

# Primary fluid bolus therapy for infection-associated hypotension in the emergency department

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Hypotensive sepsis carries a high risk of death,<sup>1</sup> and its initial haemodynamic management may have a significant impact on the outcome.<sup>2-4</sup> International treatment guidelines<sup>5,6</sup> strongly recommend fluid bolus therapy (FBT) and early goal-directed therapy (EGDT), a therapy associated with a mean dose of fluid administration of about 5 L in the first 6 hours.<sup>4</sup> Hypotension is the commonest trigger used by clinicians to begin such fluid bolus resuscitation.<sup>7</sup>

Despite the guidelines and ongoing controversy,<sup>2,8</sup> there are no data on the volume of fluid that should be given, or the immediate physiological changes and renal outcomes associated with primary resuscitation (in the first 6 hours) in hypotensive adult patients with infection presenting to the emergency department (ED). Moreover, although a major aim of FBT is to at least increase blood pressure, no studies have assessed the extent of this effect in these patients.

We hypothesised that, in the ED of an Australian teaching hospital, the mean volume of fluid given during FBT in the first 6 hours (primary resuscitation) would be low (> 2 L less than with EGDT); that such FBT would be associated with incomplete success in correcting hypotension; and that, in contrast, noradrenaline therapy would correct hypotension in all patients who are unresponsive to FBT. To test these hypotheses, we studied a cohort of patients admitted to our hospital with an infection-related diagnosis and hypotension (on arrival or during the first 6 hours after presentation) who received FBT while in the ED.

## Materials and methods

Our study was approved by the Human Research Ethics Committee of the Austin Hospital which waived the need for informed consent because of its retrospective, non-interventional nature.

We performed a retrospective, observational study at the ED of the Austin Hospital, a large tertiary hospital in Melbourne, Australia. The aim of the study was to include at least 100 patients with infection-associated hypotension who had received one or more fluid boluses as resuscitation for hypotension. Our study had a >90% power to detect a 2 L difference in the amount of fluid given for resuscitation in the first 6 hours, compared with the amount of fluid given during the EGDT trial, at an alpha level of 0.01.

## ABSTRACT

**Objectives:** The physiological changes associated with fluid bolus therapy (FBT) for patients with infection-associated hypotension in the emergency department (ED) are poorly understood. We describe the physiological outcomes of FBT in the first 6 hours (primary FBT) for patients presenting to the ED with infection-associated hypotension.

**Methods:** We studied 101 consecutive ED patients with infection and a systolic blood pressure (SBP) < 100 mmHg who underwent FBT in the first 6 hours.

**Results:** We screened 1123 patients with infection and identified 101 eligible patients. The median primary FBT volume given was 1570 mL (interquartile range, 1000–2490 mL). The average mean arterial pressure (MAP) did not change from admission to 6 hours in the whole cohort, or in patients who were hypotensive on arrival at the ED. However, the average MAP increased from its lowest value during the first 6 hours (66 mmHg [SD, 10 mmHg]) to its value at 6 hours (73 mmHg [SD, 12 mmHg];  $P < 0.001$ ). The mean heart rate, body temperature, respiratory rate and plasma creatinine level decreased ( $P < 0.05$ ). In patients who were severely hypotensive (SBP < 90 mmHg) on arrival at the ED, the MAP increased from 54 mmHg (SD, 8 mmHg) to 70 mmHg (SD, 14 mmHg) ( $P < 0.001$ ). At 6 hours, however, SBP was still < 100 mmHg in 44 patients and < 90 mmHg in 17 patients. When noradrenaline was used, in 10 patients, hypotension was corrected in all 10 and the MAP increased from 58 mmHg (SD, 9 mmHg) to 75 mmHg (SD, 13 mmHg).

**Conclusion:** Among ED patients admitted to an Australian teaching hospital with infection, hypotension was uncommon. FBT for hypotension was limited in volumes given and failed to achieve a sustained SBP of > 100 mmHg in 40% of cases. In contrast, noradrenaline therapy corrected hypotension in all patients who received it.

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We screened all patients who had the appropriate discharge diagnostic codes (see Appendix Table A1; all Appendix material is available online at [cicm.org.au/journal.php](http://cicm.org.au/journal.php)). We used a modified version of the severe sepsis consensus

**Table 1. Physiological changes over time in hypotensive patients treated with fluid bolus therapy**

Physiological parameter	Time after arrival in the emergency department			
	On arrival	2 hours	4 hours	6 hours
Median fluid administered, mL (IQR)				
Crystalloids	NA	500 (0–1000)	500 (250–955)	500 (250–750)
Colloids	NA	0 (0–500)	0 (0–750)	0 (0–700)
Packed red cells	NA	0 (0–0)	0 (0–0)	0 (0–150)
Fresh frozen plasma	NA	0 (0–0)	0 (0–0)	0 (0–300)
Platelets	NA	0 (0–0)	0 (0–0)	0 (0–200)
Median FiO <sub>2</sub> (IQR)	0.21 (0.21–0.36)	0.21 (0.21–0.36)	0.28 (0.21–0.32)	0.28 (0.21–0.32)*
Mean body temperature, °C (SD)	37.3 (1.4)	36.9 (1.4)	36.7 (1.2)	36.6 (1.1)*
Mean heart rate, beats/minute (SD)	107 (27)	98 (26)	93.8 (21)	92 (22)***
Mean systolic BP, mmHg (SD)	105 (23)	104 (19)	103 (17)	102 (18)
Mean diastolic BP, mmHg (SD)	63 (15)	60 (12)	57 (13)	59 (14)*
MAP, mmHg (SD)	78 (16)	75 (12)	72 (13)	73 (13)
Median RR, breaths/minute (IQR)	20 (16–24)	20 (17–25)	19 (17–24)	18 (16–22)*
Median SaO <sub>2</sub> , % (IQR)	97 (94–99)	98 (96–100)	98 (96–100)	98 (97–99)**
Mean arterial pH (SD)	7.35 (0.10)	7.33 (0.1)	7.36 (0.11)	7.37 (0.11)
Mean PaO <sub>2</sub> , mmHg (SD)	82 (70)	95 (104)	114 (71)	111 (51)
Mean PaCO <sub>2</sub> , mmHg (SD)	44 (14)	45 (18)	42 (10)	40 (12)**
Mean plasma base excess, mmol/L (SD)	–2.1 (5.1)	–2.9 (5.6)	–2.3 (5.6)	–2.4 (4.7)
Median plasma lactate, mmol/L (IQR)	2.0 (1.3–2.4)	1.9 (1.5–3.6)	2.7 (2.0–3.8)	1.8 (1.5–2.6)
Mean haemoglobin, g/L (SD)	123 (23)	122 (23)	116 (22)	118 (20)
Median WBC count, × 10 <sup>9</sup> /L (IQR)	11 (7.6–17.9)	9.7 (4.2–16.9)	18.4 (11.5–20.7)	10.6 (6.9–11.9)
Mean plasma sodium, mmol/L (SD)	135 (5)	135 (5)	134 (5)	134 (5)
Mean plasma potassium, mmol/L (SD)	4.2 (0.7)	4.2 (0.7)	4.2 (0.7)	4 (0.8)
Mean plasma chloride, mmol/L (SD)	101 (5)	102 (6)	102 (7)	104 (6)
Median plasma creatinine, µmol/L (IQR)	123 (76–160)	131 (76–160)	148 (48–184)	82 (71–94)*
Mean plasma albumin, g/L (SD)	32 (7)	32 (7)	30 (5)	25 (9)

IQR = interquartile range. NA = not applicable. SD = standard deviation. BP = blood pressure. MAP = mean arterial pressure. RR = respiratory rate. WBC = white blood cell. \*  $P < 0.05$ . \*\*  $P < 0.01$ . \*\*\*  $P < 0.001$ . All  $P$  values calculated for change over 0–6 hours.

definitions<sup>9,10</sup> and included patients with the following criteria:

- the presence of two or more systemic inflammatory response syndrome criteria; *and*
- suspected infection on arrival to the ED (subsequently confirmed as discharge diagnosis); *and*
- systolic blood pressure (SBP) < 100 mmHg at least once within 6 hours of arrival to the ED; *and*
- fluid bolus administration (defined as > 250 mL/h fluid administered within 6 hours of arrival to the ED) during primary resuscitation.

Exclusion criteria included:

- the presence of limitations of medical therapy within 24 hours of hospital admission
- lack of detailed data on FBT
- lack of detailed data on vital signs

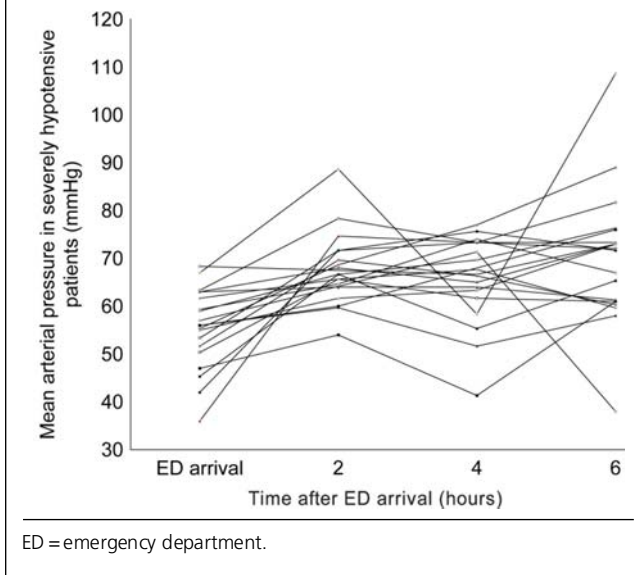
- age < 18 years.

We collected data on physiological parameters, available biochemical tests, fluids administered on arrival at the ED and at 2, 4 and 6 hours and before and after FBT, demographic parameters, comorbidities, vital status at 28 days, lengths of stay in the intensive care unit and in hospital, and focus of sepsis. The amount and type of fluid used in FBT were recorded, as was the duration of infusion. Therapeutic interventions such as the duration of invasive ventilator support, the duration of administration and volume of vasopressors or inotropic agents used, and the use and duration of renal replacement therapy (RRT) were collected.

#### Statistics

Normally distributed data are presented as means and standard deviations. Paired  $t$  tests, analysis of variance (ANOVA)

**Figure 1. Changes in mean arterial pressure in severely hypotensive patients during the first 6 hours after arrival in the ED**



tests for repeated measurements or the Wilcoxon matched-pairs test and the Friedman ANOVA tests were used as appropriate. Non-normally distributed data are presented as medians with interquartile ranges (IQRs) unless otherwise stated. A  $P < 0.05$  was considered significant.

**Results**

**Study patients**

We screened 1123 patients admitted to the ED with infection in 2010 and identified 157 patients who fulfilled the study criteria and had adequate data for analysis. A total of 56 patients did not undergo FBT, despite having an SBP < 100 mmHg and infection. Of these patients, five were admitted to the ICU. Of the remaining 51 patients who did not undergo FBT and were not admitted to the ICU, five died during their hospital admission.

The final cohort of 101 patients had a median age of 67 years (IQR, 53–82 years) and 47 patients were women (for clinical details and comorbidities, see Appendix Table A1). Overall, 74 patients were admitted to the ward and 26 to the ICU. One patient died in the ED 5 hours after arrival.

Patients admitted to the ward had a median hospital length of stay (LOS) of 5 days (IQR, 3–8 days), patients admitted to the ICU had a median hospital LOS of 8 days (IQR, 4–16 days), and the median ICU LOS was 2 days (IQR, 2–3 days). One patient underwent RRT. Overall 28-day mortality was 26%. Patients presented in four clinically definable groups:

- 25 patients were hypotensive on arrival (SBP < 100 mmHg)
- 21 were severely hypotensive on arrival (SBP < 90 mmHg)
- 20 became hypotensive during their first 6 hours in the ED
- 35 became severely hypotensive during their first 6 hours in ED.

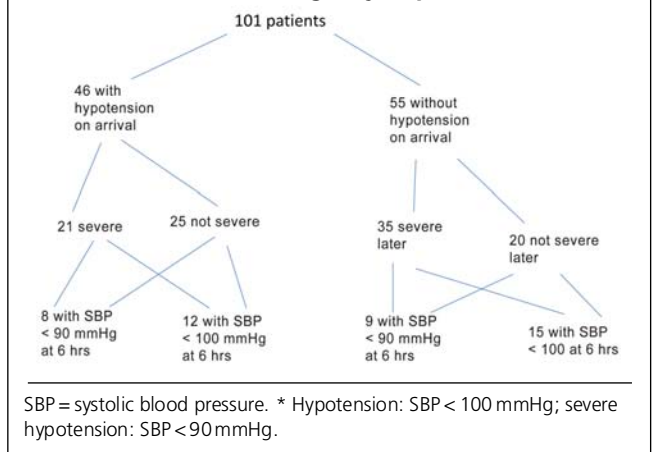
**Physiological parameters and other outcomes**

Overall, the mean body temperature, heart rate (HR), diastolic blood pressure, respiratory rate (RR),  $Paco_2$  and plasma creatinine levels decreased over time, and the  $Fio_2$  and  $Sao_2$  increased (Table 1).

The average mean arterial pressure (MAP) did not change from ED admission to 6 hours in the whole cohort, or in patients who were hypotensive on arrival at the ED. However, the MAP increased from its lowest level (during the first 6 hours) to the value recorded at 6 hours after ED presentation in patients who were hypotensive on arrival (lowest MAP, 64 mmHg [SD, 7 mmHg]; 6-hour MAP, 76 mmHg [SD, 17 mmHg];  $P < 0.01$ ), patients who were severely hypotensive on arrival (lowest MAP, 54 mmHg [SD, 8 mmHg]; 6-hour MAP, 70 mmHg [SD, 14 mmHg];  $P < 0.001$ ), and patients who became severely hypotensive in the ED (lowest MAP, 61 mmHg [SD, 9 mmHg]; 6-hour MAP, 73 mmHg [SD, 13 mmHg];  $P < 0.001$ ).

The MAP did not change from its lowest value to its value at 6 hours in patients who became hypotensive in the ED (lowest MAP, 71 mmHg [SD, 8 mmHg]; 6-hour MAP, 73 mmHg [SD, 9 mmHg]) (see Appendix). The evolution of MAP for individual patients with severe hypotension on arrival at the ED is shown in Figure 1. At 6 hours after arrival, the SBP was still < 100 mmHg in 44 patients and < 90 mmHg in 17 patients (Figure 2), only two of whom had received 2 L of fluid or more.

**Figure 2. Evolution of SBP during the first 6 hours after arrival in the emergency department\***



**Table 2. Changes in physiological variables after fluid bolus therapy, by bolus type**

Variable	Bolus 1 <sup>†</sup> (n = 86)		Bolus 2 (n = 53) <sup>‡</sup>		Bolus 3 (n = 30) <sup>§</sup>		Bolus 4 (n = 15) <sup>¶</sup>	
	Before	After	Before	After	Before	After	Before	After
Heart rate, beats/minute <sup>††</sup>	102 (25)	95 (23) <sup>***</sup>	102 (28)	98 (21)	98 (21)	96 (20)	102 (20)	102 (19)
Systolic blood pressure, mmHg <sup>††</sup>	99 (24)	101 (18)	92 (13)	95 (15)	89 (14)	97 (14) <sup>**</sup>	91 (10)	99 (12)
Diastolic blood pressure, mmHg <sup>††</sup>	58 (16)	58 (12)	51 (10)	56 (12) <sup>**</sup>	53 (9)	55 (11)	51 (9)	57 (15)
Mean arterial pressure, mmHg <sup>††</sup>	72 (13)	72 (12)	65 (8)	69 (10) <sup>*</sup>	65 (8)	68 (9)	62 (9)	72 (12) <sup>*</sup>
Median arterial oxygen saturation, % (IQR)	98 (96–100)	98 (96–100)	98 (97–100)	98 (97–100)	99 (98–100)	98 (97–100)	98 (97–99)	98 (97–100)

IQR = interquartile range. SD = standard deviation. † Bolus 1: median volume, 1000 mL (IQR, 500–1000 mL); median rate, 860 mL/hour (IQR, 500–1090 mL/hour). ‡ Bolus 2: median volume, 1000 mL (IQR, 500–1000 mL); median rate, 750 mL/hour (IQR, 460–1000 mL/hour). § Bolus 3: median volume, 500 mL (IQR, 250–1000 mL); median rate, 630 mL/hour (IQR, 440–800 mL/hour). ¶ Bolus 4: median volume, 500 mL (IQR, 250–1000 mL); median rate, 550 mL/hour (IQR, 390–1500 mL/hour). †† Mean (SD). \*  $P < 0.05$ . \*\*  $P < 0.01$ . \*\*\*  $P < 0.001$ . All  $P$  values are differences between values before and after fluid boluses were given. Fifteen patients did not receive fluid boluses that ended within 6 hours of arrival in the emergency department; seven patients received > four fluid boluses (data not shown).

Mortality at 28 days among patients who were normotensive on arrival in the ED but hypotensive at 6 hours was 32%. It was 20% among patients who were hypotensive on arrival and 29% in patients who were severely hypotensive on arrival. Nine patients were mechanically ventilated for a median duration of 2 days (IQR, 1–2 days; range 1–21 days).

#### Fluid management in the first 6 hours after hospital arrival

The fluid management and physiological parameters recorded during the first 6 hours are shown in Table 1. The median volume of fluid administered during the first 6 hours was 1570 mL (IQR, 1000–2490 mL; range 250–6200 mL). There was no difference in the amount of fluid administered during the first 6 hours, calculated by hypotension groups.

For the whole cohort, the median number of boluses was two (IQR, 2–4 boluses; range, 1–11 boluses) with a median volume of 500 mL (IQR, 250–1000 mL) and a median administration rate of 600 mL/hour (IQR, 335–1000 mL) (Table 2). The mean HR decreased by 7 beats/minute after the first fluid bolus ( $P < 0.001$ ). The MAP of the cohort was unchanged until the second bolus, when it increased by a mean of 4 mmHg ( $P < 0.05$ ). At the time of the fourth bolus it increased by a mean of 8 mmHg (before v after bolus) ( $P < 0.05$ ). No other changes were noted in before-bolus and after-bolus parameters. The MAP was lower after 39% of all fluid boluses in the whole cohort and after 36% of fluid boluses among severely hypotensive patients.

There was no association between the total volume of fluids given and the MAP or HR changes between 0 and 6 hours (MAP:  $\rho = 0.07$ ; HR:  $\rho = -0.25$ ) for the whole cohort. In patients who were hypotensive (SBP < 100 mmHg) on

arrival at the ED, the MAP decreased by 15 mmHg for each 1 L of fluid given ( $\rho = -0.43$ ;  $P < 0.05$ ) but, in patients who were severely hypotensive (SBP < 90 mmHg), it increased by 6 mmHg for each 1 L of fluid during the first 6 hours ( $\rho = 0.52$ ;  $P < 0.05$ ; see Appendix). Of nine patients with an SBP < 90 mmHg and an SBP increase of > 15 mmHg after the first bolus, an SBP > 100 mmHg was sustained in six patients and this effect lasted a mean of 2.9 hours (IQR, 2.7–3 hours).

#### The effects of noradrenaline infusion

Ten patients who were unresponsive to FBT were given a noradrenaline infusion within the first 6 hours in the ED. Their vital signs before and after noradrenaline administration are shown in Table 3. In these patients, noradrenaline was started at a median of 3.6 hours after presentation to the ED (IQR, 2.7–5.2 hours) for a median subsequent duration of 9 hours (IQR, 7–56 hours) and a median peak rate of 9  $\mu\text{g}/\text{minute}$  (IQR, 4–30  $\mu\text{g}/\text{minute}$ ). Before the start of the noradrenaline infusion, a median volume of 3350 mL (IQR, 2250–3850 mL)

**Table 3. Vital signs before and after noradrenaline infusion and at 6 hours after arrival in the ED**

Vital sign	Before noradr.	After noradr.	6 hours
FiO <sub>2</sub> <sup>†</sup>	0.3 (0.21–0.6)	0.32 (0.28–0.5)	0.32 (0.28–0.5)
HR, beats/minute <sup>‡</sup>	106 (25)	95 (21)	98 (21)
MAP, mmHg <sup>‡</sup>	58 (9)	75 (13) <sup>*</sup>	76 (14)
RR, breaths/minute <sup>†</sup>	21 (16–25)	20 (18–22)	18 (16–22)
Body temperature, °C <sup>‡</sup>	37 (2.2)	36.7 (2.1)	36.7 (1.4)
SaO <sub>2</sub> , % <sup>†</sup>	98 (95–99)	100 (98–100)	100 (98–100)

ED = emergency department. Noradr. = noradrenaline. HR = heart rate. MAP = mean arterial pressure. RR = respiratory rate. † Median (interquartile range). ‡ Mean (SD). \*  $P < 0.05$  (before v after noradrenaline infusion).

of fluids was administered, which was twice as much as the total fluid administered during the first 6 hours in the rest of the cohort ( $P < 0.001$ ). The MAP increased in all patients from 62 mmHg (SD, 14 mmHg) to 75 mmHg (SD, 13 mmHg) ( $P < 0.05$ ) after the start of the noradrenaline infusion. This compared with a change in the MAP from 71 mmHg (SD, 16 mmHg) to 61 mmHg (SD, 15 mmHg) ( $P < 0.05$ ) with FBT initiated only before administration of noradrenaline. There were no differences in other vital signs before and after the start of the noradrenaline infusion (Table 3).

## Discussion

### Main findings

We conducted a retrospective, observational study of primary FBT for infection-associated hypotension. We found that infection-associated hypotension was uncommon, affecting fewer than 10% of ED patients admitted to hospital with infection. Patients undergoing FBT in the ED received an average of 1.6 L of fluid over 6 hours without affecting the overall MAP. However, over time, the MAP did increase by 12 mmHg in patients who were hypotensive on arrival, and by 16 mmHg in patients who were severely hypotensive on arrival. The overall association of FBT with MAP changes was weak and unpredictable and almost half of patients were still hypotensive after 6 hours in the ED. In contrast, all patients who were started on vasopressor (noradrenaline) therapy increased their MAP immediately and the effect was sustained in all. Despite persistent hypotension and limited FBT, only one patient was subsequently treated with RRT.

### Previous studies

Much of the current knowledge on fluid resuscitation dose and physiological effects comes from experimental studies only.<sup>11</sup> The implementation of EGDT achieved an improvement in outcome in severely hypotensive patients using a treatment algorithm which delivered 5L in the first 6 hours.<sup>4</sup> However, 28-day mortality was still high, at 33%, and management of hypotensive sepsis may be possible with low mortality without EGDT.<sup>12,13</sup> To our knowledge, however, the specific clinical and early physiological associations of primary FBT with infection-associated hypotension have never been described.

FBT in sepsis led to worse outcomes in African children<sup>2</sup> and did not reverse shock to a great extent in a Western prehospital setting.<sup>14</sup> Given that the effect of FBT on MAP was weak and unpredictable in our study, the fluid volume given may have been too low. However, a prospective, multicentre observational study in 324 patients<sup>12</sup> from 32 Australian and New Zealand EDs reported a median total fluid volume of 1778 mL over the first 6 hours in patients fulfilling EGDT criteria, including an SBP  $< 90$  mmHg, suggesting that our approach reflects current Australian and

New Zealand ED fluid resuscitation practice. Other studies have shown that fluid therapy within the first 6 hours after diagnosis does not, on its own, predict outcome.<sup>15,16</sup> Finally, in a recent study on resuscitation of sepsis patients,<sup>17</sup> about 40% less fluid was administered during the first 6 hours of treatment compared with the original study of EGDT.<sup>4</sup> Despite the lower volume of fluid administered,<sup>17</sup> mortality was substantially lower than in the original EGDT trial.<sup>4</sup>

### Clinical implications

Historically, FBT has been used for hypotension with perceived hypovolaemia.<sup>18</sup> However, the physiological effects of primary FBT in infection-associated hypotension have not been studied. In keeping with our hypotheses, our fluid resuscitation protocol was similar to fluid resuscitation protocols in other Australian and New Zealand EDs, was conservative in volumes used, and the blood pressure response was limited in extent, heterogeneous and unpredictable. However, when severe hypotension persisted despite FBT, and vasopressor therapy was initiated, such therapy was associated with a predictable, significant and sustained increase in the MAP. These findings suggest that if rapid, reliable and sustained correction of hypotension is an important clinical goal, earlier use of noradrenaline may more reliably increase the MAP.

### Strengths and limitations

Our study contributes new data to the largely unexplored area of the possible initial physiological effects of primary FBT in infection-associated hypotension. A strength of the study is the pragmatic setting and collection of data on FBT as it is actually performed and the fact that practice reflected Australian and New Zealand practice in general. However, the retrospective design is a limitation. To reduce the effect of this limitation, we chose a relatively large cohort of patients and focused on routinely reliably recorded outcome variables. We applied an arbitrary cut-off value for hypotension (SBP  $< 100$  mmHg) and FBT ( $> 250$  mL/hour). These values were predefined with consideration of the facts that an SBP  $< 100$  mmHg in patients with a mean age close to 70 years is likely to induce intervention; that an SBP  $< 100$  mmHg is  $> 30$  mmHg below the normal resting daytime SBP;<sup>19</sup> and that a fall of 15 mmHg from the baseline SBP has been associated with acute kidney injury.<sup>20</sup> Finally, a fluid administration rate  $> 250$  mL/hour is well over the normal maintenance fluid administration rates for a normal-sized patient. Although there is uncertainty about the trigger for or the target of blood pressure management,<sup>21</sup> no alternative published or consensus definitions exist.

Given the high number of patients with hypotension at 6 hours, it may also be argued that the volume of fluid delivered in this study was insufficient. However, the volumes are in line with the practices of other similar centres,<sup>12,22</sup> are within current guidelines for initial resuscitation,<sup>6</sup> and we

were mindful of emerging concerns about the consequences of sodium overload in critically ill patients.<sup>23,24</sup> To assess the effects of FBT despite the temporal differences in the onset of hypotension between cases, we studied the impact of each bolus. Using such detailed assessment, we found no evidence that FBT reliably improved the SBP or the MAP. However, noradrenaline did.

## Conclusions

We provide the first detailed description of the characteristics and physiological associations of primary FBT for infection-associated hypotension in an ED in a setting representative of Australian and New Zealand EDs. Such resuscitation was limited in volume; showed a weak, heterogeneous and unpredictable association with blood pressure changes, and showed a high incidence of persistent hypotension. In contrast, in patients who remained hypotensive despite FBT, noradrenaline induced a reliable and sustained increase in MAP.

## Acknowledgements

We thank Leah Peck and Glenn Eastwood for assistance with acquiring data. The Uppsala University Hospital Research Fund provided funds for our study.

## Competing interests

None declared.

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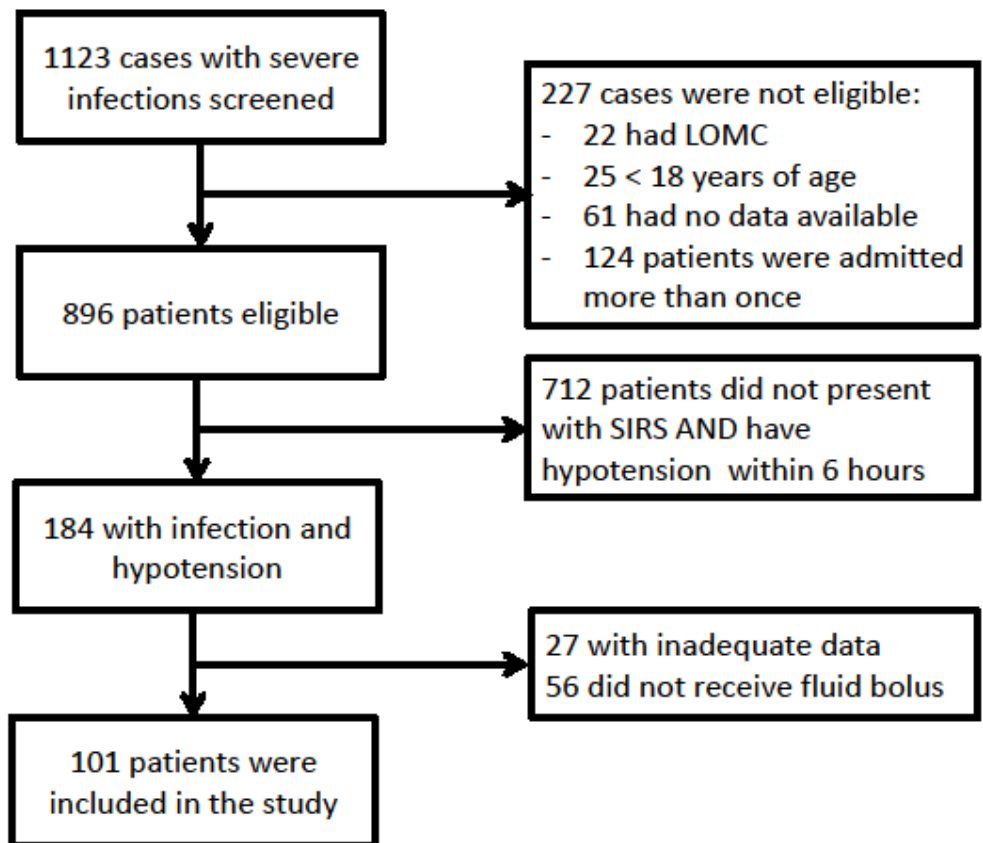
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This appendix was part of the submitted manuscript and has been peer reviewed. It is posted as supplied by the authors.

## Appendix. Supplementary figures and tables

Figure A1. Flowchart describing patient selection process

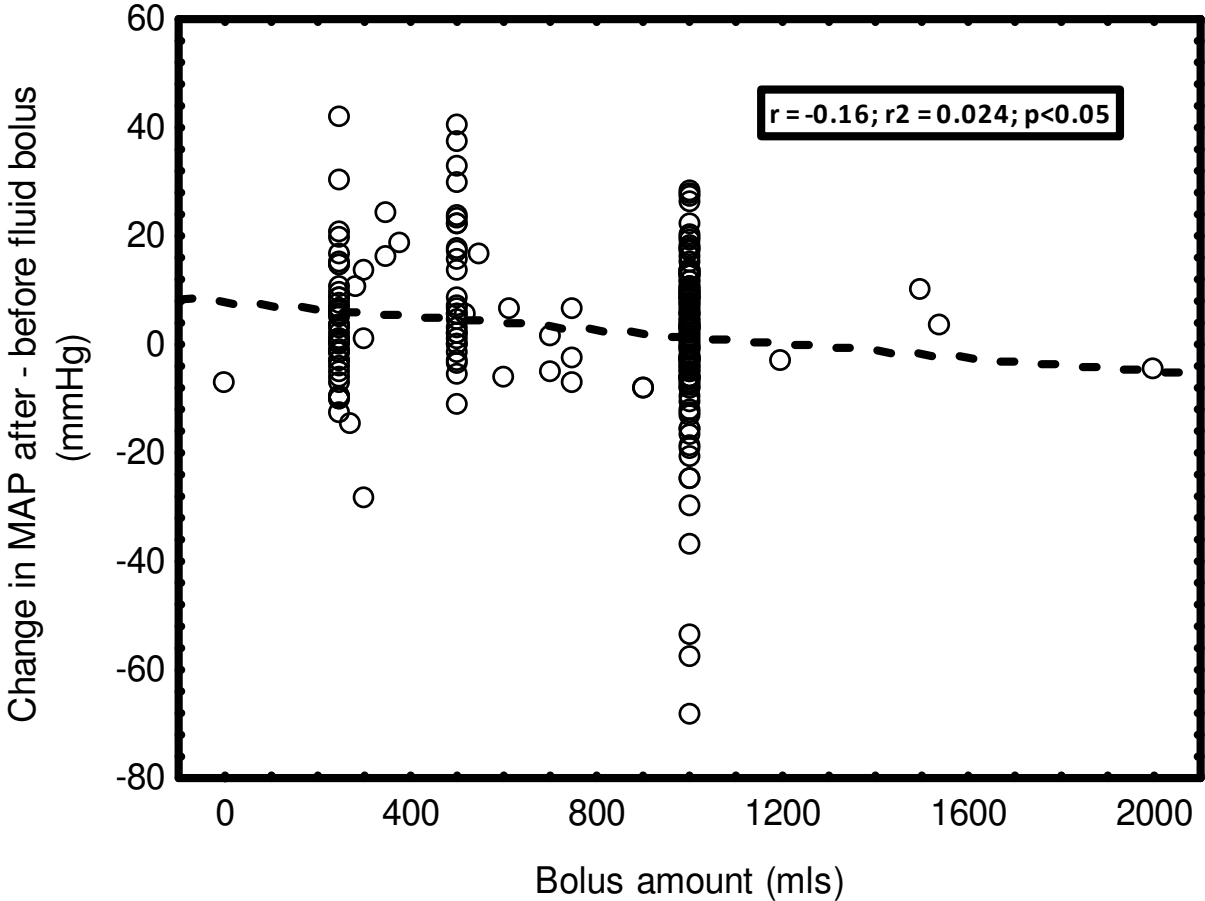


LOMC Limitations in medical care

In case of several admissions for the same patient the first chronologically was used

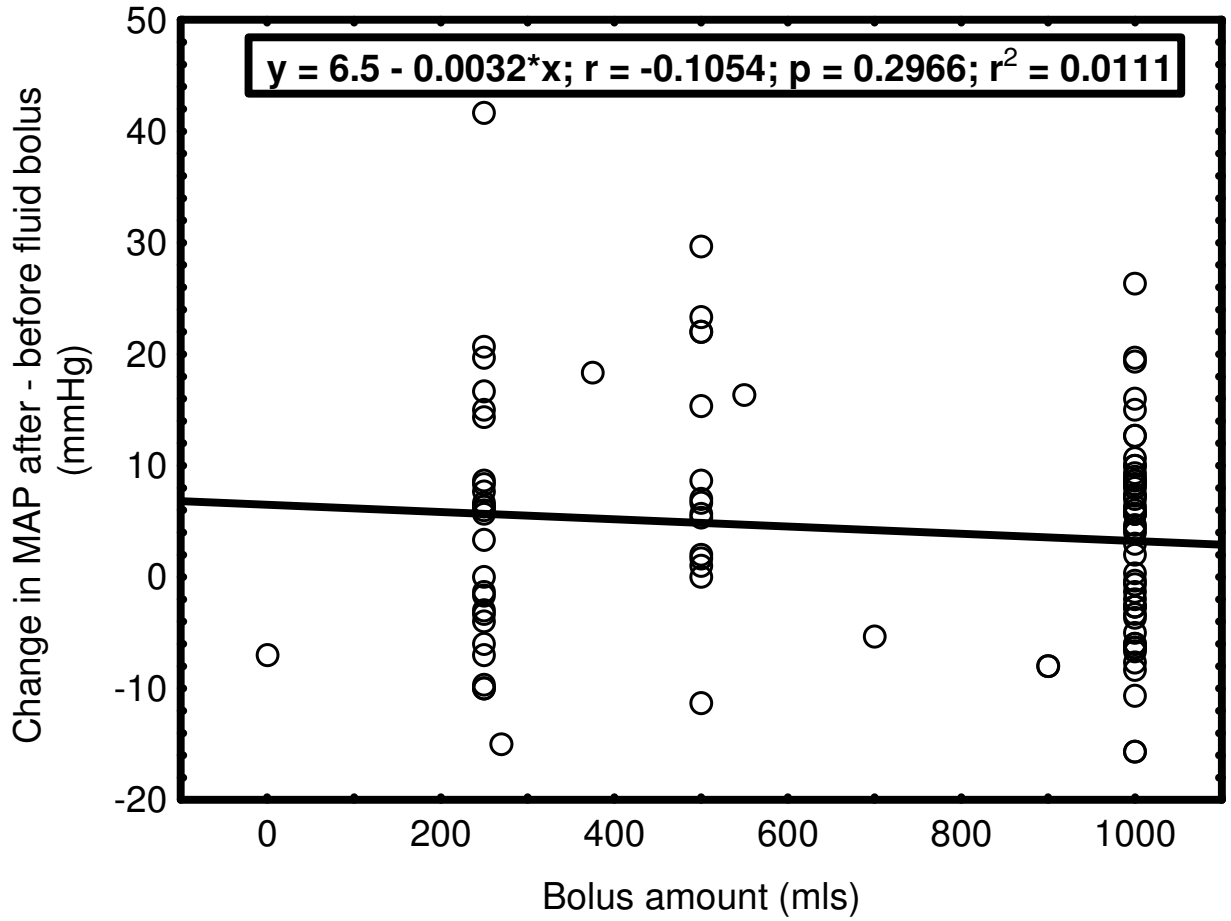
Bolus was defined as fluid administration  $> 250 \text{ mls} \times \text{h}^{-1}$

**Figure A2.** Changes in MAP with different fluid bolus volume in the whole cohort. A positive value on the Y-axis indicates a rise in blood pressure



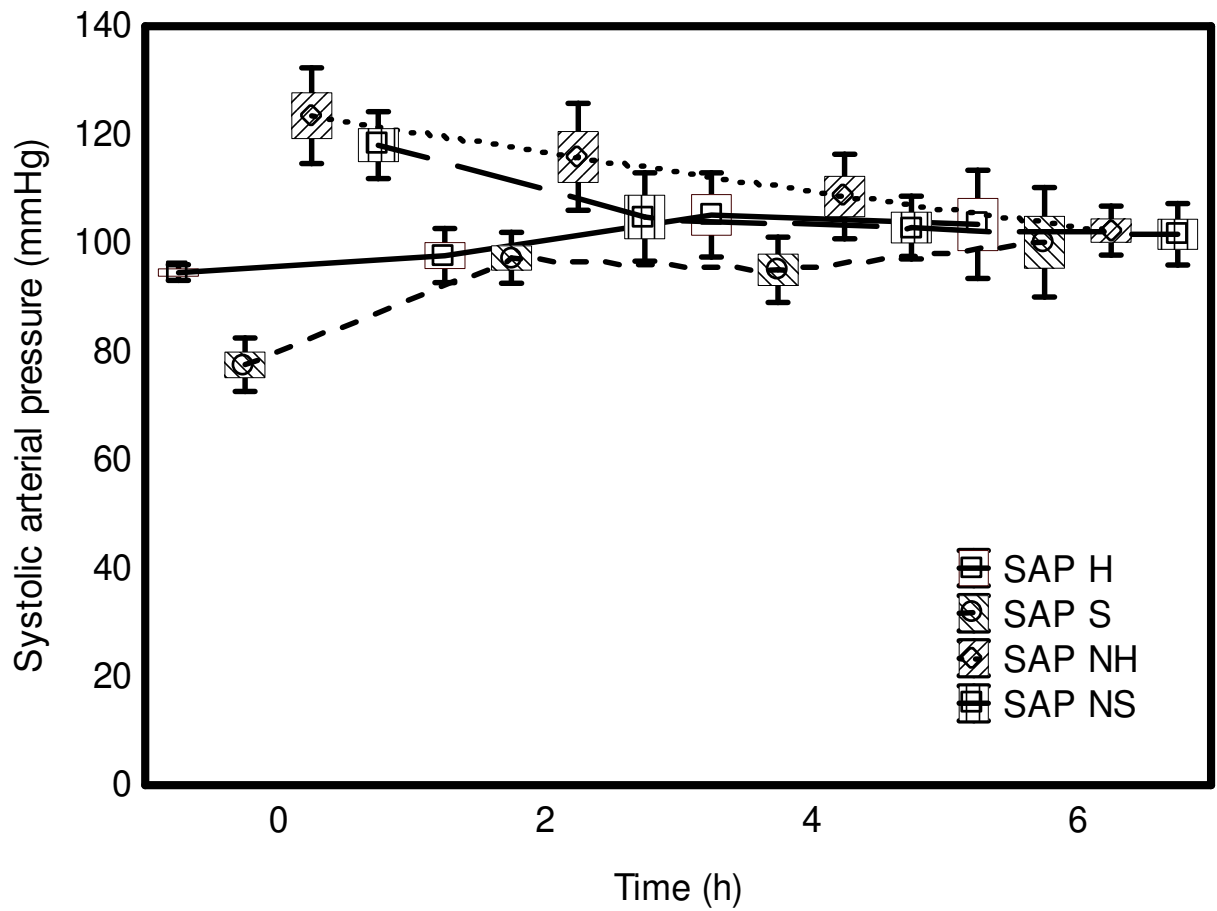


**Figure A3.** Changes in MAP with different fluid bolus volume in patients that were hypotensive or severely hypotensive on arrival to the ED. A positive value indicates a rise in blood pressure

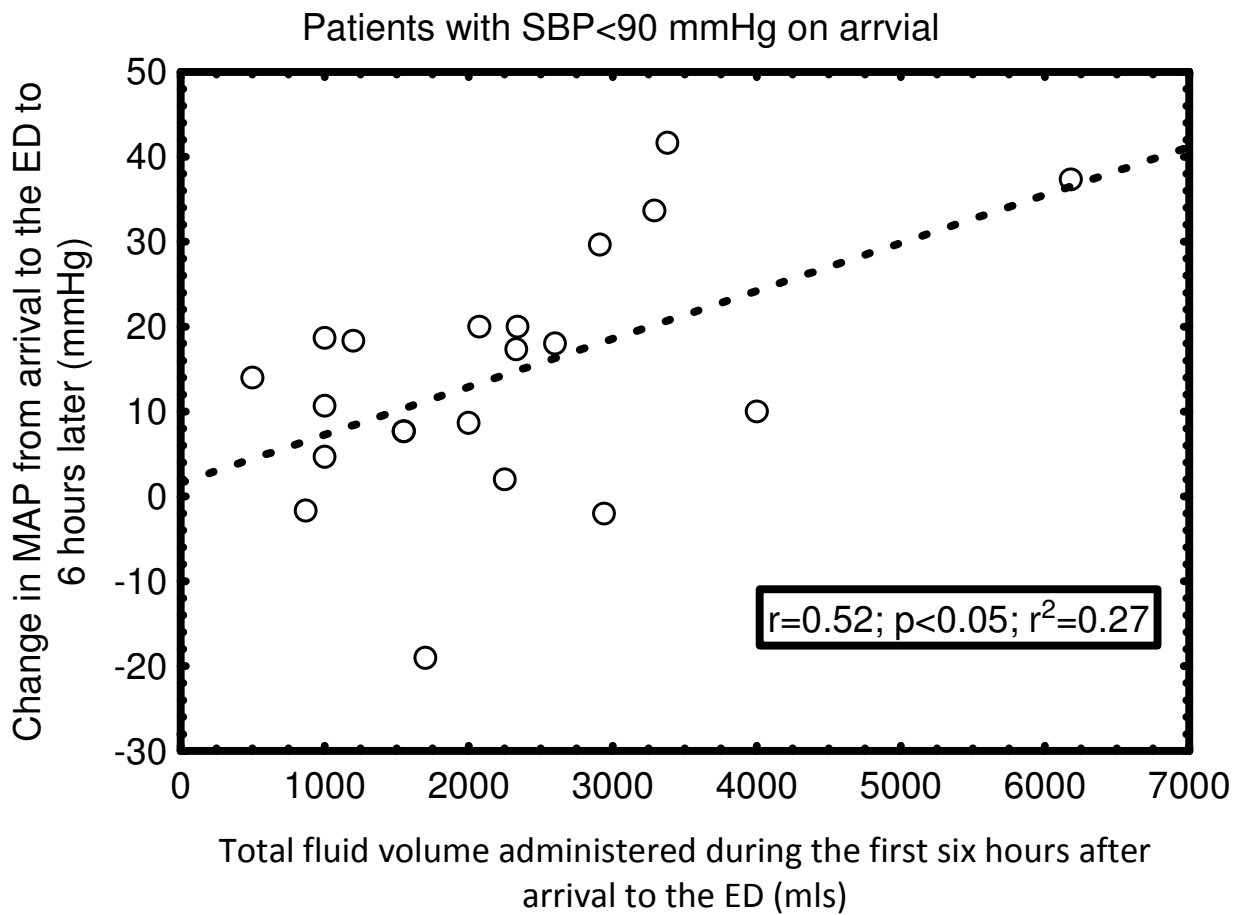




**Figure A5.** Changes in systolic arterial pressure (SAP) in patients who were hypotensive (H) on arrival (SBP < 100 mmHg; H); patients who were severely hypotensive (S) on arrival (SBP < 90 mmHg; S); patients who became hypotensive (NH) and patients who became severely hypotensive (NS) during the first six hours after arrival to the emergency department. Changes are depicted in a box plot. Box: mean  $\pm$  SE; whisker: mean  $\pm$  0.95 confidence interval



**Figure A6.** Scatterplot of the total fluid administered during the first six hours after arrival to the emergency department and the change in mean arterial pressure during the same period in severely hypotensive patients. A positive value on the Y-axis indicates a rise in blood pressure



**Table A1.** Characteristics of full study cohort and patients receiving fluid bolus therapy

<b>All ED patients screened</b>		
<u>Diagnosis and diagnosis codes</u>	Number of cases scanned	Number of patients included
Gastroenteritis and colitis of unspecified origin (A09.9)	30	3
Perforation of oesophagus (K22.3)	2	0
Urinary tract infection (N39.0)	253	8
Acute abdomen (R10.0)	9	0
Bronchopneumonia, unspecified (J18.0)	12	1
Lobar pneumonia, unspecified (J18.1)	9	1
Acute bronchitis, unspecified (J20.9)	4	0
Acute bronchitis, unspecified (J22)	326	14
Pneumonitis due to food and vomit (J69.0)	148	8
Other specified sepsis (A41.8)	26	10
Sepsis, unspecified (A41.9)	300	54
Bacterial infection, unspecified (A49.9)	8	2
<b>Fluid bolus treated patients</b>		
<u>Co-morbidities</u>	No. of observations (in 101 cases)	
Heart failure	17	
Coronary artery disease	17	
CODP	15	
Diabetes mellitus	12	
HIV	0	
Hypertension	34	
Liver failure	8	
History of malignancy	20	
Neurological disease	23	
History of smoking	35	
<u>Sepsis details</u>	50	
Urinary sepsis	12	
Peritonitis	2	
Other intra-abdominal processes	15	
Abscess in extremities	2	
Other causes of sepsis	22	
Severe sepsis	75	
Septic shock	36	
Positive blood culture	18	
Antibiotics given within 6 hours from arrival in the emergency department	83	

**Table A2.** Vital signs in different subgroups. Hypotensive patients vs. severely hypotensive patients during the first 6 hours

	Hypotensive patients n=25				Severely hypotensive patients n=21			
	On arrival	2 hours	4 hours	6 hours	On arrival	2 hours	4 hours	6 hours
Crystalloids administered (ml)		500(0-5000)	580(0-1720)	500(0-2000)		785(0-5000)	480(0-1460)	490(0-1350)
Colloids administered (ml)		0(0-0)	340(0-750)	460(0-700)		0(0-500)	0(0-750)	0(0-600)
Packed red cells administered (ml)		0(0-0)	00(0-0)	50(0-150)		0(0-0)	0(0-0)	0(0-150)
Fresh frozen plasma administered (ml)		0(0-0)	00(0-0)	30(0-180)		0(0-0)	0(0-0)	0(0-180)
Platelets administered (ml)		0(0-0)	0(0-750)	0(0-700)		0(0-0)	0(0-0)	0(0-0)
Fraction of inspired O <sub>2</sub>	0.21(0.21-0.28)	0.21(0.21-0.32)	0.21(0.21-0.32)	0.21(0.21-0.32)	0.21(0.21-0.28)	0.21(0.21-0.28)	0.30(0.21-0.34)	0.28(0.21-0.32)
Body temperature (°C)	37.4±1.4	37.0±1.4	36.7±1.2	36.8±1.2*	37.1±1.4	36.5±1.2	36.3±1.2	36.3±1.4
Heart rate (x min <sup>-1</sup> )	103±25	93±23	90±19	88±21	104±27	97±26	96±21	92±20
Systolic blood pressure (mm Hg)	106±23***	105±17	104±15*	103±17	78±11	97±10	95±13	100±21
Diastolic blood pressure (mm Hg)	65±14***	61±10*	59±12	59±15*	45±8	53±8	53±11	54±12
Mean arterial pressure (mmHg)	71±5***	73±10*	75±16*	76±17	56±8	68±8	66±9	70±14
Respiratory rate (x min <sup>-1</sup> )	18(16-23)	18(16-22)	18(16-22)	18(16-22)	18(16-20)	19(18-22)	18(16-20)	18(18-20)
Arterial SaO <sub>2</sub>	97(94-99)	98(97-100)	98(96-100)	98(97-100)	97(94-99)	99(97-100)	99(97-100)	98(97-100)
Arterial pH	7.37±0.08	7.36±0.08	7.39±0.09	7.40±0.07	7.32±0.09	7.35±0.08	7.41±0.09	7.35±0.06
Arterial PaO <sub>2</sub> (mm Hg)	87±66	151±135	122±76	113±42	32±11	53±35	115±87	112±36
Arterial PaCO <sub>2</sub> (mm Hg)	42±11	40±13	37±4	37±6	42±10	39±9	37±2	40±6
Plasma base excess (mmol x l <sup>-1</sup> )	-1.6±4.6	-2.6±5.5	-1.6±5.4	-1.4±3.7	-4.3±5.7	-3.6±5.4	-0.4±6.2	-2.5±4.8
Plasma lactate (mmol x litre <sup>-1</sup> )	2.0(1.2-2.4)	2.1(1.5-3.1)	2.2(1.9-3.2)	1.8(1.4-2.3)	2.3(1.5-3.0)	1.8(1.5-3.0)	2.8(2.1-2.8)	2.0(1.6-2.8)
Blood haemoglobin (g x l <sup>-1</sup> )	124±24	122±22	113±22	120±20	115±28	118±22	96±26	123±18
Plasma chloride (mmol x l <sup>-1</sup> )	101±5	102±6	102±7	103±6	100±5	102±4	98±6	104±3
Plasma	129(71-	140(72-	123(90-	75(57-94)	142(85-	161(131-	20(20-20)	90(77-

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creatinine ( $\mu\text{mol} \times \text{l}^{-1}$ )	149)	160)*	150)		216)	182)		103)
Plasma Albumin (g x $\text{l}^{-1}$ )	33 $\pm$ 6	32 $\pm$ 7	31 $\pm$ 5	26 $\pm$ 11	30 $\pm$ 8	28 $\pm$ 6	-	-

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<sup>R</sup> Range \* $p < 0.05$  \*\*\* $p < 0.001$

**Table A3.** Vital signs in different subgroups. Survivors vs. non-survivors patients during the first 6 hours

	Survivors at 28 days n=75				Non- survivors at 28 days n=26			
	On arrival	2 hours	4 hours	6 hours	On arrival	2 hours	4 hours	6 hours
Crystalloids administered (ml)		500(0-5000) <sup>R</sup>	580(0-1720) <sup>R</sup>	500(0-2000) <sup>R</sup>		500(0-1750) <sup>R</sup>	500(0-1500) <sup>R</sup>	400(0-2500) <sup>R</sup>
Colloids administered (ml)		0(0-0) <sup>R</sup>	0(0-750) <sup>R</sup>	0(0-700) <sup>R</sup>		0(0-500) <sup>R</sup>	0(0-620) <sup>R</sup>	0(0-500) <sup>R</sup>
Packed red cells administered (ml)		0(0-0) <sup>R</sup>	0(0-0) <sup>R</sup>	0(0-150) <sup>R</sup>		0(0-0) <sup>R</sup>	0(0-0) <sup>R</sup>	0(0-150) <sup>R</sup>
Fresh frozen plasma administered (ml)		0(0-0) <sup>R</sup>	0(0-0) <sup>R</sup>	0(0-180) <sup>R</sup>		0(0-0) <sup>R</sup>	0(0-0) <sup>R</sup>	0(0-300) <sup>R</sup>
Platelets administered (ml)		0(0-0) <sup>R</sup>	0(0-0) <sup>R</sup>	0(0-200) <sup>R</sup>		0(0-0) <sup>R</sup>	0(0-0) <sup>R</sup>	0(0-0) <sup>R</sup>
Fraction of inspired O <sub>2</sub>	0.21(0.21-0.28)	0.21(0.21-0.32)**	0.21(0.21-0.32)**	0.21(0.21-0.32)	0.28(0.21-0.50)	0.28(0.21-0.44)	0.32(0.21-0.50)	0.32(0.21-0.48)
Body temperature (°C)	37.4±1.4	37.0±1.4	36.7±1.2	36.8±1.2**	37.2±1.4	36.4±1.2	36.5±1.1	36.1±0.6
Heart rate (x min <sup>-1</sup> )	103±25*	93±23*	90±19**	88±21***	118±31	108±28	104±22	102±21
Systolic blood pressure (mm Hg)	106±23	105±17	104±15	103±17	99±21	102±25	100±20	99±20
Diastolic blood pressure (mm Hg)	65±14**	61±10	59±12**	59±15	55±16	57±15	53±16	56±13
Mean arterial pressure (mmHg)	78±16*	76±11	74±11**	74±14	69±17	73±14	68±15	71±11
Respiratory rate (x min <sup>-1</sup> )	18(16-23)**	18(16-22)***	18(16-22)**	18(16-22)	23(20-28)	24(19-28)	20(19-25)	19(18-23)
Arterial SaO <sub>2</sub>	97(94-99)	98(97-100)*	98(96-100)	98(97-100)*	97(94-99)	97(95-99)	97(96-99)	97(96-98)
Arterial pH	7.37±0.08	7.36±0.08	7.39±0.09	7.40±0.07	7.33±0.13	7.29±0.13	7.30±0.12	7.29±0.17
Arterial PaO <sub>2</sub> (mm Hg)	87±66	151±135	122±76	113±42	73±77	47±15	102±67	107±68
Arterial PaCO <sub>2</sub> (mm Hg)	42±11	40±13*	37±4	37±6*	47±18	53±22	49±13	48±19
Plasma base excess (mmol x l <sup>-1</sup> )	-1.6±4.6	-2.6±5.5	-1.6±5.4	-1.4±3.7	-3.1±6.1	-3.4±6.0	-3.5±6.0	-4.8±6.3
Plasma lactate (mmol x litre <sup>-1</sup> )	2.0(1.2-2.4)	2.1(1.5-3.1)	2.2(1.9-3.2)	1.8(1.4-2.3)	2.0(1.4-2.9)	1.8(1.5-3.6)	3.5(2.3-7.0)	2.4(1.5-4.7)
Blood haemoglobin (g x l <sup>-1</sup> )	124±24	122±22	113±22	120±20	119±23	121±24	121±23	114±21
White blood cell count (x 10 <sup>9</sup> )	11.5(7.9-18.5)	8.5(2.4-16.9)	20.2(8.6-21.1)	9.4(6.0-15.6)	10.6(5.8-15.5)	12.1(6.6-16.7)	16.6(16.6-16.6)	10.6(10.4-10.8)
Plasma sodium (mmol x l <sup>-1</sup> )	134±5	135±4	133±5	133±5	135±6	135±6	134±5	135±5
Plasma potassium	4.1±0.7	4.1±0.6*	4.1±0.7	3.8±0.7*	4.4±0.6	4.6±0.7	4.4±0.7	4.5±0.7



(mmol x l <sup>-1</sup> )								
Plasma chloride (mmol x l <sup>-1</sup> )	101±5	102±6	102±7	103±6	101±5	102±5	103±5	106±6
Plasma creatinine (μmol x l <sup>-1</sup> )	107(71-149)	129(72-160)	148(90-150)	77(57-94)	146(84-197)	150(85-162)	116(38-194)	103(77-274)
Plasma Albumin (g x l <sup>-1</sup> )	33±6	32±7	31±5	26±11	29(22-32)	32(29-38)	26(26-26)	23(18-27)

<sup>R</sup> Range \*p<0.05 \*\*\*p<0.001

**Table A4.** Mortality in severely hypotensive patients at 6 hours (i.e. the failed early resuscitation group vs. the rest)

BP at 6h	Alive at 28 days	Count	Percent
Severely hypotensive at 6h	Y	12	71
	N	5	29
Normotensive at 6h	Y	30	68
	N	14	32
Hypotensive at 6 h	Y	28	80
	N	7	20
Missing data	Y	5	

No difference between mortality ratios.

**Table A5.** Physiological changes over time in the hypotensive on arrival, severely hypotensive on arrival, hypotensive in the ED, severely hypotensive in the ED groups

Group based on timing of hypotension	Hypotensive on arrival		Severely hypotensive on arrival		Normotensive on arrival, hypotensive later		Normotensive on arrival, severely hypotensive later	
n	25		21		20		35	
Mortality at 30 days (%)	16		38		10		34	
	0h	6h	0h	6h	0h	6h	0h	6h
Crystalloids administered (ml)	-	1700(220-3670) <sup>R</sup>	-	1700(200-6000) <sup>R</sup>	-	1200(290-3630) <sup>R</sup>	-	1350(320-4400) <sup>R</sup>
Colloids administered (ml)	-	0(0-200) <sup>R</sup>	-	0(0-1370) <sup>R</sup>	-	0(0-0) <sup>R</sup>	-	0(0-1000) <sup>R</sup>
Packed red cells administered (ml)	-	0(0-0) <sup>R</sup>	-	0(0-180) <sup>R</sup>	-	0(0-0) <sup>R</sup>	-	0(0-150)
Fresh frozen plasma administered (ml)	-	0(0-0) <sup>R</sup>	-	0(0-150) <sup>R</sup>	-	0(0-0) <sup>R</sup>	-	0(0-300)
Platelets administered (ml)	-	0(0-0) <sup>R</sup>	-	0(0-0) <sup>R</sup>	-	0(0-0) <sup>R</sup>	-	0(0-200)
Fraction of inspired O <sub>2</sub>	0.21(0.21-0.36)	0.28(0.21-0.32)	0.21(0.21-0.28)	0.28(0.21-0.32)	0.21(0.21-0.21)	0.21(0.21-0.32)	0.28(0.21-0.44)	0.25(0.21-0.33)
Body temperature (°C)	37.1±1.6	37.0±1.2	37.1±1.4	36.3±1.4	37.6±1.3	36.6±0.9	37.4±1.3	36.6±0.8
Heart rate (x min <sup>-1</sup> )	104±29	96±20	104±27	92±20	110±15	92±25	108±32	89±22
Systolic blood pressure (mm Hg)	95±4	104±24	78±11	100±21	124±19	102±10	118±17	102±16
Diastolic blood pressure (mm Hg)	54±8	62±16	45±8	54±12	67±11	59±11	74±14	59±16
Mean arterial pressure (mmHg)	71±5	76±17	56±8	70±14	86±10	73±9	88±14	73±13
Respiratory rate (x min <sup>-1</sup> )	20(16-24)	20(18-22)	18(16-20)	18(18-20)	19(17-26)	19(17-24)	21(18-28)	18(16-23)
Arterial SaO <sub>2</sub>	97(94-98)	98(96-100)	97(94-99)	98(97-100)	97(94-99)	98(97-99)	98(94-100)	97(96-99)
Arterial pH	7.40±0.10	7.39±0.14	7.32±0.09	7.35±0.06	7.36±0.08	-	7.35±0.11	7.38±0.12
Arterial PaO <sub>2</sub> (mm Hg)	-	104±71	-	112±36	133±111	-	93±52	102±29
Arterial PaCO <sub>2</sub> (mm Hg)	41±8	39±11	42±9	40±6	46±17	-	46±16	41±15
Plasma base excess (mmol x l <sup>-1</sup> )	-1.4±4.7	-2.9±6.4	-4.3±5.7	-2.5±4.8	-0.5±4.8	-	-2.2±5.2	-2.0±3.9
Plasma lactate (mmol/litre)	2.1(1.4-2.4)	1.8(1.4-4.7)	2.3(1.5-3.0)	2.0(1.6-2.8)	1.3(1.2-1.9)	-	2.0(1.3-2.5)	1.7(1.5-2.2)
Blood haemoglobin (g x l <sup>-1</sup> )	123±20	110±17	115±28	123±18	129±25	-	123±22	116±17
White blood cell count (x 10 <sup>9</sup> )	10.7(7.1-16.2)	-	12.4(10.4-21.2)	-	9.6(7.4-17)	-	10.9(7.0-16.6)	-
Plasma sodium (mmol x l <sup>-1</sup> )	135±5	132±5	132±5	133±3	135±6	-	135±4	134±5
Plasma potassium (mmol x l <sup>-1</sup> )	4.0±0.6	4.0±1.1	4.4±0.8	4.3±0.6	4.0±0.6	-	4.4±0.7	3.9±0.5

Plasma chloride (mmol x l <sup>-1</sup> )	101±6	101±7	100±5	104±3	100±5	-	102±5	105±5
Plasma creatinine (μmol x l <sup>-1</sup> )	107(72- 133)	-	142(85- 216)	-	107±46	-	138(65- 160)	-
Plasma Albumin (g x l <sup>-1</sup> )	32±6	-	30±8	-	32±7	-	33±6	-

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<sup>R</sup> Range