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ORIGINAL RESEARCH

Early sepsis in Australia and New Zealand: A point-prevalence study of haemodynamic resuscitation practices

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Abstract

Objective: Optimal resuscitation of sepsis-induced hypotension is uncertain, particularly the role of restrictive fluid strategies, leading to variability in usual practice. The objective of this study is to understand resuscitation practices in patients presenting to ED with early sepsis.

Methods: Design, participants and setting: Prospective, observational, multicentre, single-day, point-prevalence study enrolling adult patients present in 51 Australian and New Zealand ICUs at 10.00 hours, 8 June 2021. Main outcome measures: Site-level data on sepsis policies and patient-level demographic data, presence of sepsis and fluid and vasopressor administration in the first 24 h post-ED presentation.

Results: A total of 722 patients were enrolled. ED was the ICU admission source for 222 of 722 patients (31.2%) and 78 of 222 patients (35%) met the criteria for sepsis within 24 h of ED presentation. Median age of the sepsis cohort was 61 (48–72) years, 58% were male and respiratory infection was the commonest cause (53.8%). The sepsis cohort had a higher severity of illness than the non-sepsis cohort (144/222 patients) and chronic immunocompromise was more common. Of 78 sepsis patients, 55 (71%) received ≥1 fluid boluses with 500 and 1000 mL boluses equally common (both 49%). In the first 24 h, 2335 (1409–3125) mL (25.3 [13.2–42.9] mL/kg) was administered. Vasopressors were administered in 53 of 78 patients (68%) and for 25 patients (47%) administration was peripheral.

Conclusions: ICU patients presenting to the ED with sepsis receive less fluids than current international recommendations and peripheral vasopressor administration is common. This finding supports the conduct of clinical trials evaluating optimal fluid dose and vasopressor timing for early sepsis-induced hypotension.

Key findings

- ICU patients presenting to the ED with sepsis receive less fluids than current international recommendations.
- Peripheral vasopressor administration is common in patients presenting to the ED with sepsis.
- Study finding supports conduct of trials evaluating optimal fluid dose and vasopressor timing for early sepsis-induced hypotension.

Key words: *fluids, haemodynamic resuscitation, sepsis, vasopressors.*

Introduction

The key principles of early sepsis management include prompt identification, antimicrobial therapy, source

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control and haemodynamic resuscitation with intravenous fluids and vasopressors to restore organ perfusion. The Surviving Sepsis Campaign (SSC) guidelines recommend at least 30 mL/kg of fluid within 3 h as first-line therapy for sepsis-induced hypoperfusion or septic shock.[1] Following 'adequate' fluid resuscitation, vasopressors, preferably noradrenaline, are recommended for refractory shock with initial infusion peripherally to prevent administration delays. Nonetheless, evidence underpinning the SSC guidelines for early haemodynamic resuscitation is low quality and recommendations are, accordingly, graded as weak.

Recently there has been debate over optimal fluid dose and timing of vasopressor administration. Purported advantages of restrictive fluid practices, in combination with earlier vasopressors, include more rapid restoration of blood pressure and organ perfusion, reduced tissue oedema and endothelial injury and decreased acute renal injury associated with rapid fluid bolus administration.[2–4] Data from observational and retrospective studies have described worse clinical outcomes with high-volume fluid resuscitation.[5,6] Interpretation of these studies is limited by factors such as indicator bias and unknown/unmeasured confounders. A mortality benefit with early vasopressor administration has also been reported.[7] Moreover, in a large, observational study evaluating a state-wide sepsis protocol in patients presenting to the ED, in-hospital mortality was not associated with time to completion of an initial fluid bolus up to 12 h after the presentation.[8]

Several small, randomised, pilot studies evaluating a conservative fluid approach have demonstrated the feasibility and safety of a restrictive fluid strategy in septic shock. An association with improved clinical outcomes compared with usual care has been reported.[9–11] A large, multicentre, randomised trial of fluid restriction for septic shock patients admitted to ICU has recently been completed (Conservative versus Liberal Approach to Fluid Therapy of Septic Shock in Intensive Care [CLASSIC]).[12] Ninety-day mortality was not different between treatment groups; albeit fluid separation after the first 24 h was less than 1000 mL.

Notably, the CLASSIC intervention was delivered for the duration of the ICU stay. In contrast, there are three large, multicentre, open-label randomised trials currently evaluating a restricted fluids/early vasopressor strategy wherein the intervention period is limited to the early resuscitation period in patients presenting to the ED with sepsis-induced hypotension (CLOVERS conducted in the United States, ARISE FLUIDS Australia and New Zealand, EVIS United Kingdom). The CLOVERS trial was recently ceased for futility after 1563 of a planned 2320 patients were enrolled. Fluid dose and vasopressor administration were different between the restrictive and fluid groups, but hospital mortality was not different (14.0% *vs* 14.9%).[13]

As background for conducting the ARISE FLUIDS trial (NCT04569942), we undertook a point prevalence survey to understand the initial haemodynamic resuscitation of sepsis patients admitted to the ICU from the ED. The survey was undertaken on a single day (June 8 or June 23, 2021) in collaboration with the Australian and New Zealand Intensive Care Society Clinical Trials Group (CTG)-endorsed Point Prevalence Program (PPP) (Study Day 13) and The George Institute for Global Health. The aim was to determine the

TABLE 1. *Hospital characteristics*

Characteristic	$n = 51$
ICU CICM accreditation, *n* (%)†	
Level III	34 (66.7)
Level II	16 (31.4)
Level I	1 (2.0)
Hospital system, *n* (%)‡	
Public	45 (88.2)
Private	5 (9.8)
Combined public	1 (2.0)
Hospital location, *n* (%)§	
Metropolitan	46 (90.2)
Rural	5 (9.8)
Documented sepsis identification/management policy, *n* (%)	37 (75.5)¶
Sepsis identification tool	35 (68.6)
Fluid management	33 (64.7)
Vasopressor administration	23 (45.1)
All protocol elements	21 (41.2)
No protocol elements	0 (0)
Documented peripheral vasopressor administration policy, *n* (%)	32 (65.3)¶

†ICU level classified according to the CICM. ‡Public hospital systems funded by local, state and federal governments; private hospitals include health care providers owned and managed privately. §Metropolitan and rural locations classified according to the Rural, Remote and Metropolitan Area Australian Institute of Health and Welfare classification system. ¶Data available for 49 hospitals. CICM, College of Intensive Care Medicine.

presence of sepsis protocols across Australian and New Zealand hospitals and, in adult patients admitted to ICU from the ED with sepsis, to describe fluid and vasopressor practices in the first 24-h period post-ED presentation.

Methods

All Australian and New Zealand CTG-affiliated ICUs were invited to participate in this prospective, cross-sectional, observational audit. A waiver for individual patient consent was obtained from either the National Mutual Acceptance Low or Negligible Risk pathway approved by the lead ethics committee (Sydney Local Health District) (most sites) or from participating site local ethics committees.

TABLE 2. *Characteristics of all patients admitted direct from ED to ICU*

Variable	Sepsis ($n = 78$)	Non-sepsis ($n = 144$)	*P*-value
Age, years, median (IQR)	61 (48–72)	58 (44–73)	0.805
Male sex, *n* (%)	45 (58)	89 (62)	0.550
Weight, kg, median (IQR)	84 (70–101)	84 (70–100)	0.941
Chronic co-morbidities, *n* (%)†			
Liver	2 (2.6)	7 (4.9)	0.499
Renal	3 (3.8)	4 (2.8)	0.699
Cardiovascular	1 (1.3)	6/143 (4.2)	0.426
Respiratory	10 (12.8)	10 (6.9)	0.144
Immunocompromised	15 (19.2)	9 (6.3)	0.003
APACHE II, median (IQR)	20.5 (15–26)	16 (10–22)	<0.001
ICU admission diagnosis, *n* (%)‡			<0.001
Sepsis or sepsis with shock	24 (30.7)	2 (1.4)	
Respiratory	29 (37.2)	22 (15.3)	
Cardiovascular	9 (11.5)	32 (22.2)	
Gastro-intestinal	4 (5.1)	5 (3.5)	
Renal	1 (1.3)	6 (4.2)	
Cellulitis/soft tissue	2 (2.6)	1 (0.7)	
Neurologic	8 (10.3)	19 (13.2)	
Metabolic	1 (1.3)	18 (12.5)	
Trauma	0 (0)	36 (25.0)	
Other	0 (0)	3 (2.1)	
Infection source, *n* (%)§			
Respiratory	42 (53.8)		
Intra-abdominal	10 (12.8)		
Urinary tract	3 (3.8)		
Skin/soft tissue	6 (7.7)		
Central nervous system	3 (3.8)		
Blood	9 (12)		
Other	4 (5.1)		
Unknown	1 (1.3)		
Lactate, mmol/L¶, median (IQR)	2.8 (1.7–5.7)		

†Chronic comorbidities defined according to APACHE III chronic health conditions. ‡ICU admission diagnosis according to APACHE III codes as per treating clinician. Sepsis or sepsis with shock included APACHE III codes 501 (non-urinary sepsis), 502 (urinary sepsis), 503 (non-urinary sepsis with shock) and 504 (urinary sepsis with shock). §Main source of infection in the 24 h from ED presentation in the sepsis cohort. ¶Highest serum lactate in the 24 h from ED presentation in the sepsis cohort (not collected for non-sepsis cohort). APACHE, Acute Physiology and Chronic Health Evaluation; IQR, interquartile range.

Hospital-level data were collected from all sites including ICU category, the presence of a documented policy for vasopressor administration via the peripheral route and the presence of a protocol or guideline for the identification and/or management of patients with sepsis, particularly a sepsis identification tool, fluid management (boluses, type of fluid), and vasopressor route.

Individual-level data on all patients 16 years or older and present in participating ICUs at a 10-am census point on study day was collected. Data included demographics (age, sex and weight), ICU admission source and diagnosis, Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores, co-morbidities, admission and discharge information and vital status 28 days after the study day.

Additional data were collected on those patients admitted directly to the ICU from the ED and meeting the criteria for sepsis within the 24 h from ED presentation ('sepsis cohort'). Sepsis criteria were defined as a focus of infection and ≥2 Systemic Inflammatory Response Syndrome (SIRS) criteria (core temperature >38°C or <36°C; white cell count $>12 \times 10^9$/L or $<4 \times 10^9$/L or >10% immature bands; heart rate >90 beats per minute; respiratory rate >20 breaths per minute or $PaCO_2$ <32 mmHg or mechanical ventilation). Data for the sepsis cohort included infection source and, in the 24 h from ED presentation, highest serum lactate, fluid administration including boluses (defined as ≥250 mL intravenous fluid given in <1 h) and vasopressor route, type and duration.

Data from each participating site were de-identified and entered into an electronic data capture system (REDCap; Vanderbilt University, Nashville, TN, USA)[14,15] hosted at The George Institute for Global Health, New South Wales.

Statistical analysis

Variables are presented as proportions for categorical data and median (interquartile range [IQR]) for continuous data. Differences between the sepsis and non-sepsis cohorts were analysed using χ^2 test for categorical variables and the student's *t*-test or rank-sum test for continuous variables as appropriate.

Missing data are reported if >10% and no imputation undertaken. Given the observational nature of the study, *P*-values are provided for distributional perspective, no adjustment is made for multiple comparisons and no 'statistical significance' implied. All analyses were undertaken in Stata MP/17 (StataCorp LLC, College Station, TX, USA).

Results

Hospital characteristics

Fifty-one metropolitan and rural hospitals participated, of which 45 (88.2%) were public hospitals (Table 1). Thirty-seven of 49 hospital EDs and/or ICUs (75.5%) had a documented policy for identification and/or management of sepsis with a sepsis identification tool and fluid management the most common individual protocol elements (Table 1). Only 21 hospitals (41.2%) incorporated all three policy elements (identification, fluid management and vasopressor administration route). The presence of a policy was greater in public (81.4%) *versus* private (20.0%) hospitals ($P = 0.01$) but not between metropolitan *versus* rural hospitals ($P = 0.32$) (Table S2). A sepsis identification tool was more common in public (73.3%) *versus* private (20.0%) hospitals. Other elements of the sepsis protocol were similar across hospital systems and locations (Table S2).

A documented policy for vasopressor administration via a peripheral venous cannula was present in 32 of 49 (65.3%) hospital EDs and/or ICUs (Table 1). The presence of a policy was similar across public *versus* private hospitals ($P > 0.99$) and metropolitan *versus* rural hospitals ($P = 0.15$) (Table S2).

Patient characteristics

A total of 712 patients were present in the ICU at 10 am on study day and enrolled in the survey. Of these, 222 patients (31.2%) were admitted direct to ICU from ED. Seventy-eight of the 222 patients (35%) had a defined focus of infection and ≥2 SIRS criteria within 24 h of ED presentation (sepsis cohort). Patient characteristics for the sepsis and non-sepsis cohorts with an ED admission source are displayed in Table 2 and Table S3. The sepsis cohort had a higher severity of illness than the non-sepsis cohort (APACHE II score 20 [15–26] *versus* 16 [10–22]; $P < 0.001$) and chronic immunocompromise was more common in the sepsis cohort (19.2% *versus* 6.3%; $P < 0.001$). The commonest source of infection in the sepsis cohort was respiratory (54%).

Hospital mortality was similar between the sepsis (15.4%) and non-sepsis cohorts (13.2%) ($P = 0.65$). However, hospital duration of stay was longer in the sepsis *versus* non-sepsis cohort; 298 (193–459) *versus* 237 (112–377) hours ($P = 0.016$) (Table 3).

TABLE 3. *Outcomes of all patients admitted direct from ED to ICU*

Variable	Sepsis ($n = 78$)	Non-sepsis ($n = 144$)	*P*-value
ICU mortality, *n* (%)	10 (12.8)	15 (10.4)	0.589
Hospital mortality, *n* (%)	12 (15.4)	19 (13.2)	0.653
ICU duration of stay, hours, median (IQR)	135 (91–409)	108 (45–251)	0.002
Hospital duration of stay, hours, median (IQR)	298 (193–459)	237 (112–377)	0.016

TABLE 4. *Haemodynamic resuscitation of sepsis cohort*

Variable	Sepsis ($n = 78$)
Received i.v. fluid bolus, *n* (%)	55 (71)
Number of i.v. fluid boluses, *n* (%)	55
1	15 (27)
2	12 (22)
3	8 (15)
4	7 (13)
5	6 (11)
6 or more	7 (13)
i.v. bolus volume, mL, *n* (%)	55
250	16 (29)
500	27 (49)
750	2 (4)
1000	27 (49)
Other	8 (15)
Total i.v. fluid volume†, median (IQR)	
mL	2335 (1409–3125)
mL/kg	25.3 (13.2–42.9)
Vasopressors, *n* (%)	53 (68)
Vasopressor type, *n* (%)‡	
Noradrenaline	45 (85)
Adrenaline	9 (17)
Metaraminol	20 (38)
Vasopressin	12 (23)
Other	3 (5.7)
Vasopressor route, *n* (%)‡	
CVC	42 (79)
PVC	25 (47)
Vasopressor duration, hours, median (IQR)	
Via CVC	19.8 (9.0–23.0)
Via PVC	5.0 (2.0–12.0)

†Total volume includes boluses and maintenance (but not medication volumes); weight actual (estimated or measured). ‡Total greater than 100% as some patients received more than one vasopressor type or route. CVC, central venous catheter; i.v., intravenous; PVC, peripheral venous catheter.

Haemodynamic resuscitation in the sepsis cohort

Fifty-five patients (71%) in the sepsis cohort received ≥1 i.v. fluid boluses in the first 24 h after ED presentation (Table 4). A single bolus was the most common number of boluses received (27%) and 500 or 1000 mL were the commonest volumes administered (49% for both). In seven patients (13%), ≥6 boluses were administered. The total volume of i.v. fluid administered in the first 24 h was 2335 (1409–3125) mL or 25.3 (13.2–42.9) mL/kg. Fifty-three patients (68%) received a vasopressor in the first 24 h after ED presentation and noradrenaline was the commonest agent administered (85%). Twenty-five patients (47%) received a vasopressor peripherally, 11 of whom (21%) also received a vasopressor centrally. Duration of vasopressor infusion via the central and peripheral routes was 19.8 (9.0–23.0) and 5.0 (2.0–12.0) hours, respectively.

Discussion

This Australian and New Zealand point-prevalence study was conducted in mainly public level III metropolitan hospitals with two thirds of sites having a documented policy for sepsis identification and fluid management. A policy for vasopressor route was less common. Approximately one-third of critically ill patients for whom ED was the ICU admission source fulfilled the sepsis criteria in the first 24 h from ED presentation and most received one to three i.v. fluid boluses of 500–1000 mL through the same period. The majority also received a vasopressor infusion, predominantly noradrenaline, with both central and peripheral administration routes commonly reported.

Recently, there has been a growing interest among researchers and clinicians in more restrictive fluid practices combined with early vasopressor administration for the initial resuscitation of sepsis-induced hypoperfusion and septic shock. Observational studies, administrative databases and meta-analyses have suggested worse clinically important outcomes with large volume fluid resuscitation and positive fluid balance, including increased mortality and decreased ventilator-free days.[16–20] However, a recent meta-analysis found no difference in all-cause mortality between lower *versus* higher fluid volumes during initial sepsis management.[21] Notably, many of the studies included in these meta-analyses are small, single-centre trials with serious risk of bias. Finally, a randomised trial of protocolised resuscitation of adult patients with septic shock has reported increased in-hospital mortality associated with increased fluid administration over the first 6 h.[22]

The total volume of intravenous fluid administered in the first 24 h for the sepsis cohort (25 mL/kg) is less

than the 2021 adult SSC guidelines recommendation of 'at least 30 mL/kg of i.v. crystalloid' as first-line treatment for sepsis-induced hypoperfusion or septic shock and may suggest a trend to adopting more restrictive practices in Australia and New Zealand.[1] Similarly, in the CLASSIC trial the standard fluid group received 1.7 L of i.v. fluid in the first 24 h (approximately 22 mL/kg).[12] Conversely, the volume of fluid the CLOVERS liberal fluid group received (3.4 L) is more consistent with current guidelines.[13] Notably, evidence supporting the fluid dose recommendation is low quality and graded as weak. Nonetheless, despite this lack of robust data, the suggested volume of fluid resuscitation has increased over time from a fixed 500–1000 mL in 2004[23] to the current recommendation.[1]

Several small, randomised, feasibility studies have evaluated restrictive fluid resuscitation combined with early vasopressor administration to maintain blood pressure and organ perfusion in patients presenting to the ED with sepsis-induced hypotension. The REFRESH trial reported that fluid separation was achieved at 6 h in the conservative fluid *versus* usual care group, the time to vasopressor initiation was shorter and the proportion of patients receiving a vasopressor in ED was increased. The CENSER trial found that early fixed-dose norepinephrine (0.05 μg/kg/min for 24 h) *versus* usual care was associated with decreased cardiovascular complications (new-onset atrial arrhythmia and cardiogenic pulmonary oedema) and a trend to decreased 28-day mortality.

Nonetheless, two recent, large, multi-centre randomised trials evaluating a restrictive *versus* liberal fluid strategy in patients with sepsis-induced hypotension have failed to demonstrate a mortality difference, despite achieving treatment separation for both fluid and vasopressor administration. Important distinctions between these trials and the ARISE FLUIDS trial preclude translating these results into Australian and New Zealand practice, including differences in patient population, usual practice, duration of the intervention and baseline mortality.

Integral to prompt vasopressor receipt in ED and evaluation of a conservative fluid approach for initial resuscitation is the ability to administer a vasopressor via the peripheral venous route. In the CLOVERS trial, only 27% of the restrictive group had a central line inserted within the first 72 h, despite 59% receiving vasopressors. In our study, we found that 68% of patients received a vasopressor and, in 85% of those, noradrenaline was administered. Moreover, in nearly 50% of patients receiving a vasopressor, infusion was peripherally. These findings are consistent with other studies reporting that peripheral vasopressor infusion for a limited period is common, safe and associated with a shorter time to initiation.[24]

Strengths and limitations

This 1-day cross-sectional point prevalence study represents a snapshot of haemodynamic resuscitation practices in early sepsis and the results must be interpreted with caution. However, the survey was conducted in over 50 metropolitan and rural public and private hospitals across Australia and New Zealand using robust methods to ensure the accuracy of data monitoring procedures.[25] Notably, while 35% of patients admitted direct to the ICU from ED were identified by trained research coordinators as meeting the pre-defined survey inclusion criteria for sepsis, in less than one-third of those patients the ICU admission APACHE III diagnostic code extracted from the patient's medical record was sepsis or sepsis with shock. This apparent underestimation of community-onset sepsis case detection in hospital administrative databases, as compared with clinical review of medical records, is consistent with previous reports.[26]

While most participating sites reported having documented policies that facilitate timely identification and haemodynamic resuscitation, specific policy details were not collected in this survey. Nonetheless, the wide variation in fluid management practices, ranging from no fluid boluses in approximately one-third of patients to ≥6 boluses in some patients indicates significant scope to support a randomised trial evaluating restricted fluids and early vasopressors *versus* a more liberal approach to fluid management in patients presenting to the ED with septic shock. The finding that vasopressors were administered peripherally in approximately 50% of the sepsis cohort also supports the feasibility of conducting a trial of early vasopressors. This finding is consistent with a previous report by our group whereby 42% of patients presenting to the ED with early septic shock received a vasopressor via the peripheral route.[27] Moreover, peripheral vasopressor administration was associated with a shorter time to initiation and a shorter duration of stay in the ED.

Conclusion

This point-prevalence study represents a snapshot of current Australian and New Zealand practices for the initial resuscitation of patients presenting to the ED with sepsis-induced hypotension and admitted to the ICU. We found that most hospitals have a sepsis policy *in situ*, vasopressors are commonly administered via the peripheral route and the average volume of fluid administered in the first 24 h is less than the current international recommendations. Understanding usual care is essential for the design, conduct and interpretation of the ARISE FLUID trials and other trials evaluating a restrictive *versus* liberal fluid strategy in this patient population.

Competing interests

SM is a section editor for *Emergency Medicine Australasia*.

Data availability statement

Requests for data should be made to the Corresponding Author. Data are available based on the data sharing policy of The George Institute for Global Health.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web site:

Table S1. Participating sites and investigators.
Table S2. Sepsis and peripheral vasopressor policies.
Table S3. Characteristics of all patients admitted direct from ED to ICU.