseline level if baseline < 30 mL/minute/1.73 m^2 and SCr no more than 1.5 times baseline level within 7 days after RRT is discontinued.
  - patient has not died within 7 days after RRT is discontinued; post-RRT eGRF level not < 15 mL/minute/1.73 m^2 within 7 days.
- Partial AKI recovery after RRT, meets all of the following:
  - independence from RRT for > 72 hours (or 3 days when hours are not recorded)
  - last recorded SCr level > 1.5 times baseline level
  - return to a lower level of RIFLE criterion (eg, 3 to 2 or 1, or 2 to 1)

Appendix 2. Staging of acute kidney injury using modified RIFLE (KDIGO)[13] recommendations

Stage	Serum creatinine criteria	Urine output criteria
1	Serum creatinine × 1.5 *or* serum creatinine rise of 0.3 mg/dL in 48 hrs	< 0.5 mL/kg/hr for 6 hrs
2	Serum creatinine × 2	< 0.5 mL/kg/hr for 12 hrs
3	Serum creatinine × 3 *or* serum creatinine ⩾ 4 mg/dL *or* had renal replacement therapy	< 0.3 mL/kg/hr for 24 hrs *or* anuria for 12 hrs

RIFLE = risk, injury, failure; loss, end-stage renal disease. KDIGO = Kidney Disease: Improving Global Outcomes.

Appendix 3. Trial sites, investigators and coordinators for the Protocolized Care for Early Septic Shock study

Advocate Christ Medical Center, Oak Lawn, Ill: E Kulstad, H Watts, K Hesse
Allegheny General Hospital, Pittsburgh, Pa: A Venkat, M Marynowski, S Livingston
Brigham and Women's Hospital, Boston, Mass: P Hou, A Massaro, S Parmar
Duke University Medical Center, Durham, NC: A Limkakeng, J Govert, W Drake
East Carolina University, Greenville, NC: T Delbridge, K Brewer, A Mainhart
George Washington University Medical Center, Washington, DC: A Dorfman, L Chawla, E Brasha-Mitchell
Intermountain Medical Center, Murray, Utah: C Grissom, T Allen, B Briggs
LAC+USC Medical Center, Los Angeles, Calif: H Belzberg, S Swadron, J Zhu
Louisiana State University Health Sciences Center, Shreveport, La: T Arnold, S Conrad, K Hutchinson
Maricopa Medical Center, Phoenix, Ariz: F LoVecchio, R Carlson, M Mulrow
Massachusetts General Hospital, Boston, Mass: M Filbin, A Waxman, B A Parry
Methodist Research Institute, Indianapolis, Ind: T Ellender, C Naum, C Lynn
North Shore University Hospital, Manhasset, NY: A Sama, T Slesinger, T Pastrana
Norwalk Hospital, Norwalk, Conn: J Fine, M Carius, C Belden
Penn State Hershey College of Medicine, Hershey, Pa: T Terndrup, M Wojnar, S Nafeei
Stanford University School of Medicine, Stanford, Calif: M Strehlow, R Pearl, V Ojha
Summa Health System, Akron, Ohio: S Wilber, B Martin, J Skruck
SUNY Downstate Medical Center, Brooklyn, NY: R Sinert, S Malhotra
Tampa General Hospital, Tampa, Fla: D Orban, R Paula, C Targal
Temple University Hospital, Philadelphia, Pa: J Ufberg, J Travaline, A Wang
UC Davis Medical Center, Sacramento, Calif: E Panacek, T Albertson, L Jones
University of Alabama at Birmingham, Birmingham, Ala: H Wang, K Lai
University of Arkansas for Medical Sciences, Little Rock, Ark: J Palmer, T Holmes, E Sides
University of Minnesota Medical Center, Fairview, Minn: N Schmiechen, C Weinert, S Nagamatsu
University of Pittsburgh Medical Center, Presbyterian Hospital, Pittsburgh, Pa: D Yealy, S Gunn, P Carey
University of Pittsburgh Medical Center, Shadyside Hospital, Pittsburgh, Pa: R Wadas, V Okwiya
University of Utah Health Sciences Center, Salt Lake City, Utah: E Kimball, E Harris, R Preston Vanderbilt
University Medical Center, Nashville, Tenn: W Self, D Dubinski
Washington Hospital Center, Washington, DC: M Goyal, C Phillips, R Migues

The Protocolised Management in Sepsis (ProMISe) trial statistical analysis plan

G Sarah Power, David A Harrison, Paul R Mouncey, Tiffany M Osborn, Sheila E Harvey and Kathryn M Rowan

ABSTRACT

Background: The Protocolised Management in Sepsis (ProMISe) trial is an open, multicentre, randomised controlled trial (RCT) of the clinical effectiveness and cost-effectiveness of early, goal-directed, protocolised resuscitation compared with usual resuscitation for patients presenting to emergency departments (EDs) in the United Kingdom with early signs of severe sepsis or septic shock. The rationale for the ProMISe trial derives from a single-centre United States RCT that reported a reduction in hospital mortality from 46.5% to 30.5%.

Objective: To describe the proposed statistical analyses for the evaluation of clinical effectiveness for the ProMISe trial. It is important to complete this plan before inspecting the data, and before completion of two related international studies, so that post-hoc, data-derived decisions are avoided.

Methods: The primary and secondary outcomes were defined precisely, and the approach to safety monitoring and data collection summarised, with a description of the planned statistical analyses including prespecified subgroup and secondary analyses.

Results: The primary outcome is all-cause mortality at 90 days. The primary analysis will be reported as a relative risk and absolute risk reduction and tested with the Fisher exact test. Prespecified subgroup analyses will be based on age, baseline Medical Emergency Department Sepsis score, baseline Sequential Organ Failure Assessment score, and time from ED presentation to randomisation. Secondary analyses include adjustment for baseline covariates, estimation of learning curve effects and adjustment for non-compliance.

Conclusion: In keeping with best practice, we have developed a statistical analysis plan for the ProMISe trial and place it in the public domain before inspecting data from the trial.

Crit Care Resusc 2013; 15: 311–317

The Protocolised Management in Sepsis (ProMISe) trial is an open, multicentre, randomised controlled trial (RCT) evaluating the clinical effectiveness and cost-effectiveness of early, goal-directed, protocolised resuscitation (EGDPR) for early signs of septic shock in the United Kingdom National Health Service (NHS). The rationale for the ProMISe trial derives from an RCT in a single United States hospital by Rivers and colleagues,[1] which compared 6 hours' of EGDPR with usual resuscitation in patients presenting to the emergency department (ED) with early signs of septic shock. Protocolised resuscitation significantly reduced hospital mortality (from 46.5% to 30.5%). We describe our proposed statistical analysis plan for the evaluation of clinical effectiveness in the ProMISe trial. It is important to complete this plan before inspecting the data, and before completion of two related international studies, so that post-hoc, data-derived decisions are avoided.[2]

Trial design

Aim

Our aim is to evaluate the clinical effectiveness and cost-effectiveness of EGDPR compared with usual resuscitation for patients presenting with early signs of severe sepsis or septic shock.

Trial sites and patients

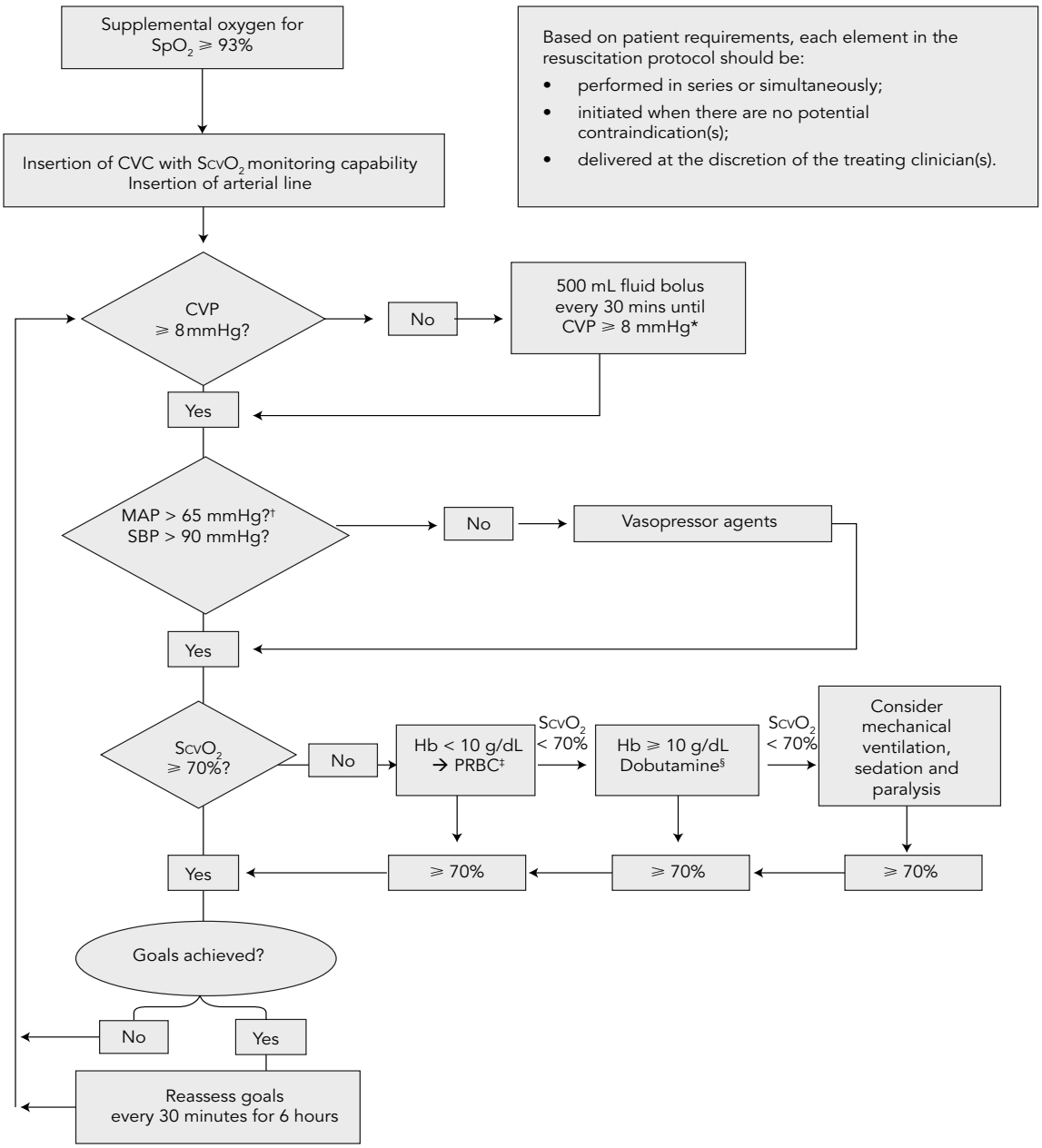
UK NHS hospitals are eligible to participate, and our target is to recruit a minimum of 48 sites. Patients who present at an ED with early signs of severe sepsis or septic shock and meet all inclusion criteria and no exclusion criteria are recruited to the trial.

Inclusion and exclusion criteria

The ProMISe trial aims to recruit patients as soon as possible after ED presentation. All inclusion criteria must be met within the ED and within 6 hours of ED presentation. Consent procedures and randomisation must occur within 2 hours of meeting the inclusion criteria. The inclusion criteria are:

- refractory hypotension or hypoperfusion:
  - refractory hypotension confirmed by the presence of a systolic blood pressure (SBP) < 90 mmHg or a mean arterial pressure (MAP) < 65 mmHg, despite a minimum intravenous (IV) fluid challenge of 1 L fixed bolus within a 60-minute period (including IV fluids administered by prehospital personnel)
  - hypoperfusion confirmed by a blood lactate concentration ⩾ 4 mmol/L;

Figure 1. Early, goal-directed resuscitation protocol



SpO_2 = oxygen saturation measured by pulse oximetry. CVC = central venous catheter. $ScvO_2$ = central venous oxygen saturation. CVP = central venous pressure. MAP = mean arterial pressure. SBP = systolic blood pressure. Hb = haemoglobin. PRBC = packed red blood cells. * Crystalloid or colloid equivalent as standard practice. † If MAP > 90 mmHg, consider vasodilator. ‡ Hb after intravenous fluid administration. § 2.5 μg/kg/min over 30 minutes initially, then increased by 2.5 μg/kg/min every 30 minutes; maximum dose 20 μg/kg/min: reduce or discontinue if concerned about drug-induced tachycardia.

- known or presumed infection; and
- two or more systemic inflammatory response syndrome (SIRS) criteria.[3]

The first dose of IV antimicrobial therapy must be initiated before randomisation. Exclusion criteria are detailed in the ProMISe trial protocol.[4]

Randomisation and treatment allocation

Eligible patients are allocated 1:1 to one of two treatment groups, by randomised permuted blocks (with variable block lengths) stratified by recruiting site, via a dedicated 24 hour, 7 days per week telephone randomisation service.

Intervention

Patients randomised to EGDPR will be treated according to the early, goal-directed resuscitation protocol (Figure 1).

Outcomes

Primary outcome

The primary outcome for the clinical evaluation is all-cause mortality at 90 days.

Secondary outcomes

The secondary outcomes for the clinical evaluation are:

- Sequential Organ Failure Assessment (SOFA) score[5] at 6 hours and 72 hours after randomisation (adjusted for baseline value)
- receipt of advanced cardiovascular, advanced respiratory and renal support (as defined by the UK Department of Health Critical Care Minimum Dataset[6])
- days alive and days free from advanced cardiovascular, advanced respiratory and renal support
- lengths of stay:
  - length of stay (LOS) in the ED, defined as the duration in hours from randomisation to the first change in location of care or death in the ED
  - LOS in critical care, defined as the sum over all admissions to critical care of the duration in days from critical care admission to discharge or death in critical care
  - LOS in an "acute hospital", defined as the duration in days from randomisation to acute hospital discharge or death in acute hospital (we define "acute hospital" as a hospital providing a range of services to diagnose, treat and care for seriously ill or injured patients; some acute hospitals provide only specialist services and others provide general services)
- duration of survival
- mortality at 28 days after randomisation, at discharge from acute hospital and at 1 year after randomisation.

Safety monitoring

Patients are monitored for adverse events within 30 days after randomisation, by the principal investigator and authorised site staff. Severity of adverse events is graded using standard definitions.[7] Any serious adverse event should be reported to the Intensive Care National Audit and Research Centre (ICNARC) Clinical Trials Unit (CTU) within 24 hours, regardless of whether it is related to participation in the trial.

Data collection and follow-up

Sites are responsible for collecting data from ED presentation to acute hospital discharge. All patients surviving to discharge from acute hospital are checked against death registrations on the NHS Health and Social Care Information Centre Data Linkage and Extract Service (DLES) for subsequent reporting of mortality at 90 days and 1 year.

In addition, as part of the integrated economic evaluation, patients recorded on the DLES as being alive at 90 days and at 1 year are sent postal questionnaires by the ICNARC CTU to record their health-related quality of life, subsequent hospital admissions and use of personal health services. Non-responders are followed up with a further postal questionnaire and then by telephone.

Sample size

Estimates for baseline mortality for the usual resuscitation group were based on the ICNARC Case Mix Programme Database. Acute hospital mortality for patients who met criteria similar[4] to the inclusion criteria was 35%. To allow for additional deaths after discharge from hospital and before Day 90, sample size calculations were based on an anticipated 90-day mortality of 40% in the usual resuscitation group.

To achieve 80% power to detect a reduction in 90-day mortality from 40% to 32% associated with EGDPR compared with usual resuscitation ($P < 0.05$, two-sided) requires a sample size of 589 patients per treatment group (1178 in total). Allowing for 6% of patients refusing consent to follow-up (in the PAC-Man trial, 2% of patients refused consent after randomisation[8]) or being lost to follow-up before 90 days, our aim is to recruit 630 patients per group (1260 in total). This sample size provides > 99% power to detect an absolute risk reduction of the magnitude observed in the trial of Rivers and colleagues (16%).[1]

Interim analysis

Unblinded comparative data on recruitment, withdrawal, compliance with the trial protocol and serious adverse events are regularly reviewed by an independent data monitoring and ethics committee (DMEC), chaired by an experienced trialist.

Without specific analysis of the primary outcome, the DMEC reviewed data from the first 50 trial participants and continue to review data at least 6 monthly to assess potential safety issues and to review compliance with the study protocol. A single, planned formal interim analysis was performed once 90-day outcome data from the first 500 patients enrolled were available. A Haybittle–Peto stopping rule ($P < 0.001$) was used to guide recommendations for early termination due to harm.

Statistical analysis

Analysis principles

All analyses will be based on the intention-to-treat principle. Patients will be analysed according to the treatment group they were randomised to, irrespective of whether the

allocated treatment was received (ie, regardless of whether they have or have not complied with the early, goal-directed resuscitation protocol).

All tests will be two-sided with significance levels set at $P < 0.05$ and with no adjustment for multiplicity. All a-priori subgroup analyses will be carried out irrespective of whether there is strong evidence of a treatment effect associated with the primary outcome.

As missing data are anticipated to be minimal, a sensitivity approach will be taken when the primary outcome is missing. The primary analysis will be repeated once, assuming that all patients allocated to EGDPR with missing primary outcome survived, and all patients allocated to usual resuscitation with missing primary outcome did not survive. The analysis will then be repeated again with the opposite assumptions. This will give the absolute range of how much the results could change if the primary outcome were complete. In adjusted analyses, missing baseline data will be handled by multiple imputation.

Trial profile

The flow of patients through the trial will be displayed in a modified Consolidated Standards of Reporting Trials (CONSORT) diagram.[9] The number of screened patients who met the trial inclusion criteria will be reported. The number of these patients who were included in the trial will be reported as well as the reasons for exclusion for those who were not included.

Baseline characteristics

Baseline demographic and clinical data will be presented by treatment group but not subjected to statistical testing. Discrete variables will be summarised as numbers and percentages, which will be calculated according to the number for whom data are available; where values are missing, the denominator will be stated in the table. Continuous variables will be summarised by standard measures of central tendency and dispersion, either mean and standard deviation and/or median and interquartile range (IQR) as specified below:

- Inclusion criteria:
  - hypotension, *n* (%)
  - SBP or MAP value at which criteria for hypotension were met, mean (SD)
  - hypoperfusion, *n* (%)
  - lactate value at which criteria for hypoperfusion were met, mean (SD)
- Age, mean (SD) and median (IQR)
- Sex, *n* (%)
- Severe comorbidity (as defined by Acute Physiology and Chronic Health Evaluation [APACHE] II past medical history [PMH] definitions[10]), *n* (%):
  - severe liver condition present in PMH
  - severe renal condition present in PMH
  - severe respiratory condition present in PMH
  - severe cardiovascular condition present in PMH
  - immunocompromised in PMH
- Prerandomisation treatment, *n* received (%) and median volume (IQR) of:
  - IV fluids (total before admission to hospital and total from ED presentation to randomisation)
  - blood products (total from ED presentation to randomisation)
- Acute severity of illness:
  - SOFA score,[5] mean (SD) and median (IQR)
  - individual SOFA score components, median (IQR)
  - Mortality in Emergency Department Sepsis (MEDS) score,[11] mean (SD) and median (IQR)
  - APACHE II score,[10] mean (SD) and median (IQR)
- Time from ED presentation to randomisation, mean (SD) and median (IQR)
- Patient likely to be admitted directly to critical care from ED if not enrolled into the ProMISe trial, *n* (%)
- Infection, *n* (%):
  - site
  - organism
  - antimicrobial change since ED presentation.

Clinical management

Clinical management of patients will be presented by treatment group but not subjected to statistical testing. As with baseline characteristics, discrete variables will be summarised as numbers and percentages. Percentages will be calculated according to the number of patients for whom data are available; where values are missing, the denominator will be stated in the table. Continuous variables will be summarised by mean (SD) and/or median (IQR).

Clinical management data will be summarised as the total over the 6-hour intervention period (T_0–T_6); the total from the end of the 6-hour intervention period to the end of the first 24 hours (T_6–T_{24}); the total from the end of the first 24 hours to the end of the first 72 hours (T_{24}–T_{72}) and from randomisation to the end of the first 72 hours (T_0–T_{72}). Fluids, vasoactive agents and dobutamine will also be reported hourly for the duration of the 6-hour intervention period. Line insertion details will be included in the T_0–T_6 table:

- Line insertion, time from randomisation to insertion: *n* (%), mean (SD) and median (IQR)
  - arterial line
  - central venous catheter (CVC) line
- Interventions received: *n* (%)
  - supplemental oxygen
  - mechanical ventilation

- Fluids: number receiving, *n* (%); and volume received: median (IQR)
  - IV colloid
  - IV crystalloid
  - packed red blood cells (PRBC)
  - platelets
  - fresh frozen plasma
- Drugs: *n* (%) received
  - vasoactive agents
  - dobutamine
  - sedatives

Compliance with allocated treatment

Non-compliance with the allocated treatment will be reported as:

- Insertion of a CVC with superior vena caval oxygen saturation ($Scvo_2$) monitoring capability to a patient allocated to usual resuscitation
- Failure to insert a CVC with $Scvo_2$ monitoring capability to a patient allocated to EGDPR
- Failure to act on a goal in the early, goal-directed algorithm for a patient allocated to EGDPR, defined as:
  - no fluid resuscitation when central venous pressure (CVP) is < 8 mmHg
  - no administration of vasopressors when MAP is < 65 mmHg or SBP is < 90 mmHg and the CVP goal was met
  - no administration of PRBC when $Scvo_2$ is < 70% and haemoglobin concentration is < 10 g/dL and the prior two goals were met, or no dobutamine administered when $Scvo_2$ is < 70% and haemoglobin concentration is ⩾ 10 g/dL and the CVP and MAP/SBP goals were met
- Early (< 6 hours) termination of EGDPR in a patient allocated to EGDPR (other than due to death).

Description of analysis

Primary outcome

The number and percentage of deaths by 90 days after randomisation will be reported for each treatment group. The primary-effect estimate will be the relative risk of 90-day mortality, reported with a 95% CI. The absolute risk reduction and 95% CI will also be reported. Deaths by 90 days after randomisation will be compared between the treatment groups, unadjusted, using the Fisher exact test.

A secondary analysis of the primary outcome, adjusted for baseline variables, will also be conducted, using multilevel logistic regression. Baseline variables adjusted for in the multilevel logistic regression model will be the components of the MEDS score (age, metastatic cancer, nursing home residence, altered mental status, septic shock, respiratory difficulty, low platelet count and low neutrophil count) and a site-level random effect. Baseline variables were selected for inclusion in the adjusted analysis according to anticipated relationship with outcome. The results of the multilevel logistic regression model will be reported as an adjusted odds ratio with 95% CI. The unadjusted odds ratio will be presented for comparison.

Secondary outcomes

The mean SOFA score at 6 hours and 72 hours after randomisation, adjusted for baseline SOFA score, will be reported for each treatment group. Differences in the mean SOFA score at 6 hours and 72 hours after randomisation will be compared using analysis of covariance (ANCOVA). The mean score for each of the six SOFA components (respiratory, neurological, cardiovascular, coagulation, hepatic and renal) will be reported but not subjected to statistical testing.

The number and percentage of patients receiving advanced cardiovascular, advanced respiratory and renal support will be reported for each treatment group. Differences in receipt of advanced cardiovascular, advanced respiratory and renal support will be compared, unadjusted, using the Fisher exact test.

The mean and SD of number of days alive and free from advanced cardiovascular, advanced respiratory and renal support, up to 28 days, within each treatment group will be reported. Differences between the treatment groups will be tested using the *t* test, using bootstrapping to account for anticipated non-normality in the distributions.[12]

The median and IQR of the LOS in the ED, in critical care and in acute hospital will be reported for each treatment group. Differences in LOS between the treatment groups will be tested using the Wilcoxon rank-sum test, stratified by survival at end of ED stay, critical care discharge and acute hospital discharge, respectively.

Kaplan–Meier curves by treatment group will be plotted up to 90 days and 1 year after randomisation and compared using the log-rank test. An adjusted comparison will be performed using a Cox proportional hazards model adjusted for the same baseline variables as the primary outcome. The number and percentage of deaths at acute hospital discharge and by 28 days, 90 days and 1 year after randomisation will be reported for the treatment groups. Differences in mortality will be compared, unadjusted, using the Fisher exact test and adjusted using multilevel logistic regression; ie, adjusted for the same baseline variables as the primary outcome.

Serious adverse events

The number and percentage of serious adverse events occurring between randomisation and 30 days will be reported for each treatment group. Serious adverse events will be compared between treatment groups using the Fisher exact test.

Subgroup analysis

These analyses will test for an interaction between the subgroup categories and the treatment group in a multilevel logistic regression model, adjusted for the same baseline variables as the analysis of the primary outcome. The primary outcome (90-day mortality) will be analysed by degree of protocolised care for patients randomised to usual resuscitation (completeness of hourly measurements with reference to known sepsis resuscitation and management bundles[13-15]), age (quartiles), MEDS score (quartiles), SOFA score (quartiles) and time from ED presentation to randomisation (quartiles).

Learning curve analysis

The delivery of a complex intervention may improve with time as those delivering the intervention gain experience and familiarity. Typically, such improvements will be more rapid at first and then tail off over time to reach a steady state; termed a "learning curve". Modelling the learning curve enables estimation of the treatment effect for an experienced team. A site-level learning curve for patients randomly allocated to EGDPR will be modelled by repeating the multilevel logistic regression on the primary outcome and including a power curve (aX^{-b}) for the sequential observation number (X) for each EGDPR patient within each site.[16]

Compliance-adjusted analysis

While the intention-to-treat analysis gives the best estimate of the clinical effectiveness of EGDPR as delivered, it is also of interest to estimate what the efficacy of this intervention may be if all elements of the protocol were delivered as intended. In an RCT, the allocated treatment can be used as an "instrumental variable", ie, a variable associated with receipt of the intervention and only associated with the outcome through its association with the intervention.[17] This relationship enables us to estimate what the treatment effect would be for patients who are compliant with all elements of the protocol. The primary analysis will be repeated, adjusting for compliance using a structural mean model with an instrumental variable of allocated treatment, assuming a linear relationship between the degree of compliance (proportion of the 6 hours that the patient is compliant with the early, goal-directed resuscitation protocol) and treatment effect.[18,19]

Figures and tables

Planned figures include:

- a CONSORT-style diagram illustrating the flow of patients through the trial
- a line graph showing the mean cumulative IV fluids received by treatment group
- a Kaplan–Meier curve showing survival to 90 days after randomisation by treatment group.

Planned tables include:

- baseline characteristics by treatment group
- clinical management by treatment group
- non-compliance with allocated treatment by treatment group
- primary and secondary outcomes by treatment group
- serious adverse events until 30 days after randomisation by treatment group
- results of subgroup and secondary analyses.

Funding, registration and ethics approval

The ProMISe trial is funded by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (07/37/47) and is registered on the NIHR Clinical Research Network (CRN) portfolio (9820) and the International Standard Randomised Controlled Trials Number register (ISRCTN36307479). The trial is endorsed by the NIHR CRN Injuries and Emergencies Specialty Group and the Critical Care Specialty Group, sponsored by the ICNARC and coordinated by the ICNARC CTU (UK Clinical Research Collaboration CTU registration 42). Approval for the trial was received from the North West London Research Ethics Committee (approval 10/H0722/42). The trial results will be published in full in *Health Technology Assessment*.

Competing interests

None declared. The views and opinions expressed are ours and do not necessarily reflect those of the Health Technology Assessment Programme, NIHR, NHS or the Department of Health.

Author details

G Sarah Power, Statistician[1]
David A Harrison, Senior Statistician[1]
Paul R Mouncey, Trial Manager[1]
Tiffany M Osborn, Trial Clinician,[1] and Associate Professor[2]
Sheila E Harvey, Manager and Senior Research Fellow[1]
Kathryn M Rowan, Chief Investigator and Director[1]

1 Clinical Trials Unit, Intensive Care National Audit and Research Centre, London, United Kingdom.

2 Department of Surgery and Division of Emergency Medicine, Washington University and Barnes-Jewish Hospital, St Louis, Mich, United States.

Correspondence: promise@icnarc.org

References

1 Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345: 1368-77.

2 The ProCESS/ARISE/ProMISe Methodology Writing Committee. Harmonizing international trials of early goal-directed resuscitation for severe sepsis and septic shock: methodology of ProCESS, ARISE, and ProMISe. *Intensive Care Med* 2013; 39: 1760-75.

3 Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest* 1992; 101: 1644-55.

4 Intensive Care National Audit & Research Centre. Protocolised Management In Sepsis (ProMISe) trial protocol. http://www.hta.ac.uk/protocols/200700370047.pdf (accessed Oct 2013).

5 Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; 22: 707-10.

6 Information Standards Board for Health and Social Care. Critical Care Minimum Dataset Full Specification. http://www.isb.nhs.uk/documents/isb-0153/amd-81-2010/0153812010spec.pdf (accessed Sep 2013).

7 US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf (accessed Oct 2013).

8 Harvey S, Harrison D, Singer M, et al. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. *Lancet* 2005; 366: 472-7.

9 Boutron I, Moher D, Altman DG, et al. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. *Ann Intern Med* 2008; 148: 295-309.

10 Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; 13: 818-29.

11 Shapiro NI, Wolfe RE, Moore RB, et al. Mortality in Emergency Department Sepsis (MEDS) score: a prospectively derived and validated clinical prediction rule. *Crit Care Med* 2003; 31: 670-5.

12 Thompson SG, Barber JA. How should cost data in pragmatic randomised trials be analysed? *BMJ* 2000; 320: 1197-200.

13 Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008; 36: 296-327.

14 Levy MM, Pronovost PJ, Dellinger RP, et al. Sepsis change bundles: converting guidelines into meaningful change in behavior and clinical outcome. *Crit Care Med* 2004; 32 (11 Suppl): S595-7.

15 Survive Sepsis. http://survivesepsis.org (accessed Sep 2013).

16 Ramsey CR, Grant AM, Wallace SA, et al. Statistical assessment of the learning curves of health technologies. *Health Technol Assess* 2001; 5: 1-79.

17 Greenland S. An introduction to instrumental variables for epidemiologists. *Int J Epidemiol* 2000; 29: 722-9.

18 White IR. Uses and limitations of randomization-based efficacy estimators. *Stat Methods Med Res* 2005; 14: 327-47.

19 Goetghebeur E, Lapp K. The effect of treatment compliance in a placebo-controlled trial: regression with unpaired data. *J R Stat Soc Ser C Appl Stat* 1997; 46: 351-64. ❑

Appendix. The Protocolised Management in Sepsis trial group

Management group

Kathy Rowan (Chief Investigator), Derek Bell, Julian Bion, Tim Coats, David Harrison, Sheila Harvey, Rahi Jahan, Paul Mouncey, Tiffany Osborne, Sarah Power, Mervyn Singer, Jermaine Tan, Duncan Young

Steering committee

Steve Goodacre (Chair), Julian Bion, Caroline Bowers, Phil Crow, Rupert Pearse, Kathy Rowan, David Yates

Data monitoring and ethics committee

Jon Nichol (Chair), Alasdair Gray, Tim Walsh

Investigators (all hospitals are in United Kingdom)

Addenbrooke's Hospital, Cambridge: V Ahmed, A Boyle, A Scott-Donkin. *Arrowe Park Hospital, Wirral:* H Black, D Jenkins, C Smalley. *Barnsley Hospital, Barnsley:* J Humphrey, J Griffiths, S A Pearson. *Bedford Hospital, Bedford:* D Subramanyam, D Niblett. *Birmingham Heartlands Hospital, Birmingham:* F Gao-Smith, T Melody, K Couper. *Bristol Royal Infirmary, Bristol:* J Benger, J Bewley, L Flintoff. *Blackpool Victoria Hospital, Blackpool:* R Nichani, E Brennan, H Kenworthy. *Broomfield Hospital, Chelmsford:* D Arawwawala, C Mitchell-Inwang, F McNeela. *Chelsea and Westminster Hospital, London:* D Bell, C Emerson, T Weldring. *Derriford Hospital, Plymouth:* P MacNaughton, A Kehoe, H McMillan. *Dorset County Hospital, Dorchester:* T Doyle, S Moreton. *Frenchay Hospital, Bristol:* J Kendall, E Oldenbourg, A Gilbertson. *Hinchingbrooke Hospital, Huntingdon:* C Borland, S Boys. *Hull Royal Infirmary, Hull:* I Smith, N Smith, P Williams. *John Radcliffe Hospital, Oxford:* D Young, R Farras Araya. *Kettering General Hospital, Kettering:* P Watt, N Spencer, P Raymode. *King's College Hospital, London:* P Hopkins, G Parsons, S Helyar. *Leicester Royal Infirmary, Leicester:* J Thompson, T Coats, D Hales. *Leighton Hospital, Crewe:* S Gilby, P Chilton, R Miller. *Manchester Royal Infirmary, Manchester:* J Butler, B Foex, A Royle. *Medway Maritime Hospital, Gillingham:* G Sanders, P Hayden, C.Plowright. *Musgrove Park Hospital, Taunton:* R Innes, D Bayford, P Richards. *New Cross Hospital, Wolverhampton:* S Gopal, N Poonit, L Phiri. *Newham University Hospital, London:* J Napier, E Warrington. *North Devon District Hospital, Barnstaple:* L Kevern, J Hunt. *North Tyneside General Hospital, North Shields:* E Sykes, J Dickson, S Duffy. *Peterborough City Hospital, Peterborough:* C Carlie, T Croft. *Poole Hospital, Poole:* N Jenkins, H Reschreiter, J Camsooksai. *Queen Elizabeth Hospital Birmingham, Birmingham:* C Snelson, J Bion, F Keats. *Queen Elizabeth Hospital, Gateshead:* V Linnett, S Christian, J Ritzema. *Queen's Medical Centre, Nottingham:* A Jabbar, P Miller, R Ravenscroft. *Royal Berkshire Hospital, Reading:* L Keating, D Mossop, E Bowley. *Royal Bournemouth Hospital, Bournemouth:* D Martin, P Swallow, E Vickers. *Royal Lancaster Infirmary, Lancaster:* S McBride, M Entwistle, J Craig. *Royal Preston Hospital, Preston:* T Owen, J Baldwin, S McMullen. *Royal Surrey County Hospital, Guildford:* M Zuleika, P Carvalho. *Royal Sussex County Hospital, Brighton:* D Agranoff, F Ingoldby. *Royal Victoria Infirmary, Newcastle upon Tyne:* I Clement, C Higham. *Salford Royal Hospital, Salford:* B Martin, C Gavin, K Clayton. *South Tyneside District Hospital, South Shields:* C Frey, A Kumar, D Miller. *Southend University Hospital, Southend:* K Iftikhar, D Higgins, V Katsande. *Stafford Hospital, Stafford:* M Chikungwa, T Bentley, C Jackson. *The Ipswich Hospital, Ipswich:* R Howard-Griffin, S Bell, H Blaylock. *The James Cook University Hospital, Middlesbrough:* I Gonzalez, P Dissmann, K Colling. *The Queen Elizabeth Hospital, King's Lynn:* J Carter, P Moondi, K Wong. *The Royal Blackburn Hospital, Blackburn:* S Hartley, J Hinchcliffe, L Phoenix. *The Royal London Hospital, London:* T Harris, J Pott. *Torbay Hospital, Torquay:* M Mercer, P Mercer. *University College Hospital, London:* D Brealey, M Singer, J H Ryu. *University Hospital of North Staffordshire, Stoke-on-Trent:* M Poulson, S Plant, I Massey. *Wansbeck General Hospital, Ashington:* E Sykes, J Dickson, S Duffy. *Whipps Cross University Hospital, London:* T Harris, I Skene. *Whiston Hospital, Prescot:* P Nee, S Dowling, A McCairn. *Worthing Hospital, Worthing:* R Duckitt, R Venn, J Margalef. *York Hospital, York:* J Redman, D Yates, M Makiela. ❑

Intensive care unit occupancy after introduction of the emergency department 4-hour discharge rule at a tertiary referral hospital in Western Australia

Peter V van Heerden, John A Blott, Mary Pinder, Peter D Cameron, Brigit L Roberts, Anne Brinkworth, Ilana Stav and Sigal Sviri

ABSTRACT

Background: The 4-hour rule has been introduced in Western Australia, requiring that emergency department (ED) patients be admitted to hospital or discharged from the ED within 4 hours of presentation. We hypothesised that this rule might have been associated with changes in medical emergency team (MET) calls and intensive care unit exit bed block.

Methods: Hospital databases were examined to determine compliance with the 4-hour rule, the effect on ICU exit bed block, and the number of MET calls, in 2008 (before introduction of the 4-hour rule) and 2011 (after introduction of the 4-hour rule). We also measured background ICU and hospital activity in 2008 and 2011.

Results: Monthly compliance with the 4-hour rule ranged from 35%–46% in 2008 to 64%–75% in 2011 ($P < 0.0001$). There was a marked increase in bed block-days for patients in the ICU between 2008 (before introduction of the 4-hour rule) and 2011 (after introduction of the 4-hour rule) ($P = 0.05$). The increase in ICU bed block-days could not be explained by a difference in ICU occupancy, as there was a reduction in ICU bed-days between 2008 and 2011 ($P = 0.014$). There was a reduction in hospital mortality rate between 2008 and 2011 ($P < 0.001$). There was no significant increase in the number of MET calls from 2008 to 2011 ($P = 0.221$). Hospital activity (separations) increased from 2008 to 2011 ($P < 0.0001$).

Discussion: The introduction of the 4-hour rule was associated with increased exit block from the ICU, but not with increased MET calls to attend to unstable or deteriorating ward patients. Introduction of the 4-hour rule was associated with a small reduction in hospital mortality.

Crit Care Resusc 2013; 15: 318–321

A recent study reported on some benefits of the introduction of the 4-hour rule in metropolitan hospitals in Western Australia.[1] This rule means that patients in the emergency department (ED) must be admitted to hospital or discharged from the ED within 4 hours of presentation. Geelhoed and de Klerk showed less ED crowding and a reduction in overall hospital mortality after introduction of the 4-hour rule.[1] The 4-hour rule was implemented by the WA government in April 2009 to reduce ED overcrowding.[1,2]

Implementation of this policy means that eventually 98% of patients in the ED would be discharged home or admitted to a ward within 4 hours of presentation to the ED. So far, the implementation of the 4-hour rule has been very successful by these measures in WA metropolitan hospitals. Compliance has improved, ED overcrowding has been reduced and overall hospital mortality has reportedly been reduced.[1]

In a hospital system which runs at high capacity (over 85% occupancy), the changing of a policy in one area may affect other acute care areas. In particular, prioritising movement of patients from the ED into ward beds (for patients admitted to hospital) might limit or impede the discharge of patients from the intensive care unit to the wards. Also, early transfer of patients from the ED to general wards may result in placement of acutely unwell patients to less well staffed areas and put them at risk. This could increase the need for medical emergency team (MET) interventions,[3-8] even when new observation charts have been implemented or early warning systems are in place in the ED, or ICU liaison services are provided.[9-11]

To assess whether the introduction of the 4-hour rule was associated with changes in exit block from the ICU, overall hospital mortality and the number of MET calls, we conducted a retrospective observational study using hospital-wide databases.

Methods

Data were collected from existing hospital databases in a tertiary referral hospital in Perth, WA. Ethics committee approval was waived due to the use of de-identified patient data only. The study was registered as an institutional quality improvement initiative. The study hospital is a metropolitan hospital of about 600 beds and provides all services except paediatrics, obstetrics and burns.

Exit block from the ICU was defined as bed-days of patients in the ICU who were deemed ready (by the attending intensivist) for discharge from the ICU, but for whom there was no ward bed available. This was decided and documented at each morning ICU handover round. Data were collected prospectively each day by the consult-

Figure 1. Total patients admitted to a ward or discharged from the emergency department (ED), and percentages admitted to a ward or discharged from the ED within 4 hours, 2008 and 2011

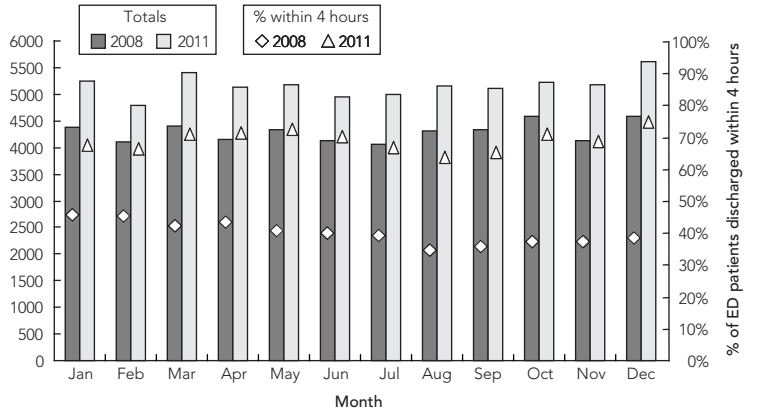


Figure 2. Intensive care unit bed block-days, 2008 and 2011

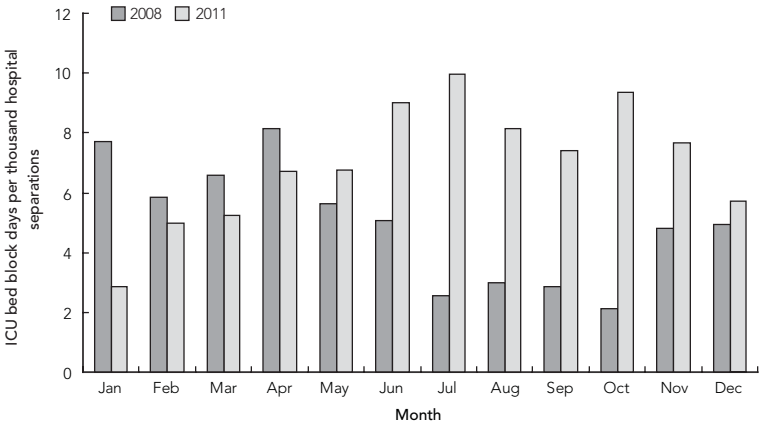
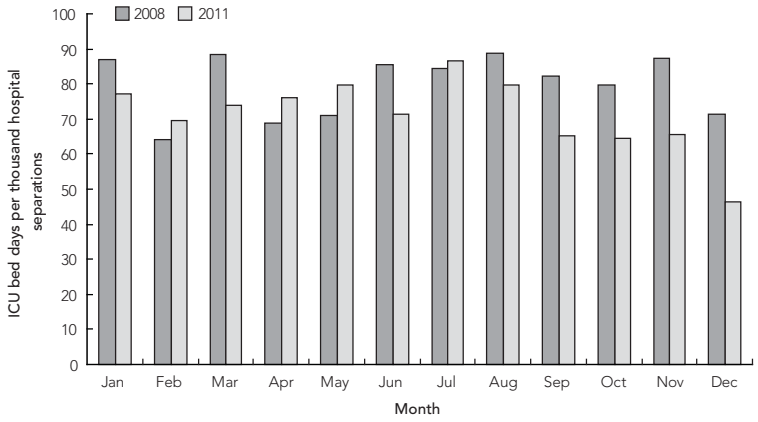


Figure 3. Intensive care unit bed-days, 2008 and 2011



ant on duty, verified by the ICU data manager and entered into the unit database. The ICU has 23 beds and handles about 1400 admissions per year.

Overall hospital mortality rate was defined as the number of deaths per year in 2008 (before implementation of the 4-hour rule) and 2011 (after implementation of the 4-hour rule), divided by total inpatient separations during the same period. The number of MET calls was monitored monthly during the same two study periods (calls per month in 2008 and 2011) as a surrogate marker for urgent attendances to ward patients before and after introduction of the 4-hour rule.

The data collected were data routinely recorded in standard electronic hospital databases. Comparisons were made using *t* tests and χ^2 tests as appropriate.

The 2 years chosen for comparison were 2008, the year immediately before the introduction of the 4-hour rule, and 2011, the most recent year for which hospital data were complete.

Results

Figure 1 shows compliance with the 4-hour rule, ie, the percentage of ED patients admitted or discharged from the ED within 4 hours. The improved compliance is evident from the ranges of compliance in 2008 (35%–46%) and 2011 (64%–75%) ($P < 0.0001$).

Figure 2 shows the ICU bed block-days per 1000 hospital separations per month, in which there was a statistically significant increase between 2008 (mean, 4.94 bed block-days/month) and 2011 (mean, 6.98 bed block-days/month) ($P < 0.05$).

There was a small decrease in ICU occupancy between 2008 (mean, 79.86 ICU bed-days/month) and 2011 (mean, 77.26 ICU bed-days/month), as measured by bed-days per 1000 hospital separations (Figure 3) ($P = 0.01$). There was an increase between 2008 and 2011 in overall hospital activity (number of separations) (Figure 4), $P < 0.0001$.

Overall hospital mortality is shown in Figure 5; there was a decrease between 2008 (1.37%) and 2011 (1.19%), $P < 0.001$. Figure 6 shows annual MET calls from 1999 to 2011; there was no significant increase in calls from 2008 to 2011 ($P = 0.221$), Figure 7.

Figure 4. Hospital activity (separations), 2008 and 2011

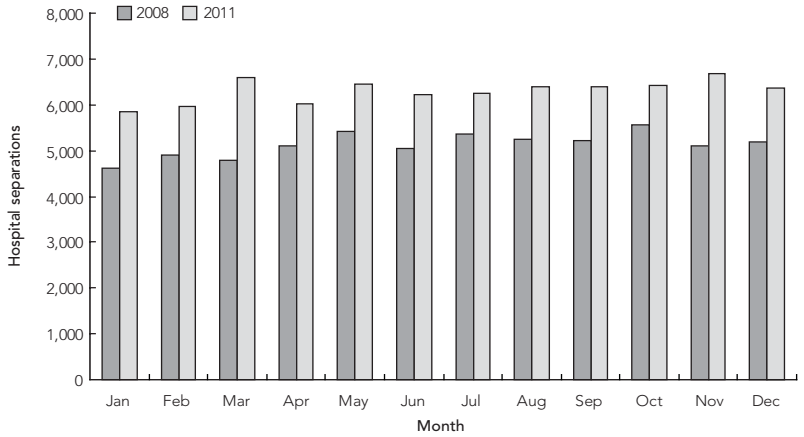


Figure 5. Hospital mortality, 2008 and 2011

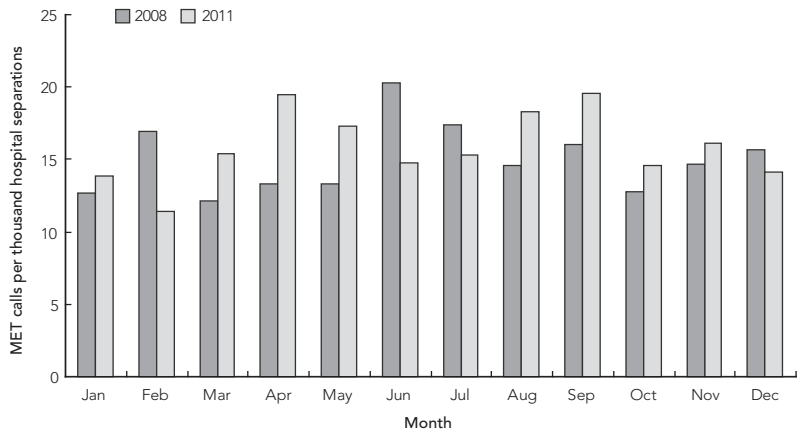
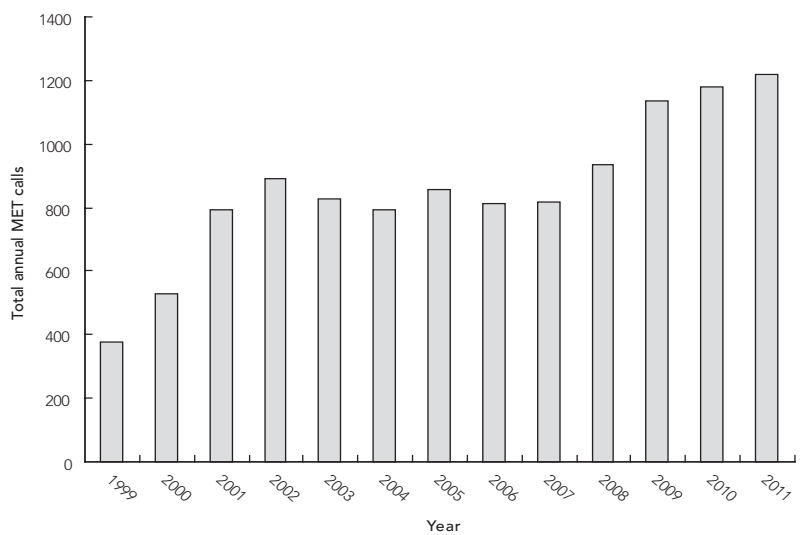


Figure 6. Medical emergency team (MET) calls, 1999–2011



Discussion

Our data show that introduction of the 4-hour rule, previously shown to reduce ED occupancy and overall hospital mortality,[1,2] was associated with increased exit block from the ICU. This is not unexpected, as the hospital we studied has a finite capacity and runs at high occupancy rates. Therefore, preferentially discharging patients from the ED to regular wards must necessarily result in strain in the system elsewhere. This is reflected in the reduced ability to discharge patients from the ICU to the general wards. The cost of caring for these dischargeable patients in the ICU should be a consideration when assessing the benefits to the institution that can be attributed to the 4-hour rule.

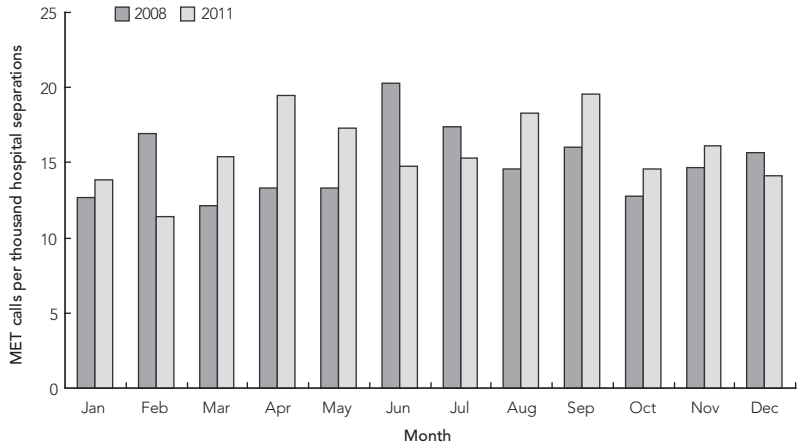
The increase in ICU exit block was not reflected by an increase in total ICU bed-days. There was a decrease in ICU activity (defined by ICU bed-days per thousand hospital separations) between the two years studied. The number of ICU refusals during the two time periods studied was not available.

It seems logical that ED patients admitted sooner to wards, and therefore separated from the greater staffing, monitoring and diagnostic capacity of the ED, may be at higher risk. However, admitting patients to the general wards more rapidly did not have an effect on the number of observed MET calls to attend unstable or deteriorating patients, nor did it increase hospital mortality.

Expeditious assessment, treatment and disposition of patients in the ED are all desirable goals. However, in a system running at high capacity, improving efficiency in one area may have the unintended consequence of affecting another. In the case of the 4-hour rule, we have shown that an increased exit block from the ICU is a possible unintended and undesirable outcome, associated with increased ICU length of stay and its potential attendant extra costs and morbidity (eg, nosocomial infections and deep vein thrombosis). Generally, ICUs are not set up for care of patients undergoing rehabilitation; there are limited bathroom facilities for ambulant patients and the units are noisy, disrupting rest and sleep.

Health care systems are complex, and system changes in one area should be carefully considered, as there may be unintended consequences in another area. Our data indicate

Figure 7. Medical emergency team (MET) calls, 2008 and 2011



that the 4-hour rule may have resulted in increased ICU exit block, but not in increased MET call activity or hospital mortality. It should be noted that there was also an increase in overall hospital activity during the same period, but all comparisons between 2008 and 2011 were corrected for hospital activity.

Of interest is the fact that as the 4-hour rule was being implemented in WA, there were already changes being made in the system in the United Kingdom, such as reducing the target (the percentage compliance with the 4-hour rule) and adding quality indicators.[12,13] There have even been calls for the abolition of the policy in the UK, on the grounds that the policy may improve patient flow through the ED, but not necessarily improve the quality of patient care.[14] Anstey and colleagues[13] state that the principal cause of ED overcrowding is the lack of available inpatient beds; this is our contention too. Pushing patients through the ED into an already crowded inpatient environment must have consequences. We have tried to assess some of these consequences (the effects on MET calls, hospital mortality and ICU exit block). While not conclusive, our results do show an associated effect on ICU exit block, with no measurable change in hospital mortality.

Study limitations include that our data were derived from existing databases, not collected in a dedicated way to test a hypothesis.

We conclude that carefully directed prospective data should be captured and analysed to measure the effect of a fundamental change such as the 4-hour rule. It may improve patient flow greatly in the ED, a worthy goal, but may also affect other acute care areas. A visible, politically advantageous improvement in one area of the health care system may be a hidden burden elsewhere.

Competing interests

None declared.

Author details

Peter V van Heerden, Intensivist[1,2,3]
John A Blott, Intensivist[2]
Mary Pinder, Intensivist[2]
Peter D Cameron, Intensivist[2]
Brigit L Roberts, Research Nurse[2]
Anne Brinkworth, Clinical Nurse Specialist[2]
Ilana Stav, Data Manager[1]
Sigal Sviri, Intensivist[1]

1 Medical Intensive Care Unit, Hadassah University Hospital, Jerusalem, Israel.
2 Department of Intensive Care, Sir Charles Gairdner Hospital, Perth, WA, Australia.
3 School of Medicine and Pharmacology, University of Western Australia, Perth, WA, Australia.

Correspondence: vernon@hadassah.org.il

References

1 Geelhoed GC, de Klerk NH. Emergency department overcrowding, mortality and the 4-hour rule in Western Australia. *Med J Aust* 2012; 196: 122-6.
2 Mountain D. Introduction of a 4-hour rule in Western Australian emergency departments. *Emerg Med Australas* 2010; 22: 374-8.
3 Flabouris A, Jeyadoss J, Field J, Soulsby T. Direct and delayed admission to an intensive care or high dependency unit following discharge from the emergency department: associated patient characteristics and hospital outcome. *Crit Care Resusc* 2012; 14: 191-7.
4 Vetro J, Natarajan DK, Mercer I, et al. Antecedents to cardiac arrest in a hospital equipped with a medical emergency team. *Crit Care Resusc* 2011; 13: 162-6.
5 Knott CI, Psirides AJ, Young PJ, Sim D. A retrospective cohort study of the effect of medicla emergency teams on documentation of advance care directives. *Crit Care Resusc* 2011; 13: 167-74.
6 Trinkle R, Flabouris A. Medical reviews before cardiac arrest, medical emergency call or unanticipated intensive care unit admission: their nature and impact on patient outcome. *Crit Care Resusc* 2011; 13: 175-80.
7 Medical Emergency Team End-of-life Care investigators. The timing of Rapid-Response Team activations: a multicentre international study. *Crit Care Resusc* 2013; 15: 15-20.
8 Morris A, Owen HM, Jones K, et al. Objective patient-related outcomes of rapid-response systems—a pilot study to demonstrate feasibility in two hospitals. *Crit Care Resusc* 2013; 15: 33-9.
9 Kansal A, Havill K. The effects of introduction of new observation charts and calling criteria on call characteristics and outcome of hospitalised patients. *Crit Care Resusc* 2012; 14: 38-43.
10 Considine J, Lucas E, Wunderlich B. The uptake of an early warning system in an Australian emergency department: a pilot study. *Crit Care Resusc* 2012; 14: 135-41.
11 Australian ICU Liaison Nurse Forum. Uptake and caseload of intensive care unit liaison nurse services in Australia. *Crit Care Resusc* 2012; 14: 221-6.
12 Maumill L, Zic M, Esson AA, et al. The National Emergency Access Target (NEAT): can quality go with timeliness? *Med J Aust* 2013; 198: 153-7.
13 Anstey MH, Gildfind SP, Litvak E. Sleep Faster! (Somebody else needs your blanket …). *Aust Health Rev* 2012; 36: 244-7.
14 Lansley A. [Letter to President of the College of Emergency Medicine.] London: Department of Health, 2010. http://www.dh.gov.uk/prod_consum_d (accessed Jul 2013). ❑

IV/Oral
ZYVOX®
(linezolid)

PBS Information: This product is not listed on the PBS.

BEFORE PRESCRIBING ZYVOX® (LINEZOLID) REVIEW FULL APPROVED PRODUCT INFORMATION AVAILABLE AT WWW.PFIZER.COM.AU OR PROVIDED BY THE REPRESENTATIVE.

Minimum Product Information ZYVOX® (linezolid 2mg/mL, 600mg, 20mg/mL) injection, tablets, granules for oral suspension. Indications: Infections due to resistant organisms, including MRSA and VRE. No clinical activity against Gram-negative pathogens. **Contraindications:** Hypersensitivity; Monoamine oxidase inhibitors; Potential interactions producing elevations of blood pressure; Potential serotonergic interactions. **Precautions:** Monitor blood in certain populations. Antibiotic associated pseudomembranous colitis. Reports of serotonin syndrome when co-administered with serotonergic agents. Symptoms of visual impairment; monitor visual function. Convulsions (rare). Safety and effectiveness following 28 days not established. Gram-negative pathogens. Caution in patients with severe renal and hepatic insufficiency. **Pregnancy**. Category B3. **Lactation**. Discontinue. **Interactions.** Tyramine; serotonergic agents; vasopressive/dopaminergic agents; rifampicin.* See full PI for details. **ADVERSE EFFECTS:** Headache, candidiasis; taste perversion; GI disturbances. Peripheral and optic neuropathy. Lactic acidosis, angioedema, rash, myelosuppression, bullous skin disorders and serotonin syndrome (very rare). Abnormal haematology and liver function tests. See full PI for details. **DOSAGE AND ADMINISTRATION:** IV (30-120 min infusion) or oral b.i.d (with or without food). **Adults and adolescents:** CAP/ nosocomial pneumonia: 600 mg IV 12 hourly or orally b.i.d for 10 to 14 days; SSTI: 400 mg to 600 mg orally b.i.d or 600 mg IV 12 hourly for 10 to 14 days; Enterococcal infections: 600 mg IV 12 hourly or orally b.i.d for 14 to 28 consecutive days. **Children:** Nosocomial pneumonia and SSTI: 10 mg/kg IV 8 hourly or orally t.d.s for 10 to 14 days. Enterococcal infections: 10 mg/kg IV 8 hourly or orally t.d.s for 14 to 28 days. **Neonates:** Refer to PI. See full PI for detailed dosing schedule. Pfizer Australia Pty Ltd, ABN 50 008 422 348, 38-42 Wharf Road, West Ryde, NSW 2114. **Pfizer Medical Information** 1800 675 229. The current product information is available at www.pfizer.com.au. *Please note change(s) in Product Information. ®Registered trademark. P2817/CMGZYV0019 12/10

*PLEASE NOTE CHANGE(S) IN PRODUCT INFORMATION.

References: 1. Wilcox M, *et al. J Antimicrob Chemother.* 2004;53:335-44. **2.** Birmingham MC, *et al. Clin Infect Dis.* 2003;36:159-68. **3.** Weigelt J, *et al. Am J Surg.* 2004;188:760-6. **4.** Wunderink RG, *et al. Clin Infect Dis.* 2012;54:621-9.

Pfizer Australia Pty Limited. ABN 50 008 422 348. 8-42 Wharf Road, West Ryde NSW 2114.
® Registered trademark. Medical Information 1800 675 229. www.pfizer.com.au PFIZYV0714 P2817 12/10

Pfizer Anti-Infectives

Near-infrared spectroscopy of the thenar eminence to estimate forearm blood flow

Nicholas CZ Woinarski, Satoshi Suzuki, Miklos Lipcsey, Natalie Lumsden, Jaye Chin-Dusting, Antoine G Schneider, Michael Bailey and Rinaldo Bellomo

ABSTRACT

Background: Near-infrared spectroscopy of the thenar eminence (NIRSth) can be used at the bedside to assess tissue oxygenation (Sto_2), the reperfusion response to ischaemia and the tissue haemoglobin index (THI). Its ability to estimate forearm blood flow (FBF) has not previously been assessed.

Objectives: We aimed to test whether short-lived venous occlusion-induced changes in NIRSth-derived THI (ΔTHI/minute) correlate with strain gauge plethysmography (SGP) measurements.

Methods: We measured FBF in nine volunteers with SGP by venous occlusion, while estimating ΔTHI. Measurements were obtained in two forearm positions (elevated and horizontal) at baseline and during induced hyperaemia.

Results: We performed 246 paired measurements at rest and after occlusion-induced hyperaemia. At rest, mean SGP-estimated FBF was 3.5–3.6 mL/dL/minute at baseline, compared with 12.9–13.6 mL/dL/minute during hyperaemia. At rest, ΔTHI was 6.1–8.2/minute, compared with 29.7–32.5/minute during hyperaemia. ΔTHI was a significant predictor of SGP FBF ($P < 0.01$), with stronger correlation during hyperaemia ($P < 0.01$). An equation was developed to convert ΔTHI/minute into FBF at mL/dL/minute (FBF = 0.362 × ΔTHI/minute + 0.864).

Conclusions: NIRSth can be used to estimate FBF. Given its portability and its ability to also measure Sto_2 and vascular reactivity, NIRSth can assist in providing a comprehensive bedside assessment of the forearm circulation in critically ill patients.

Crit Care Resusc 2013; 15: 323–326

Near-infrared spectroscopy of the thenar eminence (NIRSth) can estimate tissue oxygenation (Sto_2) and the microvascular response to induced short-lived ischaemia.[1,2] NIRSth also provides information on the tissue haemoglobin index (THI). Changes in THI during short-lived venous occlusion (representative of the speed at which blood pooling occurs) can theoretically be used to estimate forearm blood flow (FBF).[3] Thus, NIRSth may provide a non-invasive bedside technique to assess the forearm circulation.

Strain gauge plethysmography (SGP) studies have shown that near-infrared spectroscopy (NIRS) of the *forearm* can estimate FBF using changes in the THI (ΔTHI),[3-6] but NIRSth in now preferred in the intensive care unit.[7,8] No studies have confirmed or refuted whether NIRS of the *thenar eminence* can be used to estimate FBF.[9,10] Additionally, as the THI changes represent blood pooling, which should occur in the most dependent segment of the arm,[11] elevation of the arm performed in previous SGP might influence the ability of NIRSth to detect these changes in THI.

We hypothesised that changes in THI would correlate with FBF measured by SGP, that both NIRSth and SGP would be able to detect higher rates of FBF during hyperaemia, and that arm position would have an effect on NIRSth measurements.

Methods

We performed a comparative crossover study in nine healthy volunteers, simultaneously assessing FBF as measured by SGP and NIRSth-derived ΔTHI/minute in both arms. The Monash University ethics committee approved our study (approval 2012001205).

The participants fasted and abstained from caffeine for 6 hours.[12] We placed a venous cuff on the upper arm (E20 rapid cuff inflator, Hokanson). Immediately distal to the venous cuff, we placed a manual blood pressure cuff to induce arterial occlusion. The strain gauge plethysmograph (EC6 strain gauge and photo plethysmograph, Hokanson) was placed at the midpoint of the forearm, and the near-infrared spectrometer (InSpectra 325, Hutchinson Technology) was placed on the thenar eminence (Figure 1). A purpose-built apparatus was used to produce forearm elevation when required. We made four measurements at baseline, and three measurements during induced reactive hyperaemia, using 30-second venous occlusions (at 40 mmHg) and 30-second recovery periods. Reactive hyperaemia was induced by a 3-minute, 200 mmHg venous occlusion.[2] FBF was estimated in each arm in the horizontal and elevated positions.

Analysis of SGP recordings was performed using PowerLab 2005 (ADInstruments). The average slope for the steepest segment of the curve was determined for a period

Figure 1. Experimental set-up, normal arm position*

* Arm pronated, venous cuff placed as proximal as possible on the upper arm and connected to a rapid cuff inflator (40 mmHg). Manually controlled blood pressure cuff placed distal to the venous cuff to induce arterial occlusion (200 mmHg). Strain gauge plethysmograph placed at midpoint of forearm. Near-infrared spectroscopy sensor placed on thenar eminence.

after initial cuff inflation and extrapolated for 1 minute to give a flow in mL/dL/minute. THI was recorded every 5 seconds during venous occlusion. The greatest THI increase for any 5-second period during a venous occlusion was used as the estimate of FBF for that occlusion cycle, and extrapolated to 1 minute, using the equation:

$$\text{FBF (THI/minute)} = [\text{maximum } (\text{THI}_x - \text{THI}_{x-5})]/5 \times 60$$

in which FBF is forearm blood flow, THI is tissue haemoglobin index, and x and x–5 represent two time points 5 seconds apart (used to determine the THI increase for each 5-second period). The maximum function is then used to determine the greatest THI change for any 5-second period (excluding the first 5 seconds). This maximum ΔTHI in 5 seconds is divided by five to produce THI/second, which is multiplied by 60 to produce THI/minute.

Statistical analysis

Statistical analysis was performed using SPSS, version 11 (IBM Corporation) and SAS 9.2 (SAS Institute). Some data were transformed using logarithmic transformation. Non-transformed non-parametric data were used, they are presented with the median and range or interquartile range. Repeated measures analysis of variance (ANOVA) were used to assess similarity at baseline and to determine if hyperaemia induced a detectable change in FBF. A mixed linear model was applied to establish the relationship between logNIRSth and logSGP. This mixed linear model was defined with logSGP as the outcome and the following prediction variables: logNIRSth; age; sex; arm side (left or right); phase (baseline or hyperaemia); and interaction between arm position (horizontal or elevated) and phase. Interaction terms were fitted between logNIRSth and phase, and between logNIRSth and arm position. Linear regression was used to determine a simplified equation to enable conversion from NIRSth-derived THI changes into a unit of flow.

To determine if arm position had an effect, paired *t* tests and Wilcoxon matched-pairs signed-rank tests were used. Baseline and hyperaemia were considered as one group set, and then baseline and hyperaemia were analysed as separate groups.

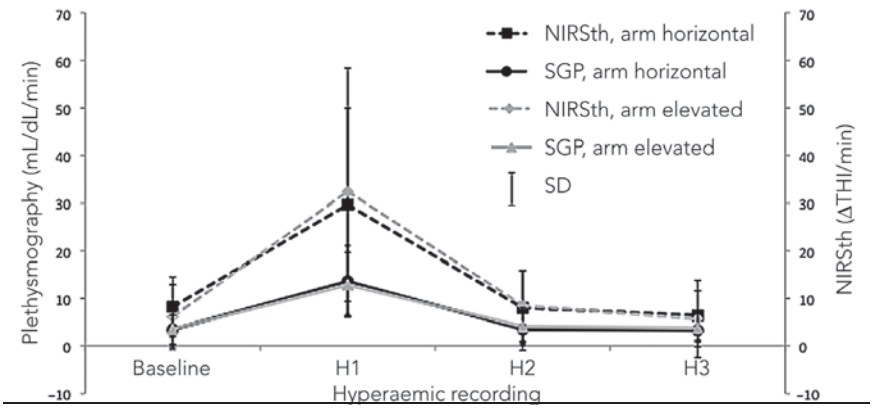
Results

The nine volunteers (including five men) had a median age of 23 years (range, 22–32 years) and median body mass index of 22.7 kg/m^2 (range, 19.3–26.8 kg/m^2).

Horizontal-arm mean SGP-derived FBF was 3.5 mL/dL/minute (SD,1.5 mL/dL/minute) at baseline and 13.6 mL/dL/minute (SD, 3.7 mL/dL/minute) during hyperaemia. Elevated-arm mean FBF was 3.6 mL/dL/minute (SD, 1.6 mL/dL/minute) at baseline, and 12.9 mL/dL/minute (SD, 3.4 mL/dL/minute) during hyperaemia.

Horizontal NIRSth-derived mean ΔTHI was 8.2/minute (SD, 3.1/minute) at baseline, and 29.7/minute (SD, 10.2/minute) during hyperaemia. Elevated ΔTHI was 6.1/minute (SD, 3.2/minute) at baseline, and 32.5/minute (SD, 13/minute) during hyperaemia. At baseline, there was no significant difference in measurements obtained in the horizontal position compared with the elevated position. In all combinations of device positions, the first hyperaemic

Figure 2. Hyperaemia estimated by a baseline recording and three hyperaemic recordings, using SGP and NIRSth



SGP = strain guage plethysmography. NIRSth = near-infrared spectroscopy of thenar eminence. THI = tissue haemoglobin index. H1 = first hyperaemic recording. H2 = second hyperaemic recording. H3 = third hyperaemic recording.

Table 1. Effect of forearm position on FBF estimates

FBF	FBF affected for NIRSth	FBF affected for SGP
Combined	Yes ($P < 0.01$)	No effect detected ($P = 0.2$)
Baseline	Yes ($P < 0.01$)	No effect detected ($P > 0.9$)
B_{mean}	Yes ($P = 0.03$)	No effect detected ($P > 0.9$)

FBF = forearm blood flow. NIRSth = near-infrared spectroscopy of thenar eminence. SGP = strain gauge plethysmography. B_{mean} = mean baseline recording.

recording of FBF (H1) was significantly different from the mean baseline recording (B_{mean}) ($P < 0.001$) (Figure 2).

LogNIRSth ($P < 0.01$), arm position ($P < 0.01$) and phase ($P < 0.01$) were independent predictors of logSGP (Figure 3). There was a significant interaction between logNIRSth, and phase ($P < 0.01$), indicating that the strength of the relationship between logNIRSth and logSGP was significantly greater in the hyperaemic phase than at baseline ($P < 0.01$). There was a trend towards an interaction between logNIRSth and arm position ($P = 0.07$).

The regression equation to convert ΔTHI/minute to mL/dL/minute was:

$$\text{FBF (mL/dL/minute)} = 0.362\ (\pm 0.044)\ \Delta\text{THI/minute} + 0.864\ (\pm 0.642)\ (P < 0.01)$$

in which FBF is forearm blood flow and ΔTHI/minute is the NIRSth-derived THI change. Table 1 indicates whether arm position influenced FBF estimates.

Discussion

We performed a comparative crossover study in healthy volunteers to test whether NIRSth can estimate SGP-derived FBF. We also aimed to determine the effect of arm position on the relationship between NIRSth and SGP, and on the results obtained with each method. We found that NIRSth-derived changes in THI were independent predictors of SGP-derived FBF, and their correlation was stronger during hyperaemia. We developed an equation to convert ΔTHI changes into SGP-FBF measurements with an acceptable degree of accuracy. Additionally, we found that arm position had an effect on the estimation of ΔTHI.

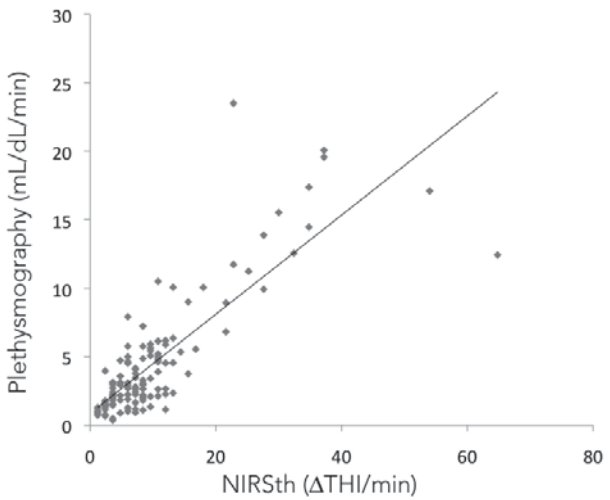
Previous studies

The value of NIRS of the forearm to estimate FBF and SGP has been previously assessed,[3-6] and some studies have used NIRS as the primary means of assessing blood flow.[13,14] However, no studies have compared the new technology of NIRS of the thenar eminence to SGP. Although our SGP-derived FBF values are consistent with previous studies, we are unable to compare NIRSth estimations with previous studies due to a proprietary algorithm.[3,15] Previous studies also assessed the effect of wrist occlusion and found no difference between FBF estimation with or without wrist occlusion.[10] This is important, as estimation of ΔTHI with NIRSth would not have been possible with wrist occlusion.

Additionally, the impact of elevation of the arm to promote venous drainage during SGP has not been rigorously tested. We hypothesised that elevation of the arm would result in blood pooling in the area of tissue adjacent to the collecting cuff under the influence of gravity. As the SGP was placed proximal to the NIRSth probe, this proximal pooling could influence results. In contrast, we proposed that with the arm in the horizontal position, blood would collect evenly throughout the arm and this pooling effect would be eliminated. As we intend to apply this technique in critically ill patients, for whom the horizontal arm position is preferred, we aimed to show that elevation of the arm would influence the result but would not be necessary to develop a predictive equation.

We found that the arm position did influence estimations of THI, as predicted, but did not influence SGP, and that we could derive a conversion equation for the horizontal position.

Figure 3. Relationship between forearm blood flow (elevated forearm) measured by strain gauge plethysmography and NIRSth-derived THI changes*



*No correlation coefficients presented; repeated-measures statistics were applied to data assessment. NIRSth = near-infrared spectroscopy of thenar eminence. THI = tissue haemoglobin index.

Strengths and limitations

Our study was performed in a controlled environment using the same simultaneous and bilateral procedures and equipment for every participant. We studied participants who were different from ICU patients, our final target population; however, this was an initial exploratory proof-of-concept study. We were unable to calculate a measurement of flow to directly compare with SGP, and these results can only be applied to similar NIRSth models, but the underlying physiology should be independent of the NIRSth device. Additionally, the NIRSth device we used had limited sensitivity in that it only reported the THI to one decimal place. Increased sensitivity may improve the accuracy of FBF NIRSth estimation.

Further research in this area will involve validation studies in critically ill patients, perhaps using Doppler ultrasound to estimate FBF and comparing it to NIRSth-derived equations.

Conclusions

We describe a relationship between NIRSth-derived THI and FBF in healthy volunteers that allows estimation of FBF in different operative conditions. Our findings justify further investigation of these estimates in critically ill patients.

Competing interests

None declared.

Author details

Nicholas CZ Woinarski, Research Fellow[1,2]
Satoshi Suzuki, Research Fellow[2,3]
Miklos Lipcsey, Research Fellow[2,4]
Natalie Lumsden, Senior Technician[5]
Jaye Chin-Dusting, Senior Researcher[5]
Antoine G Schneider, Research Fellow[2]
Michael Bailey, Biostatistician[6]
Rinaldo Bellomo, Intensive Care Specialist,[2] and Codirector[6]

1 Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, VIC, Australia.
2 Department of Intensive Care, Austin Hospital, Melbourne,VIC, Australia.
3 Okayama University Hospital, Okayama, Japan.
4 Uppsala University, Uppsala, Sweden.
5 Department of Vascular Pharmacology, Baker IDI Heart and Diabetes Institute, Melbourne, VIC, Australia.
6 Australian and New Zealand Intensive Care Research Centre, Melbourne, VIC, Australia.

Correspondence: rinaldo.bellomo@austin.org.au

References

1 Creteur J, Carollo T, Soldati G, et al. The prognostic value of muscle StO2 in septic patients. *Intensive Care Med* 2007; 33: 1549-56.
2 Lipcsey M, Eastwood GM, Woinarski NC, Bellomo R. Near-infrared spectroscopy of the thenar eminence: comparison of dynamic testing protocols. *Crit Care Resusc* 2012; 14: 142-7.
3 De Blasi RA, Ferrari M, Natali A, et al. Noninvasive measurement of forearm blood flow and oxygen consumption by near-infrared spectroscopy. *J Appl Physiol* 1994; 76: 1388-93.
4 Van Beekvelt MC, Colier WN, Wevers RA, Van Engelen BG. Performance of near-infrared spectroscopy in measuring local O(2) consumption and blood flow in skeletal muscle. *J Appl Physiol* 2001; 90: 511-9.
5 Harel F, Olamaei N, Ngo Q, et al. Arterial flow measurements during reactive hyperemia using NIRS. *Physiol Meas* 2008; 29: 1033-40.
6 Homma S, Eda H, Ogasawara S, Kagaya A. Near-infrared estimation of O2 supply and consumption in forearm muscles working at varying intensity. *J Appl Physiol* 1996; 80: 1279-84.
7 Lipcsey M, Woinarski NC, Bellomo R. Near infrared spectroscopy (NIRS) of the thenar eminence in anesthesia and intensive care. *Ann Intensive Care* 2012; 2: 11.
8 Poeze M. Tissue-oxygenation assessment using near-infrared spectroscopy during severe sepsis: confounding effects of tissue edema on StO2 values. *Intensive Care Med* 2006; 32: 788-9.
9 Wilkinson IB, Webb DJ. Venous occlusion plethysmography in cardiovascular research: methodology and clinical applications. *Br J Clin Pharmacol* 2001; 52: 631-46.
10 Lind L, Sarabi M, Millgård J. Methodological aspects of the evaluation of endothelium-dependent vasodilatation in the human forearm. *Clin Physiol* 1998; 18: 81-7.
11 Vedung T, Jorfeldt L, Henriksson J. Alterations in forearm position and environmental temperature influences the segmental volume expansion during venous occlusion plethysmography--special attention on hand circulation. *Clin Physiol Funct Imaging* 2009; 29: 376-81.
12 Casiglia E, Bongiovi S, Paleari CD, et al. Haemodynamic effects of coffee and caffeine in normal volunteers: a placebo-controlled clinical study. *J Intern Med* 1991; 229: 501-4.
13 Gurley K, Shang Y, Yu G. Noninvasive optical quantification of absolute blood flow, blood oxygenation, and oxygen consumption rate in exercising skeletal muscle. *J Biomed Opt* 2012; 17: 075010.
14 Piazza O, Zito G, Valente A, Tufano R. Effects of dopamine infusion on forearm blood flow in critical patients. *Med Sci Monit* 2006; 12: CR90-3.
15 Myers D, McGraw M, George M, et al. Tissue hemoglobin index: a non-invasive optical measure of total tissue hemoglobin. *Crit Care* 2009; 13 Suppl 5: S2. ❑

Assessment of the distribution and professional roles of the new Fellows of the College of Intensive Care Medicine of Australia and New Zealand

Bala Venkatesh and Ross Freebairn

In recent years, there have been rapid changes to and expansion of the intensive care specialist's role in Australia and New Zealand. Many intensivists are currently active in work outside the intensive care unit, such as rapid response teams, telemedicine, transport and retrievals. This has changed the demand for workforce numbers.

To assess the job status of new Fellows who have recently completed their Fellowship of the College of Intensive Care Medicine (FCICM), the College of Intensive Care Medicine (CICM) undertook an electronic survey of all new Fellows who obtained the FCICM between 2010 and 2012.

The FCICM is awarded after completion of the CICM training program, including 6 years of training in intensive care medicine, anaesthesia and internal medicine, and the successful completion of the primary and fellowship examinations, or equivalent. Fellowship of intensive care medicine is the sole credentialled training pathway to specialist or vocational registrations in intensive care medicine in Australia and New Zealand.

The aim of this survey was to describe the geographic distribution and professional roles of the new Fellows in the workforce. The new Fellows were identified from the CICM database. An anonymous user survey was conducted with the online survey software and questionnaire tool SurveyMonkey. An email with a covering letter and a link to the survey web page was sent to all eligible participants. The survey was open to the respondents from 15 April 2013 to 15 May 2013. The survey consisted of 14 questions.

Results

One hundred and eighty Fellows were eligible for the survey, of whom 133 responded (response rate of 74%). The results for each of the questions are outlined in Table 1.

Discussion

These data represent a snapshot of the geographic distribution and professional roles of the new Fellows. The response rate of the survey was acceptable. The data suggest that of those who responded, about 80% are employed as intensivists, and 70% of these are practising full-time intensive care. About 75% of those employed as intensivists obtained a job within 6 months of completing the FCICM. About 65% of these are in metropolitan ICUs and an increasing proportion (about 25%) are in regional and rural ICUs. The greater spread of Fellows to rural and regional centres will have significant implications for accreditation of regional units for training, for management of patients within the region and for minimising transfer to metropolitan ICUs. The data also suggest an increasing global spread of the Fellows of the CICM outside Australia and New Zealand. This will have implications for accreditation of units outside Australia and New Zealand for training and examinations. The CICM plans to

Figure 1. Proportion of Fellows employed as intensivists, in a full-time or part-time capacity

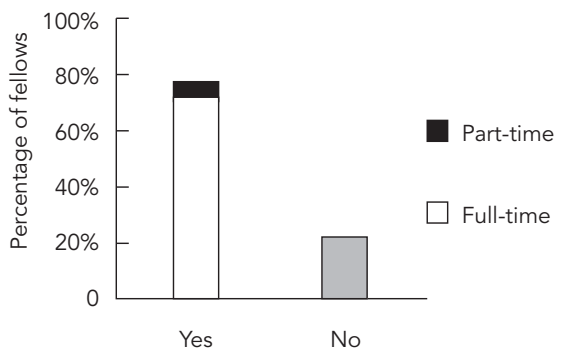


Figure 2. Distribution of Fellows' employment

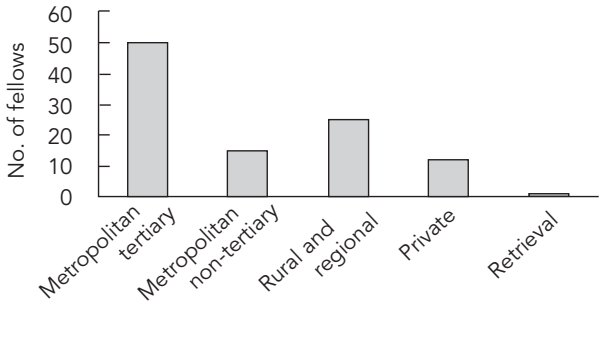


Table 1. Results of survey of distribution and professional roles of the new Fellows of the College of Intensive Care Medicine

Questions	Responses (percentage or no. of Fellows selecting response)
1. Which year did you obtain FCICM? (*n** = 132)	2010 (31%), 2011 (30%), 2012 (39%)
2. Did you pursue any other specialty training or research after obtaining FCICM? (*n* = 132)	Yes (24%), no (76%)
3. If yes, which specialty training or research did you pursue? (*n* = 16)	FRACP (37.5%), FACEM (12.5%), FANZCA (44%), PhD (13%). Nineteen free text responses were received, indicating that a large number were also undertaking echocardiography training
4. In which country is your primary employment? (*n* = 118)	Australia (88%), New Zealand (12%). Fourteen free text responses were received: Singapore (two), United States (two), Hong Kong (two), United Kingdom (two) and one each in India, Canada, Switzerland, Belgium, Ireland and South Africa
5. Are you currently employed as an intensivist? (*n* = 129)	See Figure 1
6. Is your intensivist employment full-time or part-time? (*n* = 103)	See Figure 1
7. If part-time, what fraction FTE? (*n* = 31)	Responses were as free texts: 24 Fellows worked > 0.5 FTE, seven worked < 0.5 FTE
8. Please state why you are not working full-time in intensive care, eg, personal choice, unable to obtain full-time position, etc. (*n* = 30)	Unable to get full-time ICU employment (nine), personal choice (11), dual appointments (anaesthesia or respiratory medicine) (10)
9. If working part-time in intensive care, where are you employed for the remainder of your FTE? (*n* = 19)	Anaesthesia (47%), physician (16%), emergency medicine (5%), university (11%), locum (32%)
10. Please describe your current intensive care employment and the FTE at each. Eg, "metropolitan tertiary ICU, 1.0 FTE" or "metropolitan non-tertiary ICU, 0.8 FTE, and private metropolitan ICU, 0.2 FTE", etc. (*n* = 103)	See Figure 2
11. What was the time interval between obtaining your FCICM and commencing your first consultant position as an intensivist? (*n* = 101)	0–3 months (57%), 3–6 months (17%), 6–9 months (11%), 9–12 months (6%), > 12 months (9%)
12. If greater than 6 months, can you please state what jobs you carried out in that period and what was the cause of the delay. Eg, no job available, waiting for a specific position to come up, chose to work elsewhere, etc. (*n* = 26)	Worked as Fellow or locum consultant (20), undertook additional training in research or ECMO (six)
13. If you are not currently employed as an intensivist, please give details on why not. Eg, currently undertaking other training, dual-qualified and working in the other specialty, unable to obtain an intensivist position, etc. (*n* = 29)	Unable to obtain position of choice (12), miscellaneous reasons (maternity leave, overseas training, dual training, locum work, etc) (17)
14. If you have been unable to obtain an intensivist position, how many jobs have you applied for? (*n* = 19)	< 3 jobs (nine), 3–6 jobs (three), > 6 jobs (seven)

* *n* indicates the number of respondents for that particular question. ECMO = extracorporeal membrane oxygenation. FACEM = Fellowship of the Australasian College for Emergency Medicine. FANZCA = Fellowship of the Australian and New Zealand College of Anaesthetists. FCICM = Fellowship of the College of Intensive Care Medicine. FRACP = Fellowship of the Royal Australasian College of Physicians. FTE = full-time equivalent.

repeat this survey at regular intervals to better understand the professional roles, geographic distribution and workforce needs of Fellows.

Acknowledgements

We would like to acknowledge the contribution of Phil Hart from the CICM for assistance with survey set-up and data collection.

Competing interests

None declared.

Bala Venkatesh, Pre-eminent Specialist,[1] and Deputy Director of Intensive Care[2]

Ross Freebairn, Consultant, Intensive Care Services and Clinical Director, Acute Services,[3] and Adjunct Associate Professor[4]

1 Princess Alexandra Hospital, Brisbane, QLD, Australia.

2 Wesley Hospital, Brisbane, QLD, Australia.

3 Hawke's Bay Hospital, Hastings, New Zealand.

4 Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Shatin, NT, Hong Kong, China.

Correspondence: Bala.venkatesh@health.qld.gov.au ❑

Patient comfort in the intensive care unit: a multicentre, binational point prevalence study of analgesia, sedation and delirium management

John V Green

To the Editor: Elliot and colleagues are to be congratulated for their study on managing analgesia, sedation and delirium in the intensive care unit.[1] It is a step towards improving care in ICUs in Australia and New Zealand. The principle of treating a problem (such as hypotension or hypoxia) after measuring it is well accepted in the ICU. Following many previous studies showing benefits in measurements related to the management of pain, agitation and delirium,[2,3] Elliot and colleagues have shown that there is room for improvement in our management of these common problems. It is striking that, 13 years after the publication of the article by Kress et al showing benefit from interruption of sedative infusions,[4] there is still such a high rate of sedation and analgesia used without monitoring or without planned interruption.

Pronovost and colleagues observed that "The greatest opportunity to improve patient outcomes … will probably come not from discovering new treatments but from learning how to deliver existing effective therapies".[5] This is a large challenge facing Australasian ICUs — how to convert the findings of basic research into improved quality of care.

Two important steps have been taken towards improving the quality of care relating to delirium, analgesia and sedation. The first step was to show benefit from measurement. The second was to audit performance. We now need to change our practices to improve performance, then maintain the improvement, with repeated measurement to demonstrate these improvements.[6]

John V Green, Clinical Director, Intensive Care Unit
The Northern Hospital, Melbourne, VIC, Australia.
John.green@nh.org.au

1 Elliot D, Aitken LM, Bucknall TK, et al. Patient comfort in the intensive care unit: a multicentre, binational point prevalence study of analgesia, sedation and delirium management. *Crit Care Resusc* 2013; 15: 213-9.
2 Bucknall TK, Manias E, Presneill JJ. A randomized trial of protocol-directed sedation management for mechanical ventilation in an Australian intensive care unit *Crit Care Med* 2008; 36: 1444-50.
3 Vasilevskis EE, Ely EW, Speroff T, et al. Reducing iatrogenic risks: ICU-acquired delirium and weakness—crossing the quality chasm. *Chest* 2010; 138: 1224-33.
4 Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med* 2000; 342: 1471-7.
5 Pronovost PJ, Nolan T, Zeger S, et al. How can clinicians measure safety and quality in acute care? *Lancet* 2004; 363: 1061-7.
6 McAlearney AS, Alexander JA. Improving quality in health care organizations. In: Burns LR, Bradley EH, Weiner BJ, editors. Shortell and Kaluzny's healthcare management: organization design and behaviour. 6th ed. Clifton Park, USA: Delmar, 2012: 249-81. ❑

Information for authors

Critical Care and Resuscitation *is the official journal of the College of Intensive Care Medicine of Australia and New Zealand. It is a research and educational journal for those interested in critical care and intensive care medicine and related subjects.*

Manuscripts

Address manuscripts and communications to:

Professor Rinaldo Bellomo
Chief Editor
Critical Care & Resuscitation
Department of Intensive Care, Austin Hospital,
Studley Road, Heidelberg, VIC 3084, Australia
Tel: 61-3-9496 5992; Fax: 61-3-9496 3932
E-mail: rinaldo.bellomo@austin.org.au

Manuscripts should be prepared largely in accordance with the *Uniform requirements for manuscripts submitted to biomedical journals* (*Ann Intern Med* 1997; 126: 36-47).

Articles are accepted with the understanding that they have not been, nor will be, published elsewhere. This does not refer to abstracts or oral communications presented in the proceedings of societies or symposia. The Editor reserves the right to alter and shorten material accepted for publication and to determine the priority and time of publication.

All articles should be submitted electronically as an attachment to an email, along with a covering letter, an electronic "Copyright transfer statement" (available at: http://www.cicm.org.au/cms_files/Copyright%20transfer%20statement.pdf) and a competing interests statement by the primary author on behalf of all authors, signed electronically. The last should declare any competing interests as described in the *British Medical Journal* 1998; 317: 291-2. Any substantially revised versions of the original manuscript should be approved by all authors, and signed to that effect by the primary author. A letter of permission from the copyright holder is required for the use of images from other publications.

Studies on human subjects must comply with the Helsinki Declaration of 1975, and those on animals must comply with National Health and Medical Research Council Guidelines. A statement affirming Ethics Committee (Institutional Review Board) approval should be included in the text. A copy of that approval should be available if requested.

Receipt of the article will be acknowledged, and two or more experts will review the manuscript. Authors are invited to suggest names (and email addresses) of two potential reviewers, and also any reviewers they would prefer did not see the manuscript. Authors will be advised of the outcome within 6 weeks of receipt of the manuscript.

Preparation of manuscripts

All articles must be written in English. Submit manuscripts electronically (maximum file size, 5 MB). Microsoft Word is the preferred word processing program. The document should be unformatted, and the text should be single-word and double-line spaced, with 2.5 cm margins on an A4 sized page.

On a single separate page there must be:

- title;
- each author's given name, middle initial, surname, and appointments;
- institution and department in which work was performed;
- up to five keywords chosen from the keyword list (see http://www.cicm.org.au/cms_files/Keywords%20Document.pdf); and
- name, email address and telephone and fax numbers of the author to whom correspondence and requests for reprints should be directed, plus an email address for another author or nominated person as a back-up. The proofs will be sent to the nominated author unless contrary instructions are given.

Abstracts

Articles should have an abstract of appropriate format and length as follows:

Original article or survey: Structured abstract (up to 250 words) with headings, Objective; Design; Setting; Participants; Interventions (if any); Main outcome measures; Results; and Conclusions.

Structured review or meta-analysis: Structured abstract (up to 250 words) with headings, Objective; Design; Data sources; Review methods; Results; and Conclusions.

Other review: Non-structured narrative or dotpoint abstract (up to 250 words).

Point of view: No abstract, or non-structured narrative or dotpoint abstract (up to 100–150 words), depending on article length.

Case report: Non-structured narrative abstract (up to 100 words) summarising case and reason it is notable.

Editorial, Pro-con debate, Letter, Book review, Obituary: No abstract.

Article formats

Original articles and surveys should be in IMRAD format (Introduction, Methods, Results and Discussion) (word limit, 2500 words).

Introduction (approximately 400 words) should cover why this topic is important (background); what is known and gaps in knowledge (unanswered questions); how this study will fill the gap (question addressed or relevant to this study); and specific aim and hypothesis of this study.

Methods should be clear and reproducible, and include the start and end dates of the study; any equipment (including statistical software) should have manufacturer and city of manufacture in parentheses.

Results should be presented in the most meaningful way (text, table or figure). Results presented in tables and figures should not be repeated in the text (text should cite the table or figure and highlight only its most important features). Present results in the same order as the methods, and ensure all results have a method described.

Discussion should discuss only results already presented in the results section. It should include a statement of the principal findings; how the findings fit with previous knowledge and data, including any important differences in results; what new and relevant data the study provides; meaning and implications of the study, especially for clinicians and policymakers; strengths and weaknesses of the study; relevant unanswered questions and future research; and conclusion.

Case reports should have an introduction of less than 100 words followed by the case report and discussion. In general, they should not exceed 2500 words in length.

Style

Use abbreviations sparingly and define each at first mention. Give measurements in SI units (except blood pressure in mmHg; if blood gases are given in mmHg, then include kPa in parentheses). Supply reference ranges for measurements. Refer to drugs by their Australian approved generic, not proprietary, names.

References

Number references consecutively in the order in which they are first mentioned in the text. References in tables and figures should be numbered as if mentioned where the table or figure is first cited. Identify references in text, tables and legends by superscript Arabic numerals.

Use the form of references adopted by the United States National Library of Medicine. Abbreviate journal names as in *Index Medicus*. List all authors when four or fewer; when five or more, list only the first three and add et al. For example:

Journal article:

Yamamoto S, Tsutsui H, Tagawa H, et al. A. Role of myosite nitric oxide in β-adrenergic hyporesponsiveness in heart failure. *Circulation* 1997; 95: 1111-4.

Chapter in a book:

Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology and management. 2nd ed. New York: Raven Press, 1995: 465-78.

References to personal communications and unpublished observations should not be listed as references but should be noted in the text in parentheses: eg, "(personal communication)". Articles that have been accepted for publication but not yet published should be included in the references with the words "In press" included in place of volume and page numbers.

Tables

Present all tables in double-spaced type on separate pages. Do not submit tables as images. Information in tables should not be duplicated in the text. Number tables consecutively and supply a brief title for each. Give each column a short or abbreviated heading. Place explanatory matter in footnotes, not in the heading. Explain in footnotes all non-standard abbreviations that are used in each table. Cite each table in the text in consecutive order.

Standard deviation (SD) is the accepted measure of variation in text and tables. Standard error of the mean (SEM) is acceptable in figures for the sake of graphical clarity, provided that the number of observations is clearly stated. Omit internal horizontal and vertical rules.

Figures and illustrations

Figures and illustrations should be submitted in electronic format. Two versions of each image are required:

A print-quality (high resolution) image. An acceptable image must be at least 3.5 inches (8.75 cm) across when printed at 300 dots per inch (dpi). Computer screen resolution only requires 72 dots per inch (dpi), which is not suitable for print. If the image is small to begin with, it cannot be turned into a high resolution image: it is not effective to "blow up" an image using image editing software to increase the size.

Images should be submitted in their original file format. Preferred image file formats are EPS, TIFF, Adobe Illustrator or Adobe Photoshop. JPEG images may be acceptable but should be saved at their maximum size, as JPEG compression reduces image quality. ZIP compression is acceptable. Microsoft Excel format is acceptable for graphs; it is important to provide the data table from which the graph was generated.

Critical Care and Resuscitation

Critical Care and Resuscitation (*CC&R*) is the official scientific journal of the College of Intensive Care Medicine (CICM), which is the standards and accreditation body responsible for the training and certification of all Intensive Care specialists in Australia and New Zealand.

The Journal is now in its 15th year of publication and is received and read by all Intensive Care specialists and trainee specialists in Australia and New Zealand, along with an increasing number of subscribers from around the world.

Critical Care and Resuscitation is the perfect publication to advertise your products and/or services.

2013 Publication Dates	Advertising Deadline	Material Deadline
Monday 3rd March 2014	Friday 17th January 2014	Friday 24th January 2014
Monday 2nd June 2014	Friday 18th April 2014	Friday 25th Apr 2014
Monday 1st September 2014	Friday 18th July 2014	Friday 25th July 2014
Monday 1st December 2014	Friday 17th October 2014	Friday 24th October 2014

2013 Advertising Rates	(incl. GST)
Full page 4 colour Back Cover	$2970
Full page 4 colour Inside Front Cover	$2640
Full page 4 colour Opposite First Editorial	$2640
Full page 4 colour Front Section	$2310
Full page 4 colour Rear Section	$2145
Full page 4 colour Inside Back Cover	$2310
Full page B & W Front Section	$660
Full page B & W Rear Section	$495
Half page 4 colour Front Section	$1485
Half page 4 colour Rear Section	$1285
Half page B & W Front Section	$430
Half page B & W Rear Section	$330
Quarter page B & W Front Section	$200
Quarter page B & W Rear Section	$165
Loose insert (max 275x210mm)	$1485

SPECIAL OFFER – 10% off for x 4 consecutive ads

Printing

Cover: 250gsm artboard Text: 90gsm matt art
Finishing: Perfect bound

Mechanical data

Full page trim size	275 deep x 210 mm	(+5mm bleed all edges)
Full page box advert	245 deep x 178 mm	
Half page box advert	115 deep x 178 mm	
Quarter page box advert	115 deep x 85 mm	
Half page vertical	230 deep x 85 mm	

Material requirements

Preferred file format is high resolution PDF (Fonts and images must be embedded within the PDF).

Material delivery: All artwork is to be mailed to CICM at the address below or if smaller than 5MB can be emailed.

Heather Dick Pere
College of Intensive Care Medicine
Suite 101, 168 Greville Street, Prahran VIC 3181
Ph: +61 3 9514 2888 Fax: +61 3 9533 2657
heatherd@cicm.org.au

Critical Care and Resuscitation
(ISSN 1441-2772) is the official peer reviewed journal of the College of Intensive Care Medicine of Australia and New Zealand, published quarterly by the Australasian Medical Publishing Company.

Editorial enquiries:
Professor Rinaldo Bellomo
Department of Intensive Care
Austin Hospital, Studley Road,
Heidelberg, VIC 3084
ccr@cicm.org.au

Information for authors:
<http://www.cicm.org.au/ journal.php>.

Subscription enquiries: **(see page 161)**
Heather Dick Pere
<heatherd@cicm.org.au>
Subscriptions,
Critical Care and Resuscitation
Suite 101, 168 Greville Street, Prahran VIC 3181.

Australasian Medical Publishing Co.
Locked Bag 3030, Strawberry Hills,
NSW 2012. ABN 20 000 005 854
critcareres@ampco.com.au

Change of address: The publisher must be notified 21 days in advance of any change in address.

Missing issues: Claims for damaged or missing issues should be made within three months of the date of the issue.

The Alfred Intensive Care

Upcoming Events Programme

The profits from the courses are 10% allocated to research, education, projects and equipment for The Alfred ICU.

4th International Nutrition in the Critically Ill Symposium

Two days of lectures, up-to-date reviews, recent research and case presentations. For Doctors, Nurses and Dietitians who deal with the critically ill. Our international speakers are Prof Jean-Charles Preiser from Belgium and Dr Naomi Cahill from Canada. Experts from across Australia will present the latest research findings.

27 & 28 March 2014 Fee $600 - $750 **Early Bird** $500 - $650 by 31 January 2014

Renal Support in the Critically Ill Conference

International guest speakers Prof Prasad Devarajan (USA), A/Prof Sean Bagshaw (Canada) and Dr Bill Clark (USA) will be joined by leading Australian expertsto deliver the latest news in critical care nephrology & RRT. A satellite hands on practical session is offered for nursing & interested medical staff this practical session is held concurrently in the afternoon.

16 May 2014 Fee $330 - $700 **Early Bird** $300 - $600 by 21 March 2014

8th Alfred Advanced Mechanical Ventilaton Conference (AAMVC)

Theme – Recent Advances in Mechanical Ventilation. International speakers Prof Marcelo Amato (Brasil) and A/Prof Eddy Fan (Canada). A full day of presentations on Thursday is complimented by the hands on Ventilator Waveforms Workshop (Wednesday) with a low faculty:participant ratio. (Waveforms not sold separately)

AAMVC 17 July 2014 Fee $365 - $535 **Early Bird** $315 - $485 by 24 April 2014

Waveforms16 July 2014 Fee AAMVC & Waveforms $675 - $905 **Early Bird** $620 - $850 by 24 April 2014

Advanced Life Support (ALS2) Provider Course

Two day Australian Resuscitation Council accredited adult life support provider training in advanced cardiac arrest & medical emergency management for Doctors, Nurses and Paramedics.

30 & 31 January 27 & 28 February 14 & 15 April 5 & 6 June 2014 24 & 25 July

2 & 3 October 13 & 14 November 4 & 5 December 2014 Fee $770 -$1550

Basic Assessment & Support in Intensive Care

Two day introduction Course for medical staf new to intensive care and the care of the critically ill.

4 & 5 February 5 & 6 May 4 & 5 August 5 & 6 November 2014 Fee $650

Bronchoscopy for Critical Care

All you need to know about fibre optic intubation, massive pulmonary haemorrhage, bronchial lavage, foreign body removal and safe bronchoscopy in critically ill patients. Interactive and simulation based course.

18 July 17 October Fee $800 - $990 **Early Bird** $700 - $850 by 23 May or 15 August 2014

Consultant Intensivist Transitioning (CIT)

Developed by Carole Foot this two day course is or newly appointed Consultants & Trainees soon to transition. Limited places to ensure intensity of training in areas such as mentoring, managing change, legal & ethics.

25 & 26 August 2014 Fee $1700 - $1900 **Early Bird** $1550 - $1750 by 23 June 2014

Critical Care Echocardiography Course

Two day course covering problem orientated approach to echo in critically ill patients. Emphasis on echo guided management of the critically ill. Content tailored to suit participant's echo experience with a favourable faculty:participant ratio 1:2 providing ample hands on experience using live models & Heartworks simulators.

25 & 26 June 27 & 28 October 30 & 31 October 2014 Fee $1950(The CCUltrasound Course follows Echo)

ICU & Perfusion Adult ECMO Course

Two day course for Doctors, Nurses & Perfusionists covering ECMO support of cardiac and respiratory failure. Optional third day for cannulation training.

2 Day Course 2 & 3 April Fee $880 / Course & 1 Day Cannulation 1 or 4 April 2014 Fee $2530

2 Day Course 8 & 9 October Fee $880 / Course & 1 Day Cannulation 7 or 10 October 2014 Fee $2530

The HEaRT Course – Haemodynamic Evaluation and Related Therapies

Two day course designed for Doctors and Nurses working in all critical care areas covering the physiology, measurement, monitoring & support of the cardiovascular system with practical sessions in small groups.

19 & 20 June 27 & 28 November 2014 Fee $480 - $900

TOE Course (Transoesophageal Echocardiography)

High intensity TOE simulator and wet-lab based two day hands on course covering the standard TOE views and basic pathology. Aimed at Advanced Trainees/Consultants in Anaesthesia, ICU, ED and Cardiology and covering the basics of TOE using the latest in simulator technology.

13 & 14 February 20 & 21 November 2014 Fee $1950 (Course limited to 12 places)

Critical Care Ultrasound Course (CCU)

One day course covering the practicalities of critical care ultrasound. This is a comprehensive course with tutorials and hands on sessions with models. Topics covered include chest US, abdominal ultrasound including FAST and aortic aneurysm, DVT screening and ultrasound for procedures.

27 June 29 October 2014 Fee $750 or $500 if purchased with ECHO held the 2 days prior

For further information or to register online www.alfredicu.org.au/courses

Contact: Cathy Oswald Ph: +61 3 9076 5397 E: c.oswald@alfred.org.au

TheAlfred ALS/BASIC/CRM/TOE Contact: Kate Pearce Ph: +61 3 9076 5404 E: k.pearce@alfred.org.au

MONASH University
Medicine, Nursing and Health Sciences
School of Public Health and Preventive Medicine

Prices are subject to change