

# Supplementary Appendix 1

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: The SAFE Study Investigators. A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit. *N Engl J Med* 2004;350:2247-56.

## Supplementary Appendix

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### Table S1. SAFE study inclusion and exclusion criteria

Patients were eligible for inclusion in the study if all the following requirements were met:

1. The treating clinician judged that fluid resuscitation was required for intravascular fluid depletion that was in addition to intravenous fluid that was required for nutrition or to replace ongoing insensible losses, urinary losses, ongoing losses from other sites (eg. fistula losses from the gastrointestinal tract, urinary losses from diabetes insipidus, cerebral salt wasting syndrome or the polyuric phase of acute renal failure) or to restore normonatremia.
2. The treating clinician considered that both 4% human albumin solution and 0.9% sodium chloride were equally appropriate for the patient and that no specific indication or contraindication for either existed.
3. The requirement for fluid resuscitation must have been supported by at least one of the following clinical signs:
  - a. Heart rate greater than 90 beats per minute
  - b. Systolic blood pressure (SBP) less than 100 mmHg or mean arterial pressure (MAP) less than 75 mmHg or a 40 mmHg decrease in SBP or MAP from the baseline recording. Or requirement for inotropes or vasopressors to maintain blood pressure at those levels.
  - c. Central venous pressure less than 10 mmHg
  - d. Pulmonary capillary wedge pressure less than 12 mmHg
  - e. Respiratory variation in systolic or mean arterial blood pressure of greater than 5 mmHg
  - f. Capillary refill time greater than one second
  - g. Urine output less than 0.5 mL/kg for one hour

Patients were excluded from the study if one or more of the following were present:

1. A previous adverse reaction to human albumin solution
2. A religious objection to the administration of human blood products (for example if patient was a Jehovah's Witness)
3. Patient to receive plasmapheresis during the ICU admission
4. Admission to the ICU following cardiac surgery.
5. Admission to the ICU for the treatment of body burn.
6. Admission to the ICU following liver transplantation surgery.
7. Age less than 18 years.
8. Brain dead or brain death was likely to be diagnosed within 24 hours from eligibility assessment.
9. If the patient was moribund and expected to die within 24 hours from eligibility assessment - defined as having a treatment limitation order in place that exceeded a 'not for resuscitation' order and that indicated the treating clinicians were not committed to full supportive care.
10. If the patient had previously been enrolled and had completed follow up in the SAFE study.
11. If the patient had previously received fluid resuscitation that was prescribed within the study ICU and during the current hospital admission.
12. If the patient had been transferred to the study ICU from a non-study ICU and received a fluid bolus or fluid resuscitation for the treatment of volume depletion in the non-study ICU.

Table S2:

Definition of severe sepsis:

1. Presence of a defined focus of infection as indicated by either (i) An organism grown in blood or sterile site or (ii) An abscess or volume of infected tissue (pneumonia, peritonitis, vascular line infection). A positive culture or a clinical diagnosis of infection (eg. Perforation at laparotomy) that became evident later was included provided the cultures were taken pre-randomization or the clinical condition existed pre-randomization.
2. Two or more of the four Systemic Inflammatory Response Syndrome (SIRS) criteria. The four SIRS criteria are (i) A core temperature  $>38^{\circ}\text{C}$  or less than  $36^{\circ}\text{C}$  (as measured rectally, via central line or tympanic). If oral or axillary temperature was used,  $0.5^{\circ}\text{C}$  was added to the measured value. Hypothermia less than  $36^{\circ}\text{C}$  must have been confirmed by a rectal or core temperature measurement only. (ii) A heart rate  $>90$  beats/minute. If a patient had an atrial arrhythmia, the ventricular rate was measured. If a patient was known to have a medical condition or was receiving treatment that would prevent tachycardia (for example, heart block or beta blockers), they had to meet two of the remaining three SIRS criteria. (iii) A respiratory rate  $>20$  breaths per minute or a  $\text{PaCO}_2$  less than 32 mmHg or mechanical ventilation for an acute process. (4) A white blood cell count of greater than  $12 \times 10^9/\text{L}$  or less than  $4 \times 10^9/\text{L}$  or greater than 10% immature neutrophils (band forms).
3. The presence of severe organ dysfunction caused by infection in at least one organ as recorded by the following SOFA scores: Respiratory greater than 1; Hematologic greater than 1; Hepatic greater than 1; Cardiovascular 1, 3 or 4 or Renal greater than 2.

Table S3. SOFA SCORE					
ORGAN SYSTEM	0	1	2	3	4
Respiration PaO <sub>2</sub> / FIO <sub>2</sub> (in mmHg)*	>400	301 - 400	201 - 300	101 - 200 (with respiratory support)	≤ 100 (with respiratory support)
Coagulation Platelets (x 10 <sup>3</sup> / mm <sup>3</sup> )	>150	101 - 150	51 - 100	21 - 50	≤ 20
Liver Bilirubin (mg / dl)	< 1.2	1.2 – 1.9	2.0 – 5.9	6.0 – 11.9	> 12.0
(μmol / L)	<20	20 - 32	33 - 101	102 - 204	>204
Cardiovascular Hypotension **	No hypotension	MAP < 70 mmHg	dopamine ≤ 5.0	dopamine > 5.0	dopamine > 15.0
			or any dose dobutamine	or epinephrine ≤ 0.1	or epinephrine >0.1
				or norepinephrine ≤ 0.1	or norepinephrine >0.1
Renal Creatinine (mg / dl)	< 1.2	1.2 – 1.9	2.0 – 3.4	3.5 – 4.9	> 5.0
(μmol / L)	< 110	110 - 170	171 - 299	300 - 440	> 440
<b>OR</b> Urine output				or < 500 ml / day	or < 200 ml / day

SOFA scoring system for organ function and failure<sup>13</sup> \* To convert mmHg to kPa, multiply the value by 0.1333

\*\* Adrenergic agents administered for at least 1 hour (doses are given in μg / kg / minute)

Fig. S1. Flow of patients through study.

