Clinical paper

Australasian resuscitation of sepsis evaluation (ARISE): A multi-centre, prospective, inception cohort study

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ABSTRACT

Aim: Determine current resuscitation practices and outcomes in patients presenting to the emergency department (ED) with sepsis and hypoperfusion or septic shock in Australia and New Zealand (ANZ).

Methods: Three-month prospective, multi-centre, observational study of all adult patients with sepsis and hypoperfusion or septic shock in the ED of 32 ANZ tertiary-referral, metropolitan and rural hospitals.

Results: 324 patients were enrolled (mean [SD] age 63.4 [19.2] years, APACHE II score 19.0 [8.2], 52.5% male). Pneumonia (n = 138/324, 42.6%) and urinary tract infection (n = 98/324, 30.2%) were the commonest sources of sepsis. Between ED presentation and 6 hours post-enrolment (T6hrs), 44.4% (n = 144/324) of patients received an intra-arterial catheter, 37% (n = 120/324) a central venous catheter and 0% (n = 0/324) a continuous central venous oxygen saturation (SvO2) catheter. Between enrolment and T6hrs, 32.1% (n = 104/324) received a vasopressor infusion, 7.4% (n = 24/324) a red blood cell transfusion, 2.5% (n = 8/324) a dobutamine infusion and 18.5% (n = 60/324) invasive mechanical ventilation. Twenty patients (6.2%) were transferred from ED directly to the operating theatre, 36.4% (n = 118/324) were admitted directly to ICU, 1.2% (n = 4/324) died in the ED and 56.2% (n = 182/324) were transferred to the hospital floor. Overall ICU admission rate was 52.4% (n = 170/324). ICU and overall in-hospital mortality were 18.8% (n = 60/324) and 23.1% (n = 75/324) respectively. In-hospital mortality was not different between patients admitted to ICU (24.7%, n = 42/170) and the hospital floor (21.4%, n = 33/154).

Conclusions: Management of ANZ patients presenting to ED with sepsis does not routinely include protocolised, SvO2-directed resuscitation. In-hospital mortality compares favourably with reported mortality in international sepsis trials and nationwide surveys of resuscitation practices.

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1. Introduction

Despite international guidelines for the resuscitation of patients with severe sepsis,1,2 there is variation between countries in the degree to which these guidelines have been implemented.3,4 Indirect evidence suggests that the routine management of sepsis patients in Australia and New Zealand (ANZ) does not incorporate protocolised, ScvO2-directed, early goal-directed therapy (EGDT).3,5 In 2006, 1864 patients were admitted to intensive care (ICU) from the emergency department (ED) with sepsis or septic shock (data from the Australian and New Zealand Intensive Care Society Adult Patient Database, ANZICS APD). However, in the same period, only 197 “Presep”® central venous catheters (CVCs) capable of measuring continuous ScvO2 were sold. Moreover, a retrospective analysis of 7649 patients admitted to ICU from ANZ EDs with sepsis or septic shock between 1997 and 20057 suggests that hospital mortality may be considerably lower than that observed in both the standard care and EGDT arms of the Rivers’ trial.5

There are no prospective studies examining how patients presenting to the ED with sepsis and septic shock in ANZ are currently managed and accurate mortality estimates are unknown. Accordingly, we conducted a prospective, multi-centre, inception cohort study in patients presenting to the ED of ANZ hospitals to: (1) characterise current resuscitation practices, including whether patients received EGDT; (2) determine patient outcomes and; (3) establish the feasibility of undertaking a randomised, controlled trial of EGDT in ANZ and obtain information critical to the design of such a trial.

2. Methods

2.1. Study population

A prospective, observational study was performed in 32 ANZ-ICS Clinical Trials Group (ANZICS CTG)-affiliated, tertiary-referral, metropolitan and regional hospitals (Appendix A) between September 1, 2006 and January 31, 2007. All sites screened for 3 months (individual sites commenced screening between September 1 and October 1, 2006). Screening methods included prospective assessment by ED personnel and review of daily ED presentation and hospital admission databases. The study was endorsed by the ANZ-ICS CTG and was undertaken in collaboration with the ANZ Intensive Care Research Centre. Approval to conduct the study was obtained from local institutional ethics committees at participating sites and the need for patient consent was waived.

All adult patients (≥18 years) present in ED at the time of fulfilling the following entry criteria were enrolled:

1) Presumed or confirmed infection
2) Two or more systemic inflammatory response criteria3 AND EITHER
3) Blood pressure (BP) criteria (one or more of the following): (i) systolic BP <90 mmHg OR >140 mmHg fall below premorbid systolic BP OR mean arterial pressure (MAP) >65 mmHg, after ≥500 ml intravenous fluid challenge over 30–60 min; (ii) requirement for vasoactive infusion (adrenaline, noradrenaline, dopamine, dobutamine, vasopressin, metaraminol) for ≥30 min to maintain BP OR
4) Metabolic acidosis criteria (one or more of the following): arterial or venous: (i) blood lactate >4.0 mmol/L; (ii) anion gap >20 mEq/L; (iii) serum bicarbonate <16.0 mmol/L.

Patients meeting the above criteria are herein referred to as having either sepsis with hypoperfusion or septic shock.

2.2. Data collection

The following data were recorded: demographic data (age, gender, weight); APACHE II score using the baseline physiological variables obtained closest in time, but prior, to meeting the final study inclusion criterion; concurrent medical conditions (defined as an acute disease process present during the current ED presentation) and co-morbidities (defined as conditions known to be present prior to the current ED presentation);5 source of sepsis, microbiological specimens, causative organisms and type, timing, choice and appropriateness of anti-microbial therapy; disposition post-ED (e.g. hospital floor, ICU); length of invasive ventilation and vasoactive agent support; ED, ICU and hospital length of stay (LOS) and; ICU and hospital mortality.

Physiological variables (HR, BP, central venous pressure [CVP], RR, arterial oxygen saturation [SaO2], urine output [UO]), vasoactive infusions and crystalloid, colloid and blood product administration were recorded at the time of meeting the final entry criterion for sepsis with hypoperfusion or septic shock (defined as T0hrs). Thereafter, measurements were recorded hourly between T0hrs and 72 hrs and at 72 h. Laboratory data at T0hrs, T6hrs and T72hrs was also recorded. Given the observational nature of the study, physiological and laboratory measurements were not mandated and data was only available if measurement at the specific study time-points was performed.

In addition, through the time periods T0–T6hrs and T6–T72hrs the following data were collected: type and timing of insertion of invasive cardiovascular monitoring; frequency of measuring resuscitation “goals” (UO, BP, CVP, cardiac output, arterial blood gas analysis, blood lactate and central or mixed venous oxygen saturation) and; type and timing of therapeutic interventions (vasoactive agents, mechanical ventilation, drotrecogin alfa, corticosteroids, intensive insulin therapy and renal replacement therapy).

2.3. Outcome measures

All patients were followed until hospital discharge and ICU (where appropriate) and in-hospital mortality recorded. Secondary outcomes included: time-to-antimicrobial therapy, requirement for, and duration of, invasive ventilation; use of vasoactive infusions and duration of administration; ED, ICU and hospital LOS.

2.4. Statistical analysis

Variables are tabulated and/or reported as mean (standard deviation, SD) or median (interquartile range, IQR) as appropriate. No assumptions were made about missing data. Multivariate analysis of changes over time (T0–T6hrs) was performed using repeat measures analysis of variance adjusting for age and gender. Results are displayed graphically with means and standard error bars. Comparisons between physiological variables at T6hrs and T72hrs were conducted using paired t-tests. A two-sided p-value of 0.05 was considered statistically significant. All analyses were performed using SAS 9.1 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patients

A total of 324 patients with sepsis and hypoperfusion or septic shock were enrolled over a 3-month period in 32 sites. During the same 3-month period, the total number of patients (mean, SD) presenting to the ED at each site was 10,974 (3525). Age, weight and APACHE II score were 63.4 (19.2) years, 76.3 (24.2) kg and 19.0 (8.2) respectively. One hundred and seventy patients (52.5%) were male. Baseline demographics, co-morbidities and concurrent medical conditions are given in Table 1. The incidence of patients meeting the BP and metabolic acidosis inclusion criteria was 64.5% (n = 209/324) and 50.0% (n = 162/324) respectively. Only 15.1% of patients (n = 47/324) fulfilled both the BP and metabolic acidosis
criteria (Fig. 1). The time between ED presentation and meeting the final inclusion criterion (T0hrs) was 1.6 (0.7,16.5) h. Physiological and laboratory variables at T0hrs are given in Table 2.

### 3.2. Microbiology

At study entry, 420 suspected or proven infection sources were determined to be present by the treating clinician. Of those, 82.1% (n = 345/420) were considered to be medical in origin and 14.6% (n = 61/420) were surgical. Overall, pneumonia (n = 138/324, 42.6%) and urinary tract infection (n = 99/324, 30.6%) were the commonest diagnoses at presentation. Abdominal infection (n = 45/324, 13.9%) was the commonest surgical source.

Blood cultures were obtained in the majority of patients (n = 250/324, 77.2%) prior to T0hrs. Additional microbiological specimens (e.g. sputum, urine) were collected in 55.2% of patients (n = 179/324) prior to T0hrs. A positive culture(s) from any source was subsequently identified in 67.9% of patients (n = 221/324) with gram-negative (n = 144/324, 44.4%) and gram-positive (n = 92/324, 28.4%) bacteria being the most common isolates. Blood cultures were positive in 119 patients (36.7%). Gram-negative bacteria were the commonest blood culture isolates (n = 72/119, 60.5%).

Antimicrobial therapy was commenced 2.2 h (1.1, 3.8) after ED presentation. Twenty-eight patients (n = 28/309, 9%) did not receive antimicrobial therapy either before T0hrs or in the following 6 h (time-to-antimicrobial therapy not available for 15 patients). Most patients (n = 300/324, 92.6%) were subsequently deemed by the site

### Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>0 h Mean (SD)</th>
<th>n</th>
<th>6 h Mean (SD)</th>
<th>n</th>
<th>72 h Mean (SD)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature (°C)</td>
<td>37.8 (2.1)</td>
<td>240</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>120 (20)</td>
<td>276</td>
<td>100 (22)</td>
<td>237</td>
<td>93 (20)</td>
<td>241</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>68 (20)</td>
<td>232</td>
<td>75 (13)</td>
<td>225</td>
<td>86 (14)</td>
<td>230</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>11 (8)</td>
<td>12</td>
<td>14 (5)</td>
<td>56</td>
<td>13 (7)</td>
<td>75</td>
</tr>
<tr>
<td>RR (breaths/min)</td>
<td>31 (9)</td>
<td>247</td>
<td>21 (8)</td>
<td>212</td>
<td>19 (5)</td>
<td>214</td>
</tr>
<tr>
<td>SaO2 (%)</td>
<td>96 (5)</td>
<td>281</td>
<td>97 (7)</td>
<td>221</td>
<td>96 (3)</td>
<td>225</td>
</tr>
<tr>
<td>ScvO2 (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>UO (ml/h)</td>
<td>96 (116)</td>
<td>128</td>
<td>81 (83)</td>
<td>183</td>
<td>105 (99)</td>
<td>170</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>223 (209)</td>
<td>267</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>6.9 (3.6)</td>
<td>93</td>
<td>3.2 (2.6)</td>
<td>128</td>
<td>2.1 (2.1)</td>
<td>89</td>
</tr>
<tr>
<td>pH</td>
<td>7.28 (0.52)</td>
<td>220</td>
<td>7.26 (0.14)</td>
<td>144</td>
<td>7.38 (0.08)</td>
<td>95</td>
</tr>
<tr>
<td>Base deficit</td>
<td>7.7 (6.6)</td>
<td>212</td>
<td>9.4 (6.3)</td>
<td>141</td>
<td>4.4 (3.5)</td>
<td>93</td>
</tr>
<tr>
<td>Haemocrit (%)</td>
<td>37.1 (8.0)</td>
<td>273</td>
<td>32.8 (6.3)</td>
<td>133</td>
<td>30.4 (5.2)</td>
<td>118</td>
</tr>
<tr>
<td>WCC (&gt;10^9/L)</td>
<td>18.3 (10.9)</td>
<td>220</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*pH refers to the time the patient satisfies the final entry criterion for sepsis with hypoperfusion or septic shock.

Continuous or intermittent ScvO2 measurement not performed at 0, 6 and 72 h.

For pH, measurement was obtained from arterial blood in 70.1% (n = 155), 95.1% (n = 137) and 96.0% (n = 94) of cases at 0, 6 and 72 h respectively. In the remaining cases, venous pH was measured.
A single, intermittent ScvO2 measurement was performed in 249.4%); CO, 23/324 (7.1%); ScvO2, 0/324 (0%).

The total number of patients overall in whom invasive monitoring was inserted at any time between ED presentation and T72hrs was: BP, 178/324 (54.9%); CVP, 160/324 (55.6); IQR, interquartile range; SD, standard deviation.

Renal replacement therapy, Drotrecogin alfa (activated), Intensive insulin therapy, Vasopressor agents, n

Data expressed as mean (SD) or number (%). ED, emergency department; NA, data not available; SD, standard deviation; IQR, interquartile range.

Table 3
Monitoring of key resuscitation end-points in the 6-h period after meeting inclusion criteria for sepsis with hypoperfusion or septic shock (time 0–6 h).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Invasive monitoring(a)</th>
<th>Time to catheter insertion (h) (median, IQR)</th>
<th>Continuous or intermittent measurement(b), % (n)</th>
<th>Frequency intermittent measurement (mean, SD)(d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP</td>
<td>144/178 (80.9)</td>
<td>2.3 (1.3, 4.0)</td>
<td>293/324 (90.4)</td>
<td>10.4 (7.9)</td>
</tr>
<tr>
<td>ABG</td>
<td>201/324 (62.0)</td>
<td></td>
<td>2.3 (1.6)</td>
<td></td>
</tr>
<tr>
<td>CVP</td>
<td>120/160 (75.0)</td>
<td>2.7 (1.5, 4.3)</td>
<td>83/324 (25.6)</td>
<td>3.3 (2.9)</td>
</tr>
<tr>
<td>CO</td>
<td>8/23 (34.8)</td>
<td>3.5 (1.5, 5.5)</td>
<td>4/324 (1.2)</td>
<td>2.0 (1.0)</td>
</tr>
<tr>
<td>ScvO2</td>
<td>0/0</td>
<td></td>
<td>2/324 (0.6)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Lactate</td>
<td>NA</td>
<td></td>
<td>203/324 (62.7)</td>
<td>2.2 (1.6)</td>
</tr>
</tbody>
</table>

BP, systemic blood pressure; ABG, arterial blood gas analysis; CVP, central venous pressure; CO, cardiac output; ScvO2, central venous oxygen saturation; NA, not applicable; IQR, interquartile range; SD, standard deviation.

\(a\) Number and time to catheter insertion (hours) of invasive monitoring refers to the period between ED presentation and T6hrs as, in some patients, catheters were inserted prior to meeting study inclusion criteria at T0hrs.

\(b\) Total number of patients in whom continuous or intermittent measurement performed between T0hrs and T6hrs.

\(c\) Number of times measurement performed if measured intermittently between T0hrs and T6.

\(d\) For replacement dose steroids, intensive insulin therapy, drotrecogin alfa and renal replacement therapy, data collection for the combined time periods ED to 0 h and 0–6 h.

3.3. Monitoring

The number of patients in whom invasive cardiovascular monitoring was instituted and the time-to-catheter insertion between ED presentation and T6hrs are given in Table 3.

Between T0hrs and T6hrs, CVP measurement was only performed in 69.2% (n = 83/120) of patients receiving a CVC (Table 3). A single, intermittent ScvO2 measurement was performed in 2 patients between T0hrs and T6hrs (Table 3). Sixteen intermittent measurements were subsequently performed in one additional patient between T0hrs and T72hrs. No continuous ScvO2 CVCs were inserted at any time between ED presentation and T72hrs.

3.4. Resuscitation and ancillary interventions

Fluid administration between ED presentation and T72 hrs is given in Table 4. The majority of fluid administered was crystalloid (T0–T6hrs, 88.5%; T6–T72hrs, 95%). Overall, 20.1% of patients (n = 65/324) received a blood transfusion. Twenty-four patients (7.4%) were administered blood between T0hrs and T6hrs (Table 4).

The number of patients receiving a vasopressor infusion was 44.4% (n = 144/324); with most receiving a vasopressor infusion between T0hrs and T6hrs (n = 104/144, 72.2%). The duration of vasopressor support was 35 (14, 79) h. Only 2.5% (n = 8/324) of patients received a dobutamine infusion between T0hrs and T6hrs.

Eighty patients (24.7%) received invasive and/or non-invasive ventilation between ED presentation and T6hrs (Table 4). During the same period, replacement dose steroids, intensive insulin therapy, drotrecogin alfa and renal replacement therapy were initiated in 11.4% (n = 37/324), 5.9% (n = 19/324), 0.6% (n = 2/324) and 2.8% (n = 9/324) of patients respectively.
3.5. Clinical progress

Haemodynamic and laboratory data at T6hrs and T72hrs are given in Table 2. There was a progressive increase in MAP (P < 0.001), CVP (P = 0.02) and SaO2 (P = 0.06) and a progressive decrease in HR (P < 0.001), RR (P < 0.001) and UO (P = 0.02) between T0hrs and T6hrs (RMANOVA). Over the subsequent T6–T72hrs, MAP and SaO2 continued to increase (P < 0.001 for both) and HR and UO decreased (P ≤ 0.001 for both). Lactate and haematocrit also decreased significantly over the same period (P = 0.002 and P = 0.03 respectively).

In patients in whom physiological data was available at T6hrs, 71.1% (n = 160/225) and 91.1% (n = 51/56) respectively achieved a MAP of 65–90 mmHg and a CVP ≥ 8 mmHg at the end of the 6-h period. The time to achieving these resuscitation “end-points” was 2.0 (1.0, 3.0) and 4.0 (2.0, 6.0) h respectively. Most patients also achieved a SaO2 ≥ 93% (n = 206/221, 93.2%), UO ≥ 0.5 ml/kg/h (n = 110/159, 69.8%) and haematocrit ≥ 30% (n = 92/133, 69.2%).

3.6. Outcomes

Following ED discharge, 36.4% (n = 118/324) of patients were transferred directly to ICU and 56.2% (n = 182/324) were transferred to the hospital floor (n = 121/324, 37.5%) or other clinical areas (high dependency, ED observation ward) (Fig. 2). Twenty patients were also transferred from ED directly to the operating theatre (6.2%) and 4 patients (1.2%) died in ED. ED LOS was 6.7 (4.2, 9.9) h and the time between T0hrs and ED discharge was 4.2 (2.0, 7.1) h.

An additional 52 index patients were subsequently transferred from the hospital floor to ICU during the hospital admission (total ICU admission rate 52.4%). Overall, 98 patients (30.2%) required invasive ventilation. Length of ventilation was 74 (21, 156) h. ICU and hospital LOS were 3.7 (1.7, 7.4) and 9.1 (4.1, 16.4) days respectively.

Overall in-hospital mortality was 23.1% (n = 75/324). For patients meeting either the BP or lactate (>4.0 mmol/L) criteria, hospital mortality was 23.0% (n = 48/209) and 26.9% (25/93) respectively (P = 0.56). Thirty-three percent (n = 70/209) of patients meeting the BP criterion received ≥ 20 ml/kg fluid bolus prior to study entry.

Fig. 2. Outcome of 324 patients presenting to the Emergency Department with sepsis and hypoperfusion or septic shock in 32 Australian and New Zealand hospitals. Non-ICU admissions includes direct admissions to the hospital floor (n = 121) or other clinical areas (e.g. high dependency unit, ED observation ward, coronary care) (n = 61), direct transfer to the operating theatre (n = 20) and deaths in ED (n = 4). ED, Emergency department; ICU, Intensive Care Unit.
Hospital mortality for patients with hypotension unresponsive to ≥20 ml/kg fluid and/or meeting the lactate entry criterion was 22.7% (n = 34/150). For non-ICU patients, in-hospital mortality was 21.4% (n = 33/154) and for patients admitted to ICU, overall ICU and in-hospital mortality were 18.8% (n = 32/170) and 24.7% (n = 42/170) respectively; odds ratio and 95% confidence intervals (OR, 95%CI) for mortality 1.20 (0.72, 2.02) (P = 0.48). For patients not admitted directly to ICU from ED (e.g. ICU admission via the hospital floor, operating theatre) (n = 52), in-hospital mortality (n = 9/52, 17%) was lower but not significantly different to patients transferred directly to ICU from ED (n = 33/118, 28%); OR 0.54 (95%CI 0.24, 1.23) (P = 0.14).

Fifty-one patients (15.7%) had a “do-not-resuscitate” order at ED presentation, with 11.8% (n = 6/51) admitted to ICU. In-hospital mortality for patients designated “not-for-resuscitation” (n = 24/51, 47.1%) was higher than for remaining patients (n = 51/273, 18.7%); OR 3.8 (95%CI 2.06, 7.25) (P < 0.0001).

3.7. Discussion

This prospective, multi-centre, observational study of resuscitation practices and outcomes in a cohort of patients presenting to ED with sepsis and hypoperfusion or septic shock suggests that EGDT is not currently practised in ANZ. In particular, routine management in the first 6 h after meeting the criteria for sepsis with hypoperfusion or septic shock did not incorporate integral components of the EGDT algorithm such as continuous ScvO2 monitoring and ScvO2-directed blood transfusion and dobutamine infusion. Moreover, overall in-hospital mortality was considerably lower than standard care mortality in both randomised and non-randomised studies of goal-directed resuscitation.10–12

Traditional resuscitation practices, as exemplified in the current study, characteristically involve early antimicrobial therapy, fluids, vasoactive agents and source control, with the intensity of resuscitation typically being determined by clinical end-points such as BP, UO and CVP. The institution of protocolised early, goal-directed resuscitation does not appear to be integral to the resuscitation of patients with sepsis and hypoperfusion or septic shock in ANZ. Whilst most patients achieved the physiological “EGDT goals” (e.g. MAP, SaO2, UO), no patients received a continuous ScvO2 catheter and only two patients had a single intermittent ScvO2 measurement in the first 6 h after meeting the study entry criteria. Mixed venous oxygen saturation via a pulmonary artery catheter was also uncommon.

A similar lack of implementation of EGDT has been observed in a multi-centre, observational study of 92 ICU patients with community-acquired severe sepsis or septic shock in Finland (Finnsepsis study).3 Only 6.5% of patients received all elements of the Surviving Sepsis Campaign early, goal-directed resuscitation bundle of care. Despite the introduction of a Spanish national education programme directed at implementation of the Surviving Sepsis Campaign 6-h resuscitation and 24-h management bundles for severe sepsis, compliance with the resuscitation guidelines in Spain is also low (10%).4

Our study is unable to inform as to the reasons why EGDT has not been incorporated into current resuscitation practices in ANZ. Concerns about the considerable financial and resource implications of EGDT,13 the internal and external validity of the Rivers’ trial and the potential risks associated with various elements of the EGDT resuscitation protocol such as dobutamine,14,15 aggressive fluid resuscitation16,17 and the liberal use of red cell transfusion to achieve a haematocrit >30%18 may be important factors.

Overall in-hospital mortality in our study, despite the lack of early goal-directed resuscitation, was only 23.1%. For patients admitted directly to ICU from ED, in-hospital mortality was 28%. The observed mortality is consistent with data from the ANZICS APD in which overall in-hospital mortality for medical ICU patients presenting to ED with sepsis or septic shock between 1997 and 2005 was 27.6%.7 A single-centre, retrospective Australian study of >3000 ED patients with severe sepsis also reported that inhospital mortality, in the absence of EGDT, was <30%.19 By way of comparison, reported in-hospital mortality in before–after trials of EGDT ranges from 27 to 44% pre-implementation and 18 to 21% post-introduction.12,20,21 In the Finnsepsis study, in-hospital mortality for patients transferred from ED to ICU with septic shock was 35%.3 However, differences in factors such as time to presentation, co-morbidities, incidence and duration of hypotension and variations in treatment practices limit the ability to draw valid comparisons of outcomes between our study and other single-centre or population-based cohorts.

The third aim of our observational study was to confirm the feasibility of undertaking a randomised controlled trial of EGDT in ANZ. Given the lack of implementation of ScvO2-directed resuscitation, the number of patients meeting study entry criteria and the overall in-hospital mortality, a large, multi-centre study examining the effectiveness of EGDT in ANZ is necessary and achievable.

Our study has certain limitations. The participating sites were self-selected, ANZICS CTG-affiliated sites and not all ANZ hospitals with an ED were included. Accordingly, the results may not accurately reflect clinical practice in the whole population. However, the observed hospital mortality is similar to data from the ANZICS APD which contains information from the majority of ICUs in ANZ.22,23 Moreover, the 32 participating sites included a mix of tertiary-referral, metropolitan, and rural hospitals.

Secondly, although identification and recruitment of all potentially eligible patients may be incomplete or non-representative, the total number of patients admitted directly to ICU in our survey is similar to the number of patients admitted directly to ICU from ED with sepsis or septic shock in the ANZICS APD (3.7 patients/site/3 months vs. 4.7 patients/site/3 months in the 101 ICUs contributing data to the APD in 2005); suggesting that the number of potentially missing patients is limited. Hospital mortality is also similar (23.1% vs. 21.2% respectively).

Thirdly, although the study involves prospective data collection, missing data are inevitable as the time at which measurement was deemed necessary by the treating clinician did not necessarily correlate with the specific study time points (e.g. T6hrs) Nonetheless, hospital outcome was available in 100% of patients and, for most of the physiological variables, data were available in approximately 70% of patients at each of the time points specified over the 72 h study period.

Finally, it is important to note that the study entry criteria are broader than those of the Rivers’ trial and direct comparisons are limited.8 There were no exclusion criteria in our study and the volume of fluid required to meet the BP criterion was considerably smaller than previous sepsis studies. Given that one of the aims of our study was to fully characterise the extent and variety of ANZ resuscitation practices in patients with sepsis, liberal inclusion and exclusion criteria were essential. Nonetheless, in-hospital mortality of patients meeting the BP inclusion criterion (23.0%) is similar to the mortality of all patients admitted to ICU from the ED with sepsis or septic shock in the ANZICS APD for 2005. Moreover, for those patients receiving a larger fluid bolus challenge prior to study entry (≥20 ml/kg) and/or with a lactate ≥4.0 mmol/L, hospital mortality was also similar (22.7%). Whilst it is possible that patients with concurrent acute medical conditions may not have had sepsis as the primary diagnosis, patients had to have a presumed infection to be enrolled, nearly 70% subsequently had a positive microbiological culture, and the incidence of most of the individual concurrent medical conditions was <1%. The three commonest concurrent conditions (“do-not resuscitate order” 15.7%, arrhythmia 12.3% and requirement for immediate surgery 7.4%) are not unexpected in
patients with sepsis and are unlikely to introduce misclassification bias.

3.8. Conclusions

This is the first reported prospective, multi-centre study of resuscitation practices and outcomes in patients presenting to ED with sepsis and hypoperfusion or septic shock in ANZ. The results indicate that protocolised, ScvO2-directed EGDT is not routinely practised in our countries. Nonetheless, hospital mortality compares favourably with reported mortality in international sepsis trials and nationwide multi-centre surveys of resuscitation practices. Given the already low mortality, the potential impact of EGDT in ANZ is uncertain, raising concerns regarding widespread implementation before undertaking a multi-centre, randomised controlled trial. Finally, the current study confirms the feasibility of undertaking such a trial and has provided information critical to the design, including the potential recruitment rate, baseline mortality and appropriate sample size.

Conflict of Interest

None declared.

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Appendix A. Participating sites, principal investigators (PI) and research co-ordinators (RC)

1. Alfred Hospital: D.J. Cooper (PI), R. Neville (RC)
2. Alice Springs Hospital: S. Jacobs (PI)
3. Auckland Hospital: C. McArthur (PI), L. Newby (RC), J. Bell (RC)
5. Cabrini Hospital: F. Hawker (PI)
6. Canberra Hospital: I. Mitchell (PI), A. Bailey (RC)
7. Christchurch Hospital: S. Henderson (PI), J. Mehtrens (RC)
8. Flinders Medical Centre: A. Bersten (PI), E. Ryan (RC), M. O’Callaghan (RC)
9. Fremantle Hospital: I. Jenkins (PI), A. Palermo (RC), E. MacDonald (RC)
10. Geelong Hospital: N. Orford (PI), W. Flintoff (RC)
11. Joondalup Hospital: S. Webb (PI), J. Vibeert (RC)
12. Lismore Base Hospital: C. McAlman (PI), M. McLennan (RC)
13. Liverpool Hospital: M. Parr (PI), S. Micellef (RC)
14. Lyell McEwin Health Service: K. Deshpande (PI), J. Wood (RC)
15. Mackay Hospital: T. Fraser (PI), S. Ogg (RC)
16. Manly Hospital: M. Franks (PI), S. Hoy (RC)
17. Middlemore Hospital: N. Rankin (PI), J. Tai (RC)
18. Nepean Hospital: L. Cole (PI), L. Weisbrodt (RC)
19. Northern Hospital: G. Duke (PI), H. Stergiou (CI)
20. Prince of Wales Hospital: Y. Shehabi (PI), N. Hammond (RC), F. Bass (RC)
21. Prince Charles Hospital: D. Mullaney (PI)
22. Royal Darwin Hospital: D. Stephens (PI), J. Thomas (RC)
23. Royal Melbourne Hospital: J. Cade (PI), C. Chanter (RC)
24. Royal North Shore Hospital: A. Delaney (PI), S. Ankers (RC)
25. Royal Hobart Hospital: A. Turner (PI), T. Field (RC), K. Marsden (RC)
26. Royal Perth Hospital: S. Webb (PI), J. Chamberlain (RC), L. Thomas (RC), A. Gould (RC)
27. Royal Prince Alfred Hospital: D. Gattas (PI), D. Rajbhandari (RC)
28. St George Hospital: J. Myburgh (PI), A. Jovanovska (RC)
29. Sir Charles Gairdner Hospital: S. Baker (PI), B. Roberts (RC)
30. The Queen Elizabeth Hospital: S. Peake (PI), P. Williams (RC)
31. Townsville Hospital: G. Gordon (PI), K. Hutchinson (RC), M. Barrett (RC)
32. Wollongong Hospital: G. Simmons (PI), M. Gales (RC), F. Hill (RC).

References
