Epidemiology of secondary fluid bolus therapy for infection-associated hypotension

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ABSTRACT

Objective: Fluid bolus therapy (FBT) is a common therapy for hypotensive sepsis, but no studies have compared primary FBT (in the first 6 hours after presentation to the emergency department [ED]) with secondary FBT (6–24 hours after presentation to the ED). We aimed to describe the patterns of use, physiological sequelae and outcomes of patients with hypotensive sepsis who were treated with primary FBT or combined primary and secondary FBT (secondary FBT).

Design, setting and patients: A retrospective observational study of patients with hypotensive sepsis presenting to the ED of a tertiary hospital from 1 January to 31 December 2010.

Results: We studied 100 consecutive eligible patients (primary FBT, *n* = 52; secondary FBT, *n* = 48). Secondary FBT occurred in the ward (*n* = 31) or in the intensive care unit (*n* = 17). More patients receiving secondary FBT had sepsis with undefined focus or septic shock (*P* = 0.005, *P* = 0.0001, respectively), and fewer patients receiving secondary FBT had pneumonia (*P* = 0.0004). At 24 hours, the use of secondary FBT was similar for patients admitted to the ward and the ICU, and represented about 40% of all secondary fluids given. The volume of any bolus was greater during primary resuscitation, and the size of physiological changes associated with FBT diminished with time. The mortality rate at 28 days was 27%, and was similar for ward and ICU admissions.

Conclusions: Secondary FBT is given to about half of patients presenting with hypotensive sepsis, takes place in wards more often than in the ICU and delivers a significant proportion of overall fluids, but is associated with limited changes in measured physiological variables.

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Fluid bolus therapy (FBT) is a ubiquitous treatment in patients with hypotensive severe sepsis,[1] but there is no controlled evidence that such FBT leads to patient-centred benefits.[2] Further, FBT may contribute to a positive fluid balance, which has been associated with poor outcome.[3] Thus, the value of FBT in the management of patients with hypotensive severe sepsis remains unclear.[4,5]

Studies reporting FBT in hypotensive severe sepsis often focus on the first few hours after presentation (primary FBT).[6,7] Some data are also available on the FBT delivered after the initial primary resuscitation,[8] particularly in the intensive care unit.[9-14] However, no studies have investigated FBT given between 6 and 24 hours after presentation (secondary FBT) in patients with hypotensive severe sepsis who were initially treated in the emergency department (ED). There are no data on how such secondary FBT delivered in general wards compares with secondary FBT delivered to patients admitted to the ICU; and how such therapy might relate to clinically measured physiological variables. This knowledge is important to help clinicians judge the risk–benefit ratio of FBT and to design interventional studies to test its efficacy.

We hypothesised that, in patients with hypotensive sepsis, secondary FBT is common, irrespective of admission to a general ward or the ICU; that such FBT is a significant component of overall fluid therapy; and that secondary FBT is not associated with significantly altered physiological variables. To test these hypotheses, we investigated the patterns of use, frequency, extent and physiological associations of secondary FBT in a tertiary university hospital.

Methods

Our study was approved by the Human Research Ethics Committee of the Austin Hospital, which waived the need for informed consent because of the retrospective, non-interventional nature of the study. The study was conducted at the Austin Hospital, Melbourne, Australia, a large tertiary hospital.

We performed a retrospective observational study as previously described.[15] Our aim was to assess at least 100 patients with infection-associated hypotension who had undergone primary FBT in the ED.

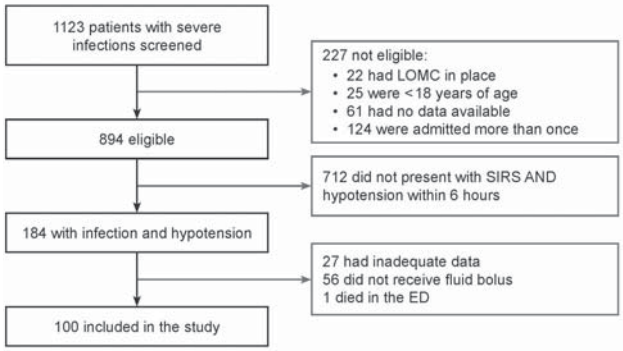
We consecutively screened all patients whose records had the appropriate discharge diagnostic codes, and who were admitted via the ED from 1 January to 31 December 2010, for hypotension within 6 hours of admission and fluid administration, until we identified 100 patients who could be included in our study.[15] Screening lists were organised consecutively according to discharge diagnosis. Once 100 patients were included, our data acquisition stopped.

Criteria

We used a modified version of the severe sepsis consensus definitions[16,17] to include patients who had:

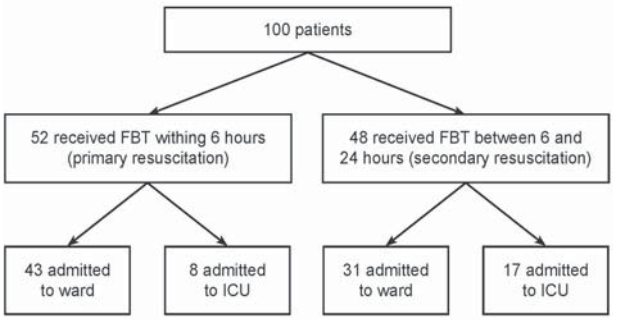
- two or more systemic inflammatory response syndrome criteria; and
- suspected infection on arrival at the ED (subsequently confirmed as discharge diagnosis); and

Figure 1. Patient selection flowchart*



LOMC = limitations of medical care. SIRS = systemic inflammatory response syndrome. ED = emergency department. * 124 patients represented repeated admissions but only the first admission was used. Bolus was defined as fluid administered > 250 mL/h.

Figure 2. Flow of patients through study



FBT = fluid bolus therapy. ICU = intensive care unit.

- systolic blood pressure (SBP) recorded as < 100 mmHg at least once within 6 hours of arrival at the ED; and
- received FBT.

We defined primary FBT as administration of intravenous fluid > 250 mL at a rate of > 250 mL/h within 6 hours of the patient arriving at the ED, and secondary FBT as administration of intravenous fluid > 250 mL/h 6–24 hours after the patient arriving at the ED.

Exclusion criteria included an order for limitation of medical therapy within 24 hours of hospital admission, a lack of detailed data on FBT, a lack of detailed data on vital signs, or age < 18 years.

Data

We extracted data from the medical records, including physiological data, biochemical test results, data on FBT events and data on overall fluids administered within 24 hours and before and after FBT. We also took data from patient notes, including demographic data, quick Sequential (Sepsis-related) Organ Failure Assessment (qSOFA) scores,[18] comorbidities, vital status at 28 days, length of ICU and hospital stays and the focus of sepsis. We recorded the amount, type and duration of infusion for each episode of FBT. Time frames were set to 6 hours to ensure that observation of vital signs and recording of fluid charts were done at least once per time interval, according to the hospital's policy. Finally, we collected data on other key therapeutic interventions (eg, mechanical ventilation, vasopressor support and renal replacement therapy).

Statistics

We used the Mann–Whitney test for group comparisons, the Wilcoxon matched-pairs test for within-group analysis, Friedman analysis of variance for within-group analysis of repeated measurements, and the *Z* test for testing proportions. We used Statistica, version 12 (StatSoft). A *P* value of < 0.05 was considered significant.

Results

We screened 1123 patients and studied 101 consecutive patients (Figure 1). One patient died shortly after arrival and was not included in the analysis because the study required assessment over 24 hours. Of the study patients, 52 were given primary FBT only and 48 patients received primary and secondary FBT. Seventy-four patients were admitted to the ward and 26 patients were admitted to the ICU (Figure 2). The median time for recording physiological data after secondary FBT was 0 minutes (interquartile range [IQR], 0–30 minutes).

Demographic data

The characteristics of the primary and secondary FBT study cohorts are shown in Table 1, and the characteristics of patients admitted to the ward or the ICU are shown in Table 2. Patients in the secondary FBT group and patients admitted to the ICU had higher qSOFA scores. Secondary FBT was more common in patients who were later admitted to the ICU, in patients without an identified focus of sepsis and in patients with septic shock, but was less common in patients with pneumonia. In the subgroup of patients treated with secondary FBT, patients admitted to the ICU had more severe forms of sepsis (see Appendix, Table S1, online at cicm.org.au/Resources/Publications/Journal).

Fluid therapy

The total volume of fluid administered was higher for patients who received secondary FBT. In these patients, the total fluid given for primary FBT was less than the fluid given for secondary FBT (Table 3). In contrast, for patients who only received primary FBT, the fluid volume given in the first 6 hours was more than the total fluid administered between 6 and 24 hours.

The ratio of FBT fluid to total fluid given (FBT and maintenance fluid) during the first 6 hours after arrival at

Table 1. Demographic data for patients receiving primary versus secondary fluid bolus therapy

Demographic variable	Both groups	Primary (*n* = 52)	Secondary (*n* = 48)	*P* (primary v secondary)
Men, *n* (%)	54 (54%)	25 (48%)	29 (60%)	NS
Median age, years (IQR)	67 (53–82)	62 (53–85)	68 (52–79)	–
Admitted from ED to ward, *n* (%)	48 (48%)	43 (83%)	31 (65%)	NS
Admitted from ED to ICU, *n* (%)	–	9 (15%)	17 (35%)	0.0203
Did not leave ED, *n* (%)	–	1 (2%)	–	–
Maximum qSOFA score after admission, *n* (%)				0.0255
1	36 (36%)	23 (44%)	13 (27%)	–
2	52 (52%)	26 (50%)	26 (54%)	–
3	12 (12%)	3 (6%)	9 (19%)	–
Alive at 28 days, *n* (%)	74 (74%)	38 (73%)	36 (73%)	NS
Diagnosis at discharge, *n* (%)				
Sepsis with no specified focus	65 (65%)	27 (52%)	38 (79%)	0.0047
Pneumonia	24 (24%)	18 (35%)	6 (12%)	0.0071
Abdominal sepsis	3 (3%)	2 (6%)	1 (2%)	NS
Urosepsis	8 (8%)	4 (8%)	4 (8%)	NS
Comorbidities, *n* (%)				
Congestive heart failure	17 (17%)	11 (21%)	6 (13%)	NS
Coronary artery disease	17 (17%)	7 (13%)	10 (21%)	NS
Chronic obstructive pulmonary disease	16 (16%)	8 (15%)	8 (17%)	NS
Diabetes mellitus	12 (12%)	4 (8%)	8 (17%)	NS
HIV	0	0	0	–
Hypertension	33 (33%)	21 (40%)	12 (25%)	NS
Cirrhosis	8 (8%)	7 (13%)	1 (2%)	0.0395
History of cancer	19 (19%)	11 (21%)	8 (17%)	NS
Neurological disease	23 (23%)	11 (27%)	9 (19%)	NS
Chronic renal failure	44 (44%)	27 (52%)	17 (35%)	NS
History of smoking	34 (34%)	13 (25%)	21 (44%)	0.0453
Details of sepsis, *n* (%)				
Pneumonia	50 (50%)	29 (56%)	21 (44%)	NS
Urosepsis	12 (12%)	7 (13%)	5 (10%)	NS
Peritonitis	2 (2%)	1 (2%)	1 (2%)	NS
Intra-abdominal infection	15 (15%)	7 (13%)	8 (17%)	NS
Abscess of arm or leg	2 (2%)	1 (2%)	1 (2%)	NS
Other infection	21 (21%)	7 (13%)	14 (29%)	0.0484
Severe sepsis	65 (65%)	43 (83%)	22 (46%)	0.0001
Septic shock	35 (35%)	9 (17%)	26 (54%)	0.0001
Positive blood culture	18 (18%)	13 (25%)	5 (10%)	NS
Antibiotics within 6 hours	82 (82%)	41 (78%)	41 (85%)	NS

NS = not significant. IQR = interquartile range. ED = emergency department. ICU = intensive care unit. qSOFA = quick Sequential (Sepsis-related) Organ Failure Assessment (range, 0–6).

the ED was an average of 77% in the primary FBT group and 91% in the secondary FBT group. In patients admitted to the ICU, fluid intake in the 0–6-hour period was 1.3 times the amount given in the 6–24-hour period. This is in contrast to patients admitted to the ward, for whom fluid intake in the 0–6-hour period was 0.9 times the amount given in the 6–24-hour period (Table 4). The ratio of volumes of overall FBT fluid to total fluid administered was similar in patients admitted to the ward versus the ICU, with FBT constituting an average of 86% v 89%, respectively, of the

Table 2. Demographic data of patients, by ward or ICU admission

Demographic variable	Both groups	Admitted to ward (*n* = 74)	Admitted to ICU (*n* = 26)	*P* (ward v ICU)
Men, *n* (%)	54 (54%)	39 (52%)	15 (60%)	NS
Median age, years (IQR)	67 (53–82)	66 (52–83)	68 (54–78)	NS
Secondary fluid bolus therapy given, *n* (%)	48 (48%)	31 (42%)	17 (68%)	0.0245
Maximum qSOFA score after admission, *n* (%)				
1	36 (36%)	34 (46%)	2 (8%)	–
2	52 (52%)	38 (51%)	13 (50%)	–
3	12 (12%)	2 (3%)	11 (42%)	–
Alive at 28 days, *n* (%)	74 (74%)	56 (76%)	18 (72%)	NS
Diagnosis at discharge, *n* (%)				
Sepsis without specified focus	65 (65%)	47 (64%)	18 (72%)	NS
Pneumonia	24 (24%)	20 (27%)	4 (16%)	NS
Abdominal sepsis	3 (3%)	2 (3%)	1 (4%)	NS
Urosepsis	8 (8%)	5 (7%)	3 (12%)	NS
Comorbidities, *n* (%)				
Congestive heart failure	17 (17%)	14 (19%)	3 (12%)	NS
Coronary artery disease	17 (17%)	13 (18%)	4 (16%)	NS
Chronic obstructive pulmonary disease	16 (16%)	12 (16%)	4 (16%)	NS
Diabetes mellitus	12 (12%)	10 (14%)	1 (4%)	NS
HIV	0	0	0	NS
Hypertension	33 (33%)	27 (36%)	5 (20%)	NS
Cirrhosis	8 (8%)	5 (7%)	3 (12%)	NS
History of cancer	19 (19%)	17 (23%)	2 (8%)	NS
Neurological disease	23 (23%)	18 (24%)	5 (20%)	NS
Chronic renal failure	44 (44%)	30 (41%)	14 (56%)	NS
History of smoking	34 (34%)	26 (35%)	8 (32%)	NS
Sepsis details, *n* (%)				
Pneumonia	50 (50%)	40 (54%)	9 (36%)	NS
Urosepsis	12 (12%)	8 (11%)	4 (16%)	NS
Peritonitis	2 (2%)	1 (1%)	1 (4%)	NS
Intra-abdominal infection	15 (15%)	7 (9%)	8 (32%)	0.0237
Abscess of arm or leg	2 (2%)	2 (3%)	0	–
Other infection	21 (21%)	17 (23%)	4 (16%)	NS
Severe sepsis	65 (65%)	63 (85%)	10 (40%)	< 0.00001
Septic shock	35 (35%)	16 (21%)	18 (72%)	< 0.00001
Positive blood culture	18 (18%)	13 (18%)	5 (20%)	NS
Antibiotics within 6 hours	82 (82%)	60 (81%)	21 (84%)	NS

ICU = intensive care unit. NS = not significant. IQR = interquartile range. qSOFA = quick Sequential (Sepsis-related) Organ Failure Assessment (range, 0–6).

total fluid given. The ratio of FBT fluid to total fluid volume administered decreased in both groups of patients over time ($P < 0.001$ for both groups).

Patients receiving secondary FBT were given less fluid if they were admitted to the ward during the first 6 hours, but ended up with similar volumes of fluids at 24 hours, despite fewer episodes of FBT (Appendix, Table S2).

Changes in vital signs

The volume of any first and second bolus was greater during primary than secondary resuscitation (Table 5). The number of fluid boluses and the physiological and noradrenaline dose changes are shown in Table 5, Figure 3 and Figure 4. These table and figures show that the number and volumes of fluid boluses, physiological changes and changes in

Table 3. Total fluid administration, patients undergoing primary versus secondary fluid bolus therapy*

Time from ED arrival, h	Fluid administered	Volume, mL (median [IQR])		
		Primary FBT	Secondary FBT	$P^{\dagger}$
0–6	Total	1550 (1000–2215)	1660 (865–2575)	
	Crystalloids	1450 (1000–2030)	1660 (865–2575)	
	Colloids	0 (0–0)	0 (0–0)	
	Packed red blood cells	0 (0–0)	0 (0–0)	
	Fresh frozen plasma	0 (0–0)	0 (0–0)	
	Platelets	0 (0–0)	0 (0–0)	
	As boluses	1000 (625–2000)	1000 (725–2000)	
	Ratio FBT fluid:total fluid administered, at 0–6 h	77% (53%–100%)	91% (62%–100%)	
6–12	Total	750 (555–1005)	1325 (830–2000)	< 0.001
	Crystalloids	750 (550–1000)	1270 (740–2000)	
	Colloids	0 (0–0)	0 (0–0)	
	Packed red blood cells	0 (0–0)	0 (0–0)	
	Fresh frozen plasma	0 (0–0)	0 (0–0)	
	Platelets	0 (0–0)	0 (0–0)	
	As boluses	0 (0–0)	0 (0–1500)	< 0.001
	Ratio FBT fluid:total fluid administered, at 6–12 h	0 (0–0)	50% (0–84%)	< 0.001
12–18	Total	500 (270–730)	810 (420–1460)	< 0.001
	Crystalloids	500 (270–730)	770 (470–1410)	
	Colloids	0 (0–0)	0 (0–100)	
	Packed red blood cells	0 (0–0)	0 (0–0)	
	Fresh frozen plasma	0 (0–0)	0 (0–0)	
	Platelets	0 (0–0)	0 (0–0)	
	As boluses	0 (0–0)	0 (0–0)	
	Ratio FBT fluid:total fluid administered, at 12–18 h	0 (0–0)	0 (0–0)	< 0.01
18–24	Total	330 (0–500)	500 (200–1450)	< 0.01
	Crystalloids	330 (0–500)	500 (200–1250)	
	Colloids	0 (0–0)	0 (0–0)	
	Packed red blood cells	0 (0–0)	0 (0–0)	
	Fresh frozen plasma	0 (0–0)	0 (0–0)	
	Platelets	0 (0–0)	0 (0–0)	
	As boluses	0 (0–0)	0 (0–125)	< 0.05
	Ratio FBT fluid:total fluid administered, at 18–24 h	0 (0–0)	0 (0–28%)	< 0.01
6–24	Total	1270 (950–1770)	2390 (1440–3500)	< 0.01
	As boluses	0 (0–0)	1000 (430–1900)	< 0.001
	Ratio FBT fluid:total fluid administered, at 6–24 h	0 (0–0)	40% (16%–54%)	< 0.001
0–24	Total	3050 (2130–3650)	4020 (3400–5100)	< 0.01
	As boluses	1000 (1000–2000)	2300 (1450–3500)	< 0.001
	Ratio FBT fluid:total fluid administered, at 0–24 h	48% (31%–53%)	59% (36%–69%)	< 0.05
	Ratio total fluids 0–6 h:6–24 h	1.2 (0.9–2.1)	0.7 (0.3–1.3)	< 0.001

IQR = interquartile range. ED = emergency department. FBT = fluid bolus therapy. * Volumes of different types of fluid were not compared. † Differences between bolus fluid during primary versus primary and secondary fluid bolus resuscitation.

vasopressor doses associated with FBT were generally small and diminished significantly with time.

Primary and combined secondary FBT groups were comparable at baseline and during the first 24 hours for physiological characteristics (Appendix, Table S3a). However, patients were given greater Fio_2 and had higher arterial oxygen saturation during the secondary resuscitation period (Appendix, Table S3b). Body temperature decreased in the

Table 4. Total fluid administration, patients admitted to ward versus ICU*

Time from ED arrival, h	Fluid administered, mL (median [IQR])	Patient admission destination		
		Ward	ICU	$P^{\dagger}$
0–6	Total	1445 (870–2000)	2250 (1550–2950)	< 0.001
	Crystalloids	1360 (870–1840)	2250 (1000–2950)	
	Colloids	0 (0–0)	0 (0–100)	
	Packed red blood cells	0 (0–0)	0 (0–0)	
	Fresh frozen plasma	0 (0–0)	0 (0–0)	
	Platelets	0 (0–0)	0 (0–0)	
	As boluses	1000 (500–2000)	2000 (1000–2600)	< 0.05
	Ratio FBT fluid:total fluid administered, at 0–6 h	86% (58%–100%)	89% (63%–97%)	
6–12	Total	1000 (650–1310)	830 (660–1350)	
	Crystalloids	980 (610–1310)	750 (400–1300)	
	Colloids	0 (0–0)	0 (0–250)	
	Packed red blood cells	0 (0–0)	0 (0–0)	
	Fresh frozen plasma	0 (0–0)	0 (0–0)	
	Platelets	0 (0–0)	0 (0–0)	
	As boluses	0 (0–500)	425 (0–1000)	< 0.05
	Ratio FBT fluid:total fluid administered, at 6–12 h	0 (0–50%)	40% (0–81%)	< 0.05
12–18	Total	600 (350–940)	730 (310–1100)	
	Crystalloids	600 (350–940)	660 (300–1100)	
	Colloids	0 (0–0)	0 (0–100)	
	Packed red blood cells	0 (0–0)	0 (0–0)	
	Fresh frozen plasma	0 (0–0)	0 (0–0)	
	Platelets	0 (0–0)	0 (0–0)	
	As boluses	0 (0–0)	0 (0–250)	
	Ratio FBT fluid:total fluid administered, at 12–18 h	0 (0–0)	0 (0–26%)	< 0.001
18–24	Total	375 (0–625)	500 (190–740)	
	Crystalloids	375 (0–625)	500 (190–740)	
	Colloids	0 (0–0)	0 (0–0)	
	Packed red blood cells	0 (0–0)	0 (0–0)	
	Fresh frozen plasma	0 (0–0)	0 (0–0)	
	Platelets	0 (0–0)	0 (0–0)	
	As boluses	0 (0–0)	0 (0–0)	
	Ratio FBT fluid:total fluid administered, at 18–24 h	0 (0–0)	0 (0–14%)	
6–24	Total	2000 (1500–3100)	2530 (1360–3200)	
	As boluses	0 (0–750)	900 (250–1500)	< 0.01
	Ratio FBT fluid:total fluid administered, at 6–24 h	0 (0–31%)	40% (9%–57%)	< 0.01
0–24	Total	3770 (2600–4860)	5050 (3885–5540)	< 0.05
	As boluses	1380 (1000–2000)	2615 (2250–3500)	< 0.001
	Ratio FBT fluid:total fluid administered, at 0–24 h	45% (27%–60%)	59% (50%–68%)	< 0.01
	Ratio total fluids 0–6 h:6–24 h	0.9 (0.4–1.4)	1.3 (0.8–2.9)	< 0.05

ICU = intensive care unit. ED = emergency department. IQR = interquartile range. FBT = fluid bolus therapy. * Amounts of different types of fluid were not compared. † Difference between patients admitted to ward versus ICU.

combined group over the first 24 hours, as did heart rate in both groups. SBP increased in the primary resuscitation group and respiratory rate decreased in the secondary group during the same period.

Organ support and outcome

Patients in the combined secondary group received a higher overall volume of noradrenaline (median, 1260 μg; IQR, 73–11 100 μg) than the primary group (median, 0 μg; IQR,

Table 5. Comparison of fluid bolus therapy and associated before-and-after physiological changes during primary versus secondary resuscitation, median (interquartile range)

	First bolus		Second bolus		Third bolus		Fourth bolus	
	1° resusc.	2° resusc.	1° resusc.	2° resusc.	1° resusc.	2° resusc.	1° resusc.	2° resusc.
Fluid bolus volume (mL)	1000 (500–1000)	500 (250–1000)*	1000 (500–1000)	500 (250–848)†	500 (250–1000)	430 (250–500)	500 (250–1000)	315 (250–500)
Parameter change								
SBP (mmHg)	3 (–7 to 13)	8 (–2 to 19)‡	2 (–11 to 10)	1 (–6 to 12)	7 (–4 to 16)§	0 (–10 to 8)	8 (–3 to 16)	–3 (–8 to 10)
DBP (mmHg)	0 (–6 to 8)	6 (0 to 15)¶‡	3 (–4 to 11)‡	1 (–2 to 17)	0 (–5 to 7)	0 (0 to 8)	5 (–5 to 13)	0 (–10 to 2)
HR (beats/min)	–5 (–12 to –1)**	–2 (–6 to 1)¶	–2 (–8 to 2)	–5 (–10 to 1)	–2 (–6 to 4)	1 (0 to 10)	1 (–4 to 5)	0 (–5 to 2)
SaO_2 (%)	0 (–1 to 2)	0 (–1 to 0)	0 (–1 to 1)	0 (–1 to 2)	0 (–1 to 1)	0 (0 to 1)	0 (–1 to 0)	0 (0 to 0)
Noradrenaline dose (μg/min)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (–1 to 0)	0 (0 to 0)	0 (–2 to 0)	0 (0 to 0)	0 (0 to 0)

1° resusc. = primary resuscitation (0–6 h). 2° resusc. = secondary resuscitation (6–24 h). SBP = systolic blood pressure. DBP = diastolic blood pressure. HR = heart rate. * $P < 0.001$ (difference between bolus during primary v secondary resuscitation). † $P < 0.01$ (difference between bolus during primary v secondary resuscitation). ‡ $P < 0.05$ (change pre- v post-bolus). § $P < 0.01$ (change pre- v post-bolus). ¶ $P < 0.05$ (difference between bolus during primary v secondary resuscitation). ** $P < 0.001$ (change pre- v post-bolus).

0–0 μg; $P < 0.001$). The combined secondary group received a higher peak dose of noradrenaline (median, 7 μg/min; IQR, 2–29 μg/min) than the primary group (median, 0 μg/min; IQR, 0–0 μg/min; $P < 0.001$). The combined secondary group also received noradrenaline for longer (median, 30 h and 27 min; IQR, 2 h to 291 h and 12 min) than the secondary group (median, 0 h; IQR, 0–0 h; $P < 0.01$).

Only one patient was treated with continuous renal replacement therapy (combined group). The median length of stay in the ICU was longer in the primary group (0 days; IQR, 0–2 days) than in the combined secondary group (0 days; IQR, 0–0 days; $P < 0.001$), but the median length of stay in hospital was similar for both groups (primary group: 5 days; IQR, 4–8 days; combined secondary group: 6 days; IQR, 3–11 days). Mortality rates at 28 days were similar (Table 2).

Discussion

Key findings

We conducted a detailed epidemiological study of secondary FBT in patients with hypotensive sepsis admitted to hospital via the ED. We found that one in two such patients was also given secondary FBT and that two-thirds of these patients received secondary FBT in the general ward. Secondary FBT also delivered a significant proportion of overall fluid and was associated with limited changes in measured physiological variables.

Previous studies

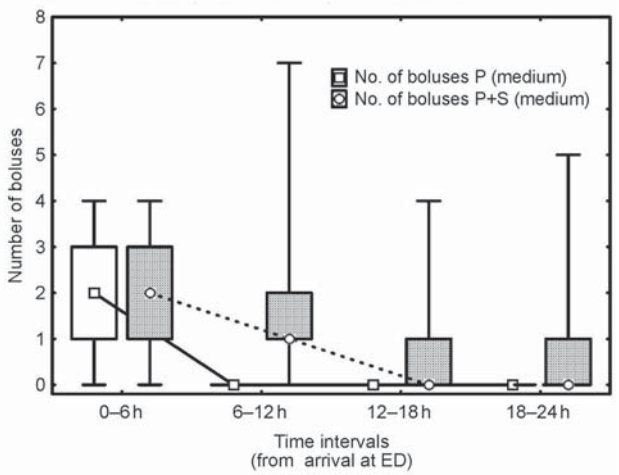
To our knowledge, for patients with sepsis admitted to the ward, there are no data on the extent and amount of and physiological changes associated with FBT in the 24 hours after primary resuscitation in the ED. One study compared the timing of fluid boluses for patients with the onset of septic shock on the ward versus onset in the ICU, but it did not report the extent or the effect of these variables.[19] Another study assessed FBT after the initial resuscitation phase in patients admitted to the ICU, but did not provide data on ward patients with severe infections.[14] Several recent studies reported the overall volumes of fluids given after the initial resuscitation, but the proportions of fluids given as FBT were not reported.[20,21] The volumes of fluids administered during primary resuscitation in our study were similar to volumes reported in recent studies of early goal-directed therapy,[20,21] making it likely that our FBT practice is consistent with current practice in other tertiary centres.

More data are available on the likely physiological effects of FBT in ICU patients with sepsis, as summarised in a recent systematic review.[5] Our study does not report why fluid boluses were given or the variables used to evaluate the effect of FBT. We chose to look at haemodynamic changes, as haemodynamic optimisation is a common reason for such practices.[10] Only the first fluid bolus seemed to have some impact on the haemodynamic response. Despite this lack of effect, several more boluses were given to these patients, with little effect. These findings are consistent with findings reported in a recent European prospective study on fluid boluses,[10] in which, despite an uncertain or negative effect of FBT, repeated boluses were given to ICU patients.

Strengths and limitations

Our study provides new data on FBT after initial resuscitation (ie, secondary resuscitation) and is the only study reporting data on FBT given to patients with sepsis after admission to the ward. Our study design decreased selection bias, as all patients admitted to the hospital with infectious diagnoses

Figure 3. Overall median number of fluid boluses administered for patients receiving primary versus combined primary and secondary FBT resuscitation

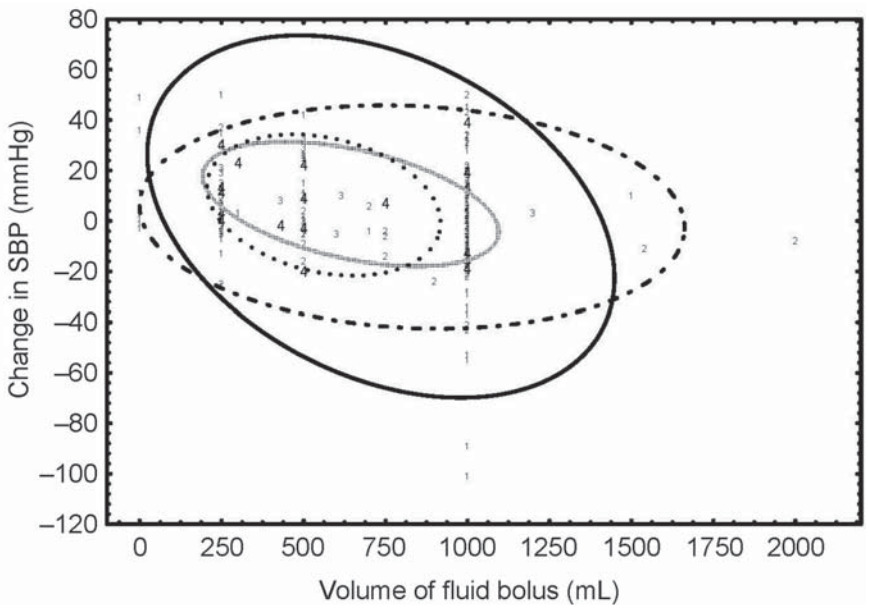


FBT = fluid bolus therapy. P = primary FBT. P+S = primary and secondary FBT. ED = emergency department. Box = interquartile range. Whisker = minimum–maximum. The number of boluses decreased in the combined group over time ($P < 0.001$).

were screened and all patients fulfilling inclusion criteria were included, thus avoiding a skewed selection of patients through the presence of study staff, consent or the logistics of data collection. Finally, the number of patients screened was large, which limited the effects of a small sample size.

Our study also had several limitations. First, it was a retrospective design, although it clearly confirmed that FBT continued during the first 24 hours, even in patients admitted to the ward. Second, it was a single-centre study, but the fluid resuscitation features were similar to those seen in recent, large multicentre studies of resuscitation of patients with sepsis, which conferred a degree of external validity. Mortality was higher in this cohort than that reported for patients in a recent sepsis trial in Australia and New Zealand.[20] However, specific selection criteria were applied to eligibility for that trial, which removed several higher risk patients. We included higher risk patients in our investigation. An additional limitation was that the amount of missing data increased over time for patients admitted to the ward, but the type of data we collected, such as fluids given and basic physiological information, was registered for all hospital patients.

Figure 4. Scatter plot of fluid bolus volume versus change in systolic blood pressure



SBP = systolic blood pressure. 1 = change in SBP after first fluid bolus. 2 = change in SBP after second fluid bolus. 3 = change in SBP after third fluid bolus. 4 = change in SBP after fourth fluid bolus.
—— first bolus. – - – - second bolus. ····· third bolus. --- fourth bolus.
Points are numbered as first, second, third or fourth fluid bolus, in order in an individual patient. Lines are an approximation of the main distribution of points. A more vertical position of the ellipse suggests greater change in SBP:fluid bolus ratio.

Implications of study findings

Our findings imply that, after initial resuscitation, secondary FBT is given to about half of patients with hypotensive severe sepsis, takes place in general wards more often than in the ICU, delivers a significant proportion of overall fluid therapy and is associated with limited changes in measured physiological variables. In the aggregate, these observations imply the need for further investigation of secondary FBT and for consideration of alternative approaches.

Conclusions

Secondary FBT is common, significant in volume and constitutes a major contribution to total fluids given to patients with systemic infection and initial hypotension, irrespective of the level of care. The value of secondary FBT is unclear, as its effects on haemodynamics appear limited. Our observations suggest the need for alternative approaches to secondary fluid therapy in patients with sepsis presenting to the ED with hypotension.

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Competing interests

None declared.

Author contributions

Rinaldo Bellomo conceived the study. Rinaldo Bellomo and Miklos Lipcsey designed the study. Data were collected and interpreted by Miklos Lipcsey, Ivan Subiakto, Jonathan Chiong, Melissa Kaufman, Antoine Schneider and Rinaldo Bellomo. The manuscript was drafted by Miklos Lipcsey and Rinaldo Bellomo. Contributions to the manuscript were made by all authors, and the final manuscript was approved by all authors.

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Appendix – This appendix was part of the submitted manuscript and has been peer reviewed. It is posted as supplied by the authors

Table S1: Demographic data for the subgroup of patients receiving combined FBT.

		Both Groups	Patients admitted to ward n=31	Patients admitted to ICU n=17	p-value Admitted to ward vs ICU
Sex	Male	29 (60)	19 (61)	10 (59)	n.s.
Age (yr) Median (IQR)		*68 (52-79)*	*62 (52-81)*	*73 (62-78)*	n.s.
Alive at 28 days		36 (73)	25 (81)	11 (65)	n.s.
Diagnoses at discharge	Sepsis with no focus	38 (79)	23 (74)	15 (88)	n.s.
	Pneumonia	6 (12)	6 (18)	0 (0)	n.s.
	Abdominal sepsis	1 (2)	1 (3)	0 (0)	n.s.
	Urosepsis	4 (8)	2 (6)	2 (17)	n.s.
Co-morbidities					
Congestive heart failure		*6 (13)*	5 (16)	*1 (6)*	n.s.
Coronary artery disease		*10 (21)*	6 (19)	*4 (24)*	n.s.
Chronic obstructive pulmonary disease		*8 (17)*	4 (13)	*4 (24)*	n.s.
Diabetes mellitus		*8 (17)*	7 (23)	*1 (6)*	n.s.
HIV		*0*	0 (0)	*0 (0)*	n.s.
Hypertension		*12 (25)*	9 (29)	*3 (18)*	n.s.
Cirrhosis		*1 (2)*	0 (0)	*1 (6)*	n.s.
History of cancer		*8 (17)*	6 (19)	*2 (12)*	n.s.
Neurologic disease		*9 (19)*	8 (26)	*1 (6)*	n.s.
Chronic renal failure		*17 (35)*	8 (26)	*9 (53)*	n.s.
History of smoking		*21 (44)*	15 (48)	*5 (29)*	n.s.
Sepsis details					
Pneumonia		*21 (44)*	16 (52)	*5 (29)*	n.s.
Urosepsis		*5 (10)*	3 (10)	*2 (12)*	n.s.
Peritonitis		*1 (2)*	0 (0)	*1 (6)*	n.s.
Intra-abdominal process		*8 (17)*	1 (3)	*7 (41)*	p=0.0007
Abscess of arm or leg		1 (2)	1 (3)	*0 (0)*	n.s.
Other infection		*14 (29)*	11 (35)	*3 (18)*	n.s.
Severe sepsis		*22 (46)*	20 (65)	*2 (12)*	p=0.0004
Septic shock		*26 (54)*	11 (35)	*15 (88)*	p=0.0004
Positive blood culture		*5 (10)*	2 (6)	*3 (18)*	n.s.
Antibiotics within 6 hours		*41 (85)*	25 (80)	*15 (88)*	n.s.

Data presented as absolute vale (% of the whole cohort) unless stated otherwise. yr: years, IQR: interquartile range, ED: emergency department, ICU: intensive care unit.

Table S2: Total fluid administration for patients receiving secondary resuscitation admitted to the wards vs. those admitted to ICU

Time interval after arrival to the ED		Patients admitted to the ward	Patients admitted to the ICU
0-6 hours	Total amount of fluids given (ml)	1210 (1000-2000)	2250 (1600-2950)*
	Amount of fluids given as bolus	1000 (250-1500)	2000 (1000-2620)**
	Ratio of FBT fluid to total amount of fluid given at 0-6 hours	89 (56-100)	89 (63-97)
6-12 hours	Total amount of fluids given (ml)	1750 (1000-2230)	900 (700-1350)
	Amount of fluids given as bolus	500 (0-1500)	430 (0-1000)
	Ratio of FBT fluid to total amount of fluid given at 6-12 hours	49 (0-84)	40 (0-81)
12-18 hours	Total amount of fluids given (ml)	850 (470-2000)	730 (310-1100)
	Amount of fluids given as bolus	0 (0-0)	0 (0-250)*
	Ratio of FBT fluid to total amount of fluid given at 12-18 hours	0 (0-0)	0 (0-26)*
18-24 hours	Total amount of fluids given (ml)	500 (230-2600)	500 (200-860)
	Amount of fluids given as bolus	0 (0-0)	0 (0-0)
	Ratio of FBT fluid to total amount of fluid given at 18-24 hours	0 (0-14)	0 (0-14)
6-24 hours	Total amount of fluid given (ml)	3240 (2300-5570)	2530 (1360-3210)
	Amount of fluids given as bolus	830 (250-2000)	1250 (500-1800)
	Ratio of FBT fluid to total amount of fluid given at 6-24 hours	33 (11-57)	43 (29-57)
0-24 hours	Total amount of fluid given (ml)	4720 (4000-7200)	5050 (3900-5550)
	Amount of fluids given as bolus	2000 (1000-3000)	3250 (2250-4000)**
	Ratio of FBT fluid to total amount of fluid given at 0-24 hours	51 (18-69)	64 (58-76)*
	Ratio of total 0-6/6-24 hours fluid amount	0.50 (0.22-0.84)	1.04 (0.62-1.69)**

* p<0.05, **p<0.01, ***p<0.001 Difference between patients admitted to the ward vs ICU. Values expressed as medians (IQR).

Table S3a: Change in physiologic variables during the first 24 hours by 6 hour intervals, for patients receiving primary only vs primary and secondary fluid bolus resuscitation*

	Admission		**6-12 hours**		**12-18 hours**		**18-24 hours**		**Change over time**	
	Primary only	Primary & Secondary	Primary only	Primary & secondary	Primary only	Primary & secondary	Primary only	Primary & secondary	Primary only	Primary & secondary
Temp. (°C)	37.4 (35.8-38.2)	37.7 (36.9-38.4)	36.5 (36.2-37.2)	36.5 (36.9-37.1)	36.5 (36.1-37.2)	36.0 (36.0-37.5)	36.6 (36.2-37.2)	36.5 (36.0-37.4)	n.s.	p = 0.009
HR (beats/min)	107 (88-122)	102 (88-126)	86 (80-96)	85 (72-95)	85 (80-95)	80 (75-98)	83 (75-94)	85 (74-100)	p = 0.0008	p = 0.001
SBP (mm Hg)	100 (89-111)	101 (90-120)	106 (100-119)	105 (98-118)	110 (100-120)	105 (95-115)	110 (103-123)	110 (100-120)	p = 0.0016	n.s.
DBP	60 (51-70)	66 (58-71)	60 (53-68)	60 (50-65)	61 (55-68)	60 (54-64)	65 (53-72)	60 (50-65)	n.s.	n.s.
RR	20 (16-28)	18 (16-24)	20 (18-20)	18 (18-22)	20 (18-22)	18 (17-20)	20 (16-22)	18 (15-20)	n.s.	p = 0.0142
SaO_2 (%)	97 (94-99)	98 (94-99)	96 (94-98)	98 (96-99)*	96 (96-99)	98 (95-99)	96 (95-98)	97 (95-99)	n.s.	n.s.

Tem=temperature; HR=heart rate; SBP=systolic blood pressure; DBP=diastolic blood pressure; RR=respiratory rate; SaO2=arterial oxygen saturation; * $p<0.05$. Difference between fluid bolus during primary only vs primary and secondary resuscitation.Values expressed as medians (IQR).

Table S3b: Physiologic data during the first 24 hours in 6 hour intervals, for patients admitted to the ward vs. ICU

	Admission		**6-12 hours**		**12-18 hours**		**18-24 hours**	
	Ward patients	ICU patients	Ward patients	ICU patients	Ward patients	ICU patients	Ward patients	ICU patients
Temp (°C)	37.8 (36.3-38.3)	37.4 (36.0-38.5)	36.5 (36.1-37.1)	36.6 (36.2-37.3)	36.5 (36.0-37.3)	37.7 (36.2-37-3)	36.5 (36.0-37.3)	36.8 (36.2-37.3)
HR (beats/min)	111 (93-124)	98 (84-128)	85 (79-97)	90 (79-95)	82 (76-97)	90 (78-95)	84 (75-95)	83 (74-102)
SBP (mm Hg)	103 (94-119)	93 (87-112)	107 (99-120)	105 (98-114)	107 (96-118)	110 (100-115)	110 (102-120)	110 (102-128)
DBP (mm Hg)	66 (56-71)	60 (51-70)	60 (50-67)	55 (55-62)	60 (55-65)	55 (50-60)*	60 (53-70)	60 (50-66)
RR (breaths/min)	20 (17-26)	18 (16-21)	20 (18-22)	18 (17-22)	18 (17-22)	19 (18-22)	18 (16-22)	18 (15-25)
SaO_2 (%)	97 (94-99)	98 (96-100)	96 (95-98)	99 (97-100)***	97 (94-98)	100 (98-100)***	96 (95-98)	98 (97-100)*
FiO_2	0.21 (0.21-0.36)	0.21 (0.21-0.28)	0.24 (0.21-0.28)	0.32 (0.28-0.48)***	0.21 (0.21-0.32)	0.32 (0.28-0.42)***	0.24 (0.21-0.31)	0.28 (0.25-0.40)*

Temp=temperature; HR=heart rate; SBP=systolic blood pressure; DBP=diastolic blood pressure; RR=respiratory rate; SaO2=arterial oxygen saturation; * p<0.05, **p<0.01, ***p<0.001 Difference between patients admitted to the ward vs ICU.Data presented as medians (IQR).