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ORIGINAL RESEARCH

Hemodynamic Resuscitation Characteristics of Emergency Department Patients with Sepsis and Hypotension who are and are not Admitted to ICU; a Prospective Cross-sectional Study

Rebecca Vella[1], Philip Jones[1,2], Gerben Keijzers[3,4,5]*

1. Gold Cost University Hospital, Gold Coast, QLD, Australia
2. Department of Emergency Medicine, Logan Hospital, QLD, Australia
3. Department of Emergency Medicine, Gold Coast University Hospital, Gold Coast, QLD, Australia
4. School of Medicine, Bond University, Gold Coast, QLD, Australia
5. School of Medicine, Griffith University, Gold Coast, QLD, Australia

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Abstract: **Introduction:** There is an evidence–practice gap in the optimal timing and volume of intravenous fluid as well as vasopressor administration in managing patients with sepsis. This study aimed to explore current hemodynamic resuscitation practice in emergency department (ED) for patients with sepsis and hypotension. **Methods:** This is a sub-analysis of the prospective multicentre ARISE FLUIDS observational study, which was conducted in 70 EDs across Australia and New Zealand. Baseline characteristics, as well as ED management and outcome of sepsis patients were compared between patients who were and were not admitted to intensive care unit (ICU) or high dependency unit (HDU). **Results:** A total of 587 patients with a median age of 65 years and even sex distribution (49% female) were available for analysis. Almost two-thirds of patients with sepsis (63.2%, n=371) were not admitted to ICU/HDU and were given lower intravenous (IV) fluid volumes over 24-hours, compared to those receiving critical care (4077ml vs. 5421ml, p<0.001). Patients not admitted to an ICU/HDU had a lower Acute Physiology And Chronic Health Evaluation (APACHE) II score (median 14 vs. 18, P<0.001) and serum lactate level (1.8 vs. 2.8 mmol/L, P<0.001) compared to those admitted to ICU/HDU and 5.9% received a vasopressor infusion in the first 24-hours. Females, patients aged <65 years, and those with urosepsis or sepsis of non-respiratory origin received a greater volume of IV fluids. **Conclusions:** Almost two-thirds of patients were not admitted to ICU/HDU. In patients not admitted to ICU/HDU, 1 in 17 received a vasopressor infusion during their ED or early hospital stay. Patients not admitted to ICU/HDU received less fluid in the first 24 hours than those who were. Greater resuscitation fluid volumes were independently associated with female sex, age <65 years, higher lactate levels, and urinary or non-respiratory source of sepsis.

Keywords: Sepsis; Infusions, intravenous; Emergency service, hospital; Intensive care units

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1. Introduction

The administration of intravenous (IV) fluids and vasopressors is widely accepted in the management of sepsis and hypotension to improve end-organ perfusion, but there is uncertainty about the optimal approach for this hemodynamic support. One option is liberal fluid resuscitation driven by clinical and physiological goals (1), with the surviving sepsis campaign recommending administration of at least 30 mg/kg of IV crystalloid within 3 hours of presentation for patients presenting with hypo-perfusion or septic shock (2). This recommendation, however, is based on low level of evidence (2) and only 50% of hemodynamically unstable patients respond to fluid challenges, a value that dramatically reduces with prolonged fluid administration (3–5). Further contributing to the clinical uncertainty associated with this approach, several multicentre trials comparing usual care to early goal-directed fluid resuscitation failed to demonstrate the benefit of the latter on mortality (6–8). The alternative to liberal fluid therapy is early commencement of vasopressors, which is suggested to be beneficial in addressing hypoperfusion and improving outcomes (9–12).

Collectively these evidence gaps suggest more data are needed to understand the optimal timing and volume of fluid and vasopressor administration in managing patients with

***Corresponding Author:** Gerben Keijzers; Gold Coast Hospital and Health Service, 1 Hospital Boulevard, Southport, QLD, 4215 Email: gerben.keijzers@health.qld.gov.au. Tel: +61 7 5687 5204, ORCID: https://orcid.org/0000-0003-1100-4552.

sepsis. Prior investigations aiming to address this have primarily focused on patients in critical care settings (9–12) and underrepresent resuscitation practices of patients with sepsis who are not admitted to an intensive care unit (ICU) or high dependency unit (HDU). This further contributes to clinical uncertainty as the majority of patients who develop sepsis are not admitted to an ICU/HDU, and are managed in regular hospital wards (13,14). Since these patients are admitted to a wide variety of wards under the care of a diverse range of clinicians, practice may vary widely. As such, describing patients with sepsis who are managed in a general ward stands to expand the scope of knowledge on fluid resuscitation practices in managing patients with sepsis and identify opportunities to improve patient outcomes.

The objectives of this study were to describe demographic and clinical features as well as the specifics of hemodynamic management of patients with sepsis and hypotension who were not admitted to ICU/HDU and compare with those who are admitted to ICU/HDU.

2. Methods

2.1. Study design and setting

The current study is a sub-analysis of the prospective multicentre ARISE FLUIDS observational study (15) that was conducted in 70 EDs across Australia and New Zealand. The full methodology of the ARISE FLUIDS observational study has previously been published (16). Participating sites self-nominated a consecutive 30-day data collection period between 13 September 2018 and 15 December 2018, with all data collection finalised by 13 January 2019.

Ethics and governance approval was obtained from all participating sites, and this ARISE FLUIDS sub-analysis adheres to the STROBE guidelines for reporting observational studies.

2.2. Participants

Patients were included in the ARISE FLUIDS observational study if they met the following criteria at the time of presentation to the ED: i) aged ≥18 years, ii) there was a clinical suspicion of infection, iii) IV antimicrobial therapy was commenced in the ED, and iv) observed to have systolic blood pressure <100mmHg at any time in the ED despite at least 1000mL IV fluid resuscitation, where fluids had to be given as bolus(es) of at least 500mL, within 60 minute per bolus, including pre-hospital fluids. Patients were ineligible for inclusion if i) hypotension was suspected to be due to a cause other than sepsis, ii) they had confirmed or suspected pregnancy, iii) they had comorbidities that precluded admission to an ICU/HDU for vasopressor admission, iv) death was imminent or inevitable as deemed by the treating clinician, v) life expectancy was <90 days due to an underlying illness or vi) they transferred from another acute care hospital. These exclusion criteria were part of the parent study, which informed the design of a multicentre RCT (https://www.arisefluids.org/synopsis) needing patients to be potentially eligible for vasopressor therapy.

2.3. Data gathering

A detailed case report form was completed for all patients meeting the inclusion criteria, allowing for the collection of demographics, clinical, and biochemical variables, as well as information on management practices and outcomes. To ensure patient privacy was maintained, local site investigators entered de-identified data into REDcap, a purpose-built web-based database hosted by the Australian and New Zealand Intensive Care – Research Centre.

2.4. Outcomes

The primary outcome measure was admission to an ICU/HDU. Patients were deemed to have been admitted to ICU/HDU if they were transferred to these units directly from ED or within 24-hours of presenting to the ED irrespective of their initial disposition. Demographic and clinical variables, as well as ED management (including fluid resuscitation volumes, vasopressor administration, type and duration, and time to commence antibiotics) were compared between patients with sepsis who were and were not admitted to ICU/HDU.

Fluid volume administered in patients who were not admitted to the ICU/HDU was a key secondary outcome measure. Associations were assessed between demographic and clinical variables and fluid administered, including total fluid administered from pre-hospital to 24 hours post-enrolment (pre-T0-T24), fluid administered from pre-hospital to 6 hours post-enrolment (pre-T0-T6) and fluid administered from 6 hours post-enrolment to 24 hours post-enrolment (T6-T24).

2.5. Statistical analysis

No formal sample size calculation was performed as this was a secondary analysis of data from a previous study. Continuous variables are reported as either mean and standard deviation (SD) or median and interquartile range (IQR), following assessment of normality. Categorical variables are presented as proportions (%). Group differences between continuous variables were assessed using t-test or analysis of variance, whilst Wilcoxon Rank Sum test was used to assess variables with marked departures from normality. Differences between categorical variables were assessed using Chi-2 test. Multivariable regression analysis was performed with backwards stepwise selection of variables, with retention significance level of $p < 0.10$. Regression model diagnostics included assessment for linearity, homoscedasticity, normality of residuals and multicollinearity. Missing data was assumed to be missing at random and was not imputed. All statistical analyses were performed using STATA 14.2.

3. Results

3.1. Baseline characteristics of studied cases

A total of 591 patients were enrolled in the parent study, with 375 (63.45%) not being admitted to ICU/HDU. Of the patients who were not admitted to ICU/HDU, 4 (1.1%) died in the ED. Data for these individuals were not included in this secondary analysis leaving 371 patients.

Table 1 compares the baseline characteristics of studied sepsis patients between cases with and without ICU/HDU admission. Patients who were not admitted to ICU/HDU were of a similar age (median age 64.5 (46.7-77.2) v 67.2 (55.8-76.9) years; p = 0.06) and had a similar sex distribution (50.9% vs 45.8% female; p = 0.22) compared to the patients who were admitted to ICU/HDU. Patients not admitted to ICU/HDU had lower severity of disease indicators (median Acute Physiology And Chronic Health Evaluation (APACHE) II score 14 (9-18) vs. 18 (14-22); p = <0.001 and lactate 1.8mmol/L (1.3-2.7mmol/L) vs. 2.8 mmol/L (1.7-4.4mmol/L); p = <0.001) and less derangement in biochemical parameters, including pH (p = <0.001), international normalized ratio (INR) (p = 0.004), blood urea nitrogen (p = <0.001), creatinine (p = <0.001), bilirubin (p = 0.003), and albumin (p = <0.001). Patients not admitted to ICU/HDU had lower proportions of cardiac (28.3% vs 38.0%; p = 0.02) or respiratory (22.4% vs 30.1%; p = 0.04) comorbidities.

3.2. Fluid resuscitation

Patients who were not admitted to ICU/HDU received less IV fluids than those who were admitted (mean 24-hour total IV fluid administration 4077 ± 1716ml vs. 5421 ± 2095ml; p < 0.01) (Table 2; Figure 1A). This observation of non-ICU/HDU patients receiving smaller volumes of IV fluids was also seen in the pre-T0-T6 (mean IV fluid volume 2955 ± 1243ml vs 3873 ± 1474ml; p < 0.001) and T6-T24 (mean IV fluid volume 1121 ± 1065ml vs 1553 ± 1132ml; p < 0.001) time periods.

3.3. Vasopressor administration

Of the patients not admitted to ICU/HDU, one in 17 were administered vasopressors in the first 24-hours of care, whilst almost three-quarters of patients admitted to ICU/HDU required vasopressor administration (5.9% vs 71.3%; p = < 0.001; Table 2). Vasopressors were commonly commenced in the ED for patients who were admitted to a general ward (19/22; 86.4%) and to ICU/HDU (115/154; 74.7%). If vasopressors were administered, noradrenaline and metaraminol were the most commonly used agents in patients admitted to both general ward (noradrenaline 5.1%; metaraminol 3.0%) and ICU/HDU (noradrenaline 53.2%; metaraminol 28.7%), with patients at times requiring more than one vasopressor. On average patients not admitted to ICU/HDU required vasopressor infusions for a shorter period than those who were admitted to a high acuity unit (median duration 3.8 (2.0-31.8) vs 29.8 (16.7-51) hours; p <0.001; table 2).

3.4. Antibiotic administration and mortality

Patients who were not admitted to ICU/HDU had a longer time to antibiotic commencement compared to those who were admitted (median time of 94 (47-176) vs 60 (34-118) minutes; p < 0.001; Table 2). Mortality rates for patients not admitted to ICU/HDU were also lower in hospital (2.4% vs 11.1%; p < 0.001) and within the first 28 days (1.9% vs 10.1%; p < 0.001), when compared to patients who were admitted to ICU/HDU (Table 2).

3.5. Volume of fluid administered to patients not admitted to an ICU/HDU

In patients who were not admitted to ICU/HDU, females and patients <65 years received more IV fluids up to 6 hours post-enrolment than males and patients aged >65 years (3130 ± 1273ml vs 2773 ± 1187ml and 3131 ± 1314ml vs 2774 ± 1140ml, respectively (Table 3).

Non-ICU/HDU patients with a systolic blood pressure (SBP) <90mmHg had a greater volume of IV fluids administered up to 6 hours post-enrolment compared to those with an SBP>90 mmHg (3214 ± 1293ml vs 2881 ± 1220ml). Greater volumes of IV fluids were also administered to non-ICU patients with elevated lactate levels between 6-24 hours post-enrolment (lactate >2mmol/L 1234 ± 1074ml vs <2mmol/L 978 ± 1040ml; lactate >4mmol/L 1398 ± 1179ml vs <4mmol/L 989 ± 982ml). Likewise, non-ICU patients who commenced vasopressors in the ED were given greater volumes of IV fluids up to 6 hours post-enrolment (4091 ± 2081ml vs 2899 ± 1164ml) and in the first 24 hours (5118 ± 2367ml vs 3971 ± 1669ml) compared to those who did not receive vasopressors (Table 3).

The source of sepsis was associated with the volume of IV fluids administered at all time points. Non-ICU patients with sepsis of respiratory origin had smaller volumes of IV fluids administered up to 6 hours post-enrolment (2675 ± 1166ml vs 3092 ± 1258ml), between 6 to 24 hours post-enrolment (854 ± 944ml vs 1250 ± 1098ml) and in the first 24 hours (3487 ± 1729ml vs 4300 ± 1594ml) compared to patients with sepsis of non-respiratory origin (Table 3). Inversely, non-ICU patients with sepsis of urinary origin had larger volumes of IV fluids administered up to 6 hours post-enrolment (3215 ± 1448ml vs 2855 ± 1143ml), between 6 to 24 hours post-enrolment (1361 ± 1137ml vs 1027 ± 1023ml) and in the first 24 hours (4576 ± 1788ml vs 3827 ± 1660ml) compared to sepsis of non-urinary origin (Table 3).

3.6. Independent predictors of fluid resuscitation volume

Multivariable regression analysis indicated that higher age and respiratory source of sepsis were associated with lower volumes of fluid administered in the pre-T0 to T24 period, whereas urinary source of sepsis, lactate greater than 2 and vasopressor requirement predicted higher fluid volume administration (Table 4). Examples of predicted fluid volume administered by age is displayed in Figure 1B.

4. Discussion

We describe current practice of hemodynamic management in patients with sepsis and hypotension in Australian and New Zealand emergency departments. Almost two-thirds (63.2%) of patients with sepsis were not admitted to ICU/HDU. As expected (13,17,18), patients not admitted to ICU/HDU had lower mortality rates, lower lactate levels, lower APACHE scores and received smaller volumes of IV fluid in the first 24 hours. Six percent of these patients received a vasopressor infusion in the first 24 hours of care, however the duration of vasopressor infusion was significantly shorter than administered for ICU/HDU patients.

Whilst nearly two-thirds of the study population were admitted to a general ward for management of sepsis, this is lower than previously published data (13,14). For example, in a nationwide mixed methods longitudinal study, 77.7% of patients admitted to all Australian public hospitals with sepsis were not admitted to an ICU for cares (14). Similarly in a multicentre observational study, 88% of patients who were diagnosed with sepsis were not admitted for ICU care (13). Key differences between enrolment and exclusion criteria likely explain the differences in ICU/HDU admission rates, as patients required a systolic blood pressure of <100mmHg despite administration of 1 litre of fluid to be eligible for inclusion in the current investigation. Further, patients not appropriate for ICU/HDU admission at enrolment were excluded. Of the patients not admitted to ICU/HDU for management of sepsis, 5.9% required vasopressor infusions in the first 24 hours of care, and 86.4% of these patients had the vasopressor infusion commenced in ED. It is unclear if the commencement of vasopressors in the ED for these patients was instrumental in preventing admission to ICU/HDU or if they could have been managed without. The low number of these patients prevent further granular interrogation, but future research may consider focusing on predictors for this subgroup and their characteristics and outcomes.

Amongst patients not admitted to ICU/HDU in our study, patients aged <65 years and those with urosepsis or sepsis of non-respiratory origin received greater volumes of IV fluids. Somewhat fitting with clinical expectations, previous studies have shown younger age is associated with increased likelihood and greater volumes of IV fluid administration in septic patients (19,20) possibly due to concerns that liberal fluid loading could be detrimental in elderly patients due to age-related diastolic dysfunction that occurs in this population (21,22). Likewise, patients with urosepsis received more liberal administration of IV fluids, whilst sepsis of respiratory origin was associated with more conservative administration of intravenous fluids across all time points. These observations are in keeping with the aim to limit the possibility of pulmonary oedema in patients already susceptible to the development of acute respiratory distress syndrome. Overall, these observations fit with the paradigm that fluid resuscitation in sepsis is often an individualised approach directed by the treating team and adjudicated based on age, severity of disease indicators, and source of infection.

As/Since patients not admitted to ICU/HDU could have been admitted to a variety of wards, including medical and surgical subspecialities, a variation in the volume of fluids administered in the first 24 hours of care may have been expected. Notably, the low mortality rate in this cohort suggests no clear correlation between variations in fluid volume administered and mortality, and likely reflects purposeful clinical practice.

5. Limitations

An important limitation of the current paper was that this is a post-hoc analysis of the ARISE FLUIDS observational study and thus was not designed or powered to compare differences between patients with sepsis who were and were not admitted to ICU/HDU. Since patients who were not deemed appropriate for intensive care (i.e. due to an existing advanced health care directive, significant co-morbidities) were excluded, the mortality rate was low. Additionally, the criteria used to define ICU/HDU admission may not have captured all patients. It is possible some patients were admitted from the ED to the ward and then admitted to ICU/HDU after 24 hours. Furthermore, ICU/HDU admission criteria may vary between hospitals due to patient and system factors, and the management of patients admitted to a ward will also vary per hospital due to different staff skill mix. Although we are unable to comment on the overall size and direction of any effect of these factors, our data represents real world practice. Missing data was present for multiple outcome and predictor variables; however, this generally comprised less than 5% of data and is thus thought unlikely to significantly bias the results. Causality cannot be inferred due to the observational nature of the study and significance testing was not adjusted for multiplicity; thus, findings are best interpreted as hypothesis generating.

6. Conclusions

This study provides insight into the haemodynamic resuscitation of patients presenting to Australian and New Zealand emergency departments with sepsis and hypotension. Almost two-thirds of patients did not require ICU/HDU admission. Of the patients not admitted to ICU/HDU, 1 in 17 received a vasopressor infusion during their ED or early hospital stay. Patients not admitted to ICU/HDU received less fluid in the first 24 hours than those who were. Greater resuscitation fluid volumes were associated with female sex, age <65 years, higher lactate levels, and urinary or non-respiratory causes of sepsis, suggesting an individualised approach to the quantity of fluids administered.

7. Declarations

7.1. Acknowledgments

We acknowledge the ARISE FLUIDS observational Steering committee and study sites.

7.2. Conflict of interest

The authors have no conflicts of interests to declare.

7.3. Funding

The parent study received funding from the Emergency Medicine Foundation. This sub-study was unfunded.

7.4. Authors' contribution

RV: Analysis of data, drafting and revision of manuscript and intellectual discussions
PJ: Conception and study design, acquisition and analysis of data, revision of manuscript and intellectual discussions
GK: Conception and study design, acquisition and analysis of data, revision of manuscript and intellectual discussions
All authors read and approved the final version of manuscript.

7.5. Data availability

Data is available on reasonable request to the corresponding author.

7.6. Using artificial inteligence chatbots

No AI chatbots were used for any part of this study.

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Table 1: Comparing the demographics, clinical, and biochemical variables of sepsis patients between cases who were and were not admitted to ICU/HDU

Variable	Admitted to ICU/HDU		P-value
	No (n = 371)	Yes (n = 216)	
Female			
n (%)	189 (50.9)	99 (45.8)	0.22
Body weight, kg			
Median (IQR)	70.9 (60.0 – 86.0)	79.5 (65.0 – 90.0)	0.01
Age, years			
Median (IQR)	64.5 (46.7 – 77.2)	67.2 (55.8 – 76.9)	0.06
>65 years	183 (49.3)	119 (55.1)	0.18
Vitals			
Temperature, oC	37.6 (36.8 – 38.4)	37.6 (36.6 – 38.5)	0.82
Pulse, /minutes	96 (82 – 110)	105 (86 – 120)	<0.001
SBP, mmHg,	96 (90 - 104)	90 (81 - 97)	<0.001
DBP, mmHg	57 (50 – 64)	54 (48 – 60)	<0.001
RR, BrPM	20 (18-24)	23 (19 – 28)	<0.001
SpO2, %	97 (95 – 98)	96 (93 – 98)	0.003
Glasgow coma scale score			
Median (IQR)	15 (15 - 15)	15 (15 - 15)	<0.001
APACHE II score			
Median (IQR)	14 (9-18)	18 (14-22)	<0.001
Septic origin, n (%)			
Respiratory	121 (32.6)	76 (35.2)	0.11
Urinary	101 (27.2)	44 (20.4)	
Skin / soft tissue	37 (10.0)	29 (13.4)	
Blood	9 (2.4)	5 (2.3)	
Abdominal / pelvic	47 (12.7)	33 (15.3)	
Neurological	3 (0.8)	3 (1.4)	
Bone / joint	2 (0.5)	5 (2.3)	
Other	5 (1.3)	2 (0.9)	
Unidentified	43 (11.6)	17 (7.9)	
Multiple sources	0 (0)	2 (0.9)	
Comorbidities, n (%)			
Cardiac	105 (28.3)	82 (38.0)	0.02
Respiratory	83 (22.4)	65 (30.1)	0.04
Renal	18 (4.9)	9 (4.2)	0.70
Hospital type, n (%)			
Metro	77 (20.8)	49 (22.7)	0.15
Tertiary	211 (56.9)	109 (50.5)	
Regional	72 (19.4)	44 (20.4)	
Private	11 (3.0)	14 (6.5)	
Haematological			
Haemoglobin, g/L	127 (111 - 138)	128 (111 - 143)	0.27
WBC, $x10^9$/L	12.5 (8.3 – 17.0)	11.5 (6.9 – 16.4)	0.13
Platelets, $x10^9$/L	221 (165 – 278)	190 (139 – 259)	0.001
INR	1.2 (1.1 – 1.4)	1.3 (1.2 – 1.5)	0.004
Blood gas			
pH	7.41 (7.37 – 7.45)	7.37 (7.31 – 7.42)	<0.001
pCO2, torr	40 (35 – 45)	39 (34 – 46)	0.46
FiO2,	0.21 (0.21 – 0.21)	0.21 (0.21 – 0.32)	<0.001
Lactate, mmol/L	1.8 (1.3 – 2.7)	2.8 (1.7 – 4.4)	<0.001
>2 mmol/L, n (%)	209 (56.3)	159 (73.6)	<0.001
>4 mmol/L, n (%)	122 (32.9)	88 (40.7)	0.056
Bicarbonate, mmol/L	25 (23 – 27)	22 (19 - 26)	<0.001
Metabolic			
Glucose, mmol/L	6.7 (5.6 – 8.1)	6.6 (5.5 – 8.2)	0.43
Sodium, mmol/L	136 (133 - 138)	135 (132 - 139)	0.18
Chloride, mmol/L	101 (98 - 104)	100 (96 - 103)	0.01

Table 1: Comparing the demographics, clinical, and biochemical variables of sepsis patients between cases who were and were not admitted to ICU/HDU (continue)

Variable	Admitted to ICU/HDU		P-value
	No (n = 371)	Yes (n = 216)	
Potassium, mmol/L	4 (3.6 – 4.3)	4 (3.6 – 4.6)	0.29
Creatinine, µmol/L	86 (66 - 122)	126 (90 – 197)	<0.001
BUN, mmol/L	6.5 (4.5 – 9.6)	9.7 (6.6 – 15.6)	<0.001
Bilirubin, µmol/L	13 (9 – 20)	16 (10 – 24)	0.003
Albumin, g/L	33 (29 – 38)	30 (26 – 35)	<0.001

Data are presented as median (interquartile range (IQR)) or frequency (%). BrPM: breaths per minute;
BUN: blood urea nitrogen; DBP: diastolic blood pressure; FiO2: fraction of inspired oxygen; INR: international normalised ratio;
IQR: interquartile range; pCO2: partial pressure of carbon dioxide; RR: respiratory rate; SBP: systolic blood pressure;
SpO2: oxygen saturation; WBC: white blood cells; ICU/HDU: intensive care unit/high dependency unit; APACHE II: Acute Physiology And Chronic Health Evaluation II.

Table 2: Comparing the management and outcomes of sepsis patients who were and were not admitted to an ICU/HDU

Variable	Admitted to ICU/HDU		Difference (95% CI)	P-value
	No (n = 371)	Yes (n = 216)		
Fluid administration, mL				
0-6 hours	2955 (1243)	3873 (1474)	-918 (-1143 to -693)	<0.001
6-24 hours	1121 (1065)	1553 (1132)	-432 (-618 to -247)	<0.001
First 24 hours	4077 (1716)	5421 (2095)	-1343 (-1661 to -1026)	<0.001
Vasopressor administration in ED, n (%)				
Yes	19 (5.1)	115 (53.2)	-	<0.001
Fluid volume prior to vasopressor infusion, mL				
Mean (SD)	2355 (1493)	2492 (1251)	-136 (-766 to 494)	0.67
Vasopressors commenced prior to 24 hours				
N (%)	22 (5.9)	154 (71.3)	-	<0.001
Time from triage to vasopressor infusion, hours				
Median (IQR)	5.25 (4.0 – 11.3)	4.55 (2.5 – 7.7)	-	0.09
Time from T0 to vasopressor infusion, hours				
Median (IQR)	2.8 (1.2 – 4.7)	2.3 (0.7 – 5.0)	-	0.50
Duration of vasopressor infusion, hours				
Median (IQR)	3.8 (1.95 – 31.8)	29.8 (16.7 – 51.0)	-	<0.001
Type and duration of individual vasopressors				
Noradrenaline				
N (%)	13 (3.5)	125 (57.8)	-	<0.001
Duration, hours	2.15 (0.3 – 3.8)	29.4 (14.6 – 50.2)	-	<0.001
Adrenaline				
N (%)	1 (0.3)	13 (6.0)		<0.001
Duration, hours	0	11 (2.5 – 22.7)	-	N/A
Metaraminol				
N (%)	11 (3.0)	62 (28.7)		<0.001
Duration, hours	26.6 (5.8 –59.0)	5.2 (2.8-22.7)	-	0.10
Vasopressin				
N (%)	1 (0.3)	18 (8.3)		<0.001
Duration, hours	0	21.2 (16.3-36.0)	-	N/A
Dobutamine				
N (%)	1 (0.3)	3 (1.4)		0.11
Duration, hours	0	419.5 (419.5-419.5)	-	N/A
Antibiotics				
Commenced in ED	371 (100)	216 (100)	-	N/A
Time to start	94 (47 – 176)	60 (34 – 118)	-	<0.001
Outcome				
Died in hospital	9/371 (2.4)	23/208 (11.1)	-	<0.001
Died within 28 days	7/370 (1.9)	21/208 (10.1)	-	<0.001

Data are presented as median (IQR), mean (standard deviation), or number (%). CI: confidence interval;
ED: emergency department; ICU/HDU: intensive care unit / high dependency unit; IQR: interquartile range; mL: millilitres;
min: minutes; N/A: not applicable.

Table 3: The influence of demographic and clinical variables on the volume of intravenous fluids administered to patients with sepsis who were not admitted to an ICU/HDU

Variables	N	Fluid administration time					
		0 – 6 hours	P	6 – 24 hours	P	First 24 hours	P
Sex							
Male	182	2773 (2598 to 2948)	–	1082 (925 to 1239)		3812 (3562 to 4062)	
Female	189	3130 (2946 to 3314)	–	1159 (1002 to 1316)		4239 (3991 to 4486)	
Difference		-357 (-610 to -103)	0.006	-77 (-298 to 144)	0.50	-427 (-777 to -76)	0.02
Age							
>= 65 years	183	2774 (2606 to 2942)		1049 (908 to 1191)		3791 (3559 to 4024)	
< 65 years	188	3131 (2940 to 3321)		1190 (1020 to 1360)		4261 (3998 to 4523)	
Difference		-357 (-610 to 103)	0.006	-141 (-362 to 80)	0.21	-469 (-819 to -119)	0.009
SBP							
>90 mmHg	85	2881 (2738 to 3023)		1127 (999 to 1254)		3970 (3772 to 4168)	
<90 mmHg	286	3214 (2928 to 3500)		1103 (877 to 1329)		4237 (3847 to 4627)	
Difference		-334 (-640 to -27)	0.03	24 (-241 to 288)	0.86	-267 (-690 to 155)	0.21
GCS							
>15	298	2952 (2806 to 3097)		1127 (1001 to 1252)		4036 (3835 to 4236)	
<15	66	2971 (2705 to 3237)		1095 (870 to 1321)		4002 (3640 to 4365)	
Difference		-19 (-356 to 317)	0.91	31 (-260 to 322)	0.83	33 (-431 to 498)	0.89
Septic source							
Non-Respiratory	249	3092 (2934 to 3250)		1250 (1111 to 1389)		4300 (4083 to 4517)	
Respiratory	122	2675 (2464 to 2886)		854 (681 to 1027)		3487 (3200 to 3774)	
Difference		417 (148 to 687)	0.003	-396 (163 to 628)	0.001	813 (445 to 1181)	<0.001
Non-urinary	267	2855 (2717 to 2994)		1027 (902 to 1153)		3827 (3627 to 4027)	
Urinary	101	3215 (2930 to 3501)		1361 (1136 to 1585)		4576 (4223 to 4929)	
Difference		-360 (-644 to -76)	0.01	-334 (-577 to -90)	0.008	-749 (-1139 to -360)	<0.001
Comorbidities							
No-Cardiac	264	2971 (2822 to 3121)		1171 (1033 to 1309)		4096 (3887 to 4306)	
Cardiac	107	2913 (2664 to 3163)		995 (820 to 1170)		3862 (3530 to 4194)	
Difference		58 (-226 to 342)	0.69	177 (-68 to 421)	0.16	235 (-156 to 626)	0.24
No-Respiratory	287	2955 (2806 to 3104)		1154 (1024 to 1284)		4067 (3862 to 4273)	
Respiratory	84	2954 (2703 to 3206)		1005 (800 to 1211)		3900 (3557 to 4243)	
Difference		0.72 (-306 to 307)	1.00	149 (-117 to 415)	0.27	168 (-256 to 591)	0.44
No-renal	353	2945 (2816 to 3073)		1127 (1015 to 1240)		4027 (3849 to 4205)	
Renal	18	3152 (2294 to 4011)		994 (366 to 1622)		4091 (3853 to 4206)	
Difference		-208 (-799 to 383)	0.49	134 (-387 to 655)	0.61	-64 (-886 to 757)	0.88
Hospital type							
Non-tertiary	161	2896 (2687 to 3104)		1098 (917 to 1278)		3923 (3640 to 4206)	
Tertiary	210	2999 (2837 to 3160)		1138 (999 to 1278)		4110 (3886 to 4336)	
Difference		-103 (-362 to 156)	0.43	-41 (-265 to 183)	0.72	-188 (-444 to 168)	0.30
pH							
>7.3	345	2930 (2799 to 3062)		1129 (1016 to 1242)		4010 (3830 to 4190)	
<7.3	20	3383 (2820 to 3947)		988 (428 to 1549)		4372 (3441 to 5302)	
Difference		-453 (-1014 to 108)	0.11	141 (-342 to 623)	0.57	-361 (-1142 to 419)	0.36
Lactate (mmol/L)							
>2	209	3058 (2882 to 3234)		1234 (1084 to 1382)		4244 (3997 to 4492)	
<2	162	2823 (2637 to 3009)		978 (815 to 1142)		3754 (3510 to 3999)	
Difference		235 (-22 to 492)	0.73	256 (34 to 477)	0.02	490 (137 to 842)	0.007
>4	122	2886 (2675 to 3098)		1398 (1181 to 1615)		4237 (3902 to 4572)	
<4	249	2988 (2827 to 3149)		989 (865 to 1113)		3929 (3722 to 4135)	
Difference		-102 (-375 to 172)	0.47	409 (177 to 642)	<0.001	308 (-67 to 683)	0.11
Time to antibiotics							
>60 minutes	249	2986 (2830 to 3142)		1159 (1021 to 1298)		4093 (3874 to 4312)	
<60 minutes	122	2887 (2660 to 3114)		1038 (854 to 1222)		3890 (3593 to 4188)	
Difference		99 (-177 to 375)	0.48	122 (-116 to 360)	0.32	203 (-179 to 584)	0.30
Vasopressor commenced in ED							
No	351	2899 (2777 to 3022)		1113 (1000 to 1227)		3971 (3796 to 4146)	
Yes	19	4091 (3021 to 5161)		1276 (778 to 1775)		5119 (3978 to 6259)	
Difference		-1192 (-1787 to -596)	<0.001	-163 (-684 to -358)	0.54	-1147 (-1939 to -356)	0.005

Data are presented with 95% confidence interval (CI). Data missing for fluid volume administered for 6 patients for preT0-T6 time period, 12 patients for T6-T24 time period and 1 patient in preT0-T24 time period. ED: emergency department; GCS: Glasgow coma scale; SBP: systolic blood pressure.

Table 4: Multivariable linear regression model of fluid administered pre-T0-T24 for sepsis patients with hypotension in ED

Variables	Coefficient	95% CI	P-value
Age* (years)	-13.4ml	-21.8 to -5.1ml	0.002
Respiratory source	-378ml	-779 to 22ml	0.064
Urinary source	512ml	98 to 926ml	0.015
Lactate 2mmol/L or greater	477ml	140 to 814ml	0.006
Vasopressor commenced	1267ml	493 to 2041ml	0.001
Constant	4498ml	3932 to 5063ml	–
$R^2 = 0.116$			

* Age incorporated as a continuous variable. CI: Confidence Interval; ED: emergency department.

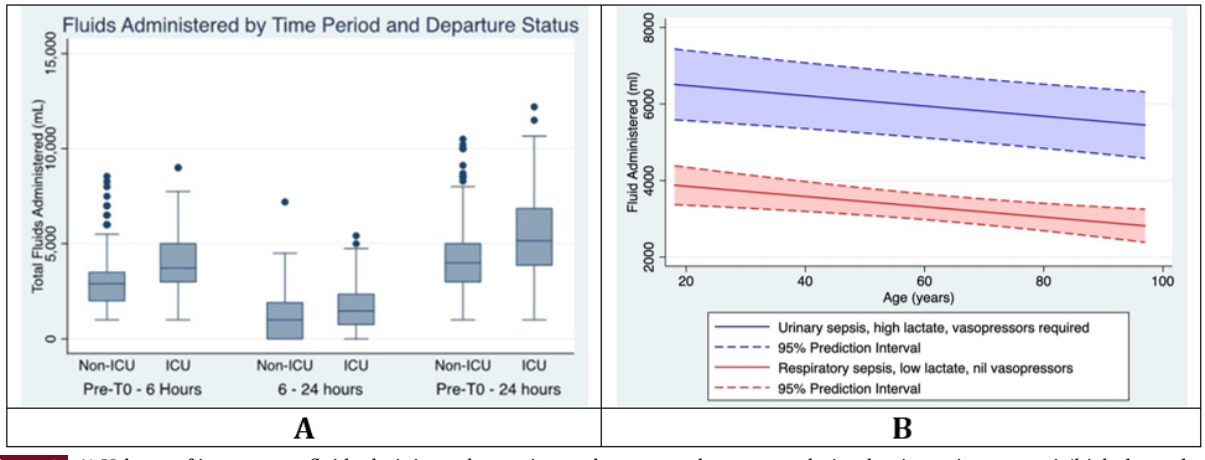

Figure 1: A) Volume of intravenous fluid administered to patients who were and were not admitted to intensive care unit/high dependency unit (ICU/HDU) prior to study enrolment and up to the first 6 hours post enrolment (Pre-T0 - T6), between 6 to 24 hours after enrolment (T6 – T24) and in the first 24 hours after enrolment in the study (Pre-T0–T24). B) Predicted fluids administered by age for patients with high predicted fluids (urinary sepsis, lactate greater than 2, and vasopressors commenced) and low predicted fluids (respiratory sepsis, lactate less than 2, nil vasopressors).