

ORIGINAL ARTICLE

# A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit

The SAFE Study Investigators\*

## ABSTRACT

### BACKGROUND

It remains uncertain whether the choice of resuscitation fluid for patients in intensive care units (ICUs) affects survival. We conducted a multicenter, randomized, double-blind trial to compare the effect of fluid resuscitation with albumin or saline on mortality in a heterogeneous population of patients in the ICU.

### METHODS

We randomly assigned patients who had been admitted to the ICU to receive either 4 percent albumin or normal saline for intravascular-fluid resuscitation during the next 28 days. The primary outcome measure was death from any cause during the 28-day period after randomization.

### RESULTS

Of the 6997 patients who underwent randomization, 3497 were assigned to receive albumin and 3500 to receive saline; the two groups had similar baseline characteristics. There were 726 deaths in the albumin group, as compared with 729 deaths in the saline group (relative risk of death, 0.99; 95 percent confidence interval, 0.91 to 1.09;  $P=0.87$ ). The proportion of patients with new single-organ and multiple-organ failure was similar in the two groups ( $P=0.85$ ). There were no significant differences between the groups in the mean ( $\pm$ SD) numbers of days spent in the ICU ( $6.5\pm 6.6$  in the albumin group and  $6.2\pm 6.2$  in the saline group,  $P=0.44$ ), days spent in the hospital ( $15.3\pm 9.6$  and  $15.6\pm 9.6$ , respectively;  $P=0.30$ ), days of mechanical ventilation ( $4.5\pm 6.1$  and  $4.3\pm 5.7$ , respectively;  $P=0.74$ ), or days of renal-replacement therapy ( $0.5\pm 2.3$  and  $0.4\pm 2.0$ , respectively;  $P=0.41$ ).

### CONCLUSIONS

In patients in the ICU, use of either 4 percent albumin or normal saline for fluid resuscitation results in similar outcomes at 28 days.

The Saline versus Albumin Fluid Evaluation (SAFE) Study is a collaboration of the Australian and New Zealand Intensive Care Society Clinical Trials Group, the Australian Red Cross Blood Service, and the George Institute for International Health. The writing committee (Simon Finfer, M.B., B.S., Rinaldo Bellomo, M.B., B.S., M.D., Neil Boyce, M.B., B.S., Ph.D., Julie French, R.N., John Myburgh, M.B., B.Ch., Ph.D., and Robyn Norton, Ph.D., M.P.H.) takes responsibility for the content of this article. Address reprint requests to Dr. Finfer at ANZICS CTG, Level 3, 10 Levers St., Carlton, VIC 3053, Australia, or at [ctg@anzics.com.au](mailto:ctg@anzics.com.au).

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THE ADMINISTRATION OF INTRAVENOUS fluids to maintain or increase intravascular volume is a common intervention in the intensive care unit (ICU), but there is uncertainty whether the choice of fluid significantly influences patients' outcomes.<sup>1-7</sup> In particular, no adequately powered randomized, controlled trials have examined the effect of fluid choice on the survival of patients in the ICU. In the absence of such trials, a number of meta-analyses have examined how the choice of crystalloid or colloid solution and of albumin-containing or albumin-free fluid affects survival in critically ill patients and in patients who are less severely ill.<sup>1-3,7</sup> A meta-analysis published by the Cochrane Injuries Group Albumin Reviewers included 24 studies involving a total of 1419 patients and suggested that the administration of albumin-containing fluids resulted in a 6 percent increase in the absolute risk of death when compared with the administration of crystalloid solutions.<sup>1</sup> However, a subsequent meta-analysis of 55 trials involving a total of 3504 patients examined the effect of resuscitation with albumin-containing fluid on the risk of death in a general population of patients and did not find a significant increase in the risk of death.<sup>3</sup>

The conflicting results of such meta-analyses have left many clinicians unsure about the effect of albumin-containing fluids on survival in critically ill patients. To address this uncertainty, we conducted the Saline versus Albumin Fluid Evaluation (SAFE) Study in 16 ICUs in Australia and New Zealand. We tested the hypothesis that when 4 percent albumin is compared with 0.9 percent sodium chloride (normal saline) for intravascular-fluid resuscitation in patients in the ICU, there is no difference in the 28-day rate of death from any cause.

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## METHODS

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### STUDY DESIGN AND TREATMENT PROTOCOL

Patients 18 years of age or older who had been admitted to the closed, multidisciplinary ICUs of 16 academic tertiary hospitals in Australia and New Zealand between November 2001 and June 2003 were assessed for eligibility for the study. Eligible patients were those whom the treating clinician judged to require fluid administration to maintain or increase intravascular volume, with this decision supported by the fulfillment of at least one objective criterion. Patients admitted to the ICU after cardiac surgery, after liver transplantation, or for the treatment of burns were excluded. Details of the inclu-

sion and exclusion criteria are given in Table S1 of the Supplementary Appendix (available with the full text of this article at [www.nejm.org](http://www.nejm.org)). A detailed description of the study design has been published elsewhere.<sup>8</sup>

The study protocol was approved by the ethics committees of the University of Sydney and of each participating institution. Written informed consent was to be obtained from all competent patients; in cases in which prior consent could not be obtained from the patient because of critical illness or the use of sedative or anesthetic drugs, consent could be delayed, and a provision for delayed consent was applied. In such cases, the patient or his or her surrogate decision maker was informed of the study as soon as practicable, and consent was sought to continue the study procedures and to access the participant's medical records for study-related data. The patients or their legal surrogates were informed of their right to request that the study procedures be discontinued and their right to refuse the study-related use of their medical records.

Eligible patients were randomly assigned to receive either 4 percent albumin (Albumex, CSL) or normal saline, with the random assignments stratified according to institution and according to whether there was a diagnosis of trauma on admission to the ICU. Randomization was carried out centrally with the use of a minimization algorithm, and the service was accessed on the Internet through a secure Web site. Study fluids were supplied in identical 500-ml bottles, and blinding was ensured through the use of specially designed masking cartons and specially designed and manufactured administration sets.<sup>8</sup> The effectiveness of the blinding was confirmed in a formal study before the trial was initiated. The treating clinicians determined the amount and rate of fluid administration according to each patient's clinical status and response to treatment. The allocated study treatment was to be used for all fluid resuscitation in the ICU until death or discharge or until 28 days after randomization. The administration of intravenous fluids outside the ICU was not controlled.

In addition to the study fluid, patients received maintenance fluids, specific replacement fluids, enteral or parenteral nutrition, and blood products at the discretion of the treating clinicians. The monitoring of central venous pressure, pulmonary-artery catheterization, and all other aspects of patient care were performed at the discretion of the treating clinicians.

**BASELINE ASSESSMENT AND FOLLOW-UP****DATA COLLECTION**

Data collected at baseline included the Acute Physiology and Chronic Health Evaluation II score,<sup>9</sup> as well as information pertaining to diagnostic criteria for severe sepsis<sup>10</sup> (Table S2 of the Supplementary Appendix) and for the acute respiratory distress syndrome.<sup>11</sup> Patients were identified as having traumatic brain injury at baseline if they had a history of trauma, a Glasgow Coma Score<sup>12</sup> while not sedated of less than 14, and an abnormality consistent with traumatic brain injury on a computed tomographic scan of the head. The cardiovascular, respiratory, renal, hematologic, and hepatic components of the Sequential Organ-Failure Assessment (SOFA) score,<sup>13</sup> as described in Table S3 of the Supplementary Appendix, were recorded at the time of randomization, daily for the next seven days, and then every third day until discharge from the ICU or until day 28. After randomization, the heart rate, central venous pressure, mean arterial blood pressure, volume of study fluid administered, volume of non-study fluid and blood products administered, net fluid balance (calculated as the total fluid input minus the total fluid output), use of mechanical ventilation, and use of renal-replacement therapy (intermittent or continuous hemodialysis, hemofiltration, or hemodiafiltration) were recorded daily until discharge from the ICU or death or until day 28.

**OUTCOME MEASURES**

The primary outcome measure was death from any cause within 28 days after randomization. Secondary outcome measures were the survival time during the first 28 days, the proportion of patients who had one, two, three, four, or five new organ failures (defined as a documented change in the cardiovascular, respiratory, renal, hematologic, or hepatic component of the SOFA score from 0, 1, or 2 at baseline to 3 or 4 during the ICU stay, where higher scores indicate increasingly severe organ dysfunction), the duration of mechanical ventilation, the duration of renal-replacement therapy, and the duration of the ICU and hospital stay.

Death from any cause within 28 days after randomization was also examined in six predefined subgroups according to the presence or absence of trauma, the presence or absence of severe sepsis, and the presence or absence of the acute respiratory distress syndrome at baseline.

**STUDY AND DATA MANAGEMENT**

Two preplanned interim analyses were performed by an independent statistician after recruitment of the first 2333 patients (33 percent of the planned total) and the first 4666 patients (67 percent), and the results were reviewed by the independent data-monitoring committee.

The George Institute for International Health at the University of Sydney performed the data management, the site management, and the data analysis, independently of the funding agencies. The manuscript was prepared by the writing committee and was revised by the study investigators, who approved the final manuscript.

**STATISTICAL ANALYSIS**

The trial was designed to enroll 7000 patients, thereby providing a power of 90 percent to detect a 3 percent difference in absolute mortality rates between the two groups from an estimated baseline mortality rate of 15 percent. The data were exported from the study database and analyzed with the use of SPSS software (version 11.5). All analyses were performed on an intention-to-treat basis. Where data were missing, we report the number of available observations, and we make no assumptions about the missing data.

Proportions were compared by means of the chi-square test or Fisher's exact test, and continuous variables were compared by means of unpaired t-tests. The results of comparisons of event rates in the two groups are presented as relative risks with 95 percent confidence intervals. Survival times were compared by means of the log-rank test and are presented as Kaplan-Meier curves without adjustment for baseline covariates. Heterogeneity of treatment effects among subgroups was assessed with the use of the test for a common relative risk.<sup>14</sup>

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**RESULTS**

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**STUDY PATIENTS**

Seven thousand random assignments to a study treatment were made (3499 to the albumin group and 3501 to the saline group). Three patients mistakenly underwent randomization twice within 28 days; they were followed for 28 days beginning at the time of the first randomization, and for purposes of data analysis were considered part of the group to which they were first assigned. Thus, the study population comprised 6997 patients, 3497 of whom

**Table 1. Baseline Characteristics of the Patients.\***

Characteristic	Albumin Group	Saline Group
Age — yr	58.6±19.1	58.5±18.7
Female sex — no. (%)	1424 (40.7)	1376 (39.3)
Reason for admission to ICU — no. (%)		
Surgical	1473 (43.0)	1465 (42.8)
Medical	1955 (57.0)	1958 (57.2)
Source of admission to ICU — no. (%)		
Emergency department	948 (27.7)	977 (28.5)
Hospital floor	614 (17.9)	573 (16.7)
Another ICU	63 (1.8)	66 (1.9)
Another hospital	323 (9.4)	341 (10.0)
Operating room (emergency surgery)	801 (23.4)	780 (22.8)
Operating room (elective surgery)	662 (19.3)	678 (19.8)
Same ICU (readmission)	17 (0.5)	8 (0.2)
Predefined subgroups — no. (%)		
Trauma	597 (17.4)	590 (17.2)
Severe sepsis	603 (18.1)	615 (18.4)
Acute respiratory distress syndrome	61 (1.8)	66 (1.9)
APACHE II score†	18.7±7.9	19.0±8.0
Physiological variables		
Heart rate — beats/min	91.4±23.5	92.3±23.5
Mean arterial pressure — mm Hg	77.8±16.4	78.2±16.3
Central venous pressure — mm Hg	9.0±4.7	8.6±4.6‡
Urine output — ml/hr	89.7±132.4	95.0±161.4
Serum albumin — g/liter	27.4±7.8	27.7±7.9
Organ failure— no. (%)§		
No failure	1962 (57.2)	1885 (55.1)
1 organ	1075 (31.4)	1148 (33.5)
2 organs	335 (9.8)	329 (9.6)
3 organs	50 (1.5)	57 (1.7)
4 organs	5 (0.1)	4 (0.1)
5 organs	1 (<0.1)	0
Mechanical ventilation — no. (%)	2186 (63.8)	2217 (64.8)
Renal-replacement therapy — no. (%)	45 (1.3)	41 (1.2)
Albumin in previous 72 hr — no. (%)	127 (3.7)	135 (3.9)

\* Plus-minus values are means ±SD. Percentages were calculated according to the number of patients for whom data were available: for sex, 3497 in the albumin group and 3500 in the saline group; for severe sepsis, 3339 in the albumin group and 3338 in the saline group; and for all the other variables, 3428 in the albumin group and 3423 in the saline group. Because of rounding, not all percentages total 100. ICU denotes intensive care unit, and APACHE II Acute Physiology and Chronic Health Evaluation II.

† Higher scores on APACHE II indicate more severe illness.

‡ P=0.03 for the comparison with the value in the albumin group (without correction for multiple-hypothesis testing).

§ Organ failure was defined as a Sequential Organ-Failure Assessment score<sup>13</sup> of 3 or 4 for any individual organ system.

were assigned to receive albumin and 3500 of whom were assigned to receive saline. The majority of the patients (6628 [94.7 percent] — 3312 of those in the albumin group [94.7 percent] and 3316 of those in the saline group [94.7 percent]) were enrolled with the use of the provision for delayed consent. Delayed consent was obtained from the patient in 2713 cases (38.8 percent) and from a surrogate decision maker (a relative, a legally recognized surrogate, or an institutional ethics committee) in the remaining cases. Prior consent was obtained from the patient in 45 cases (0.6 percent) and from a surrogate decision maker in 335 cases (4.8 percent).

At baseline, the only statistically significant difference between the two groups was a higher mean (±SD) central venous pressure in the albumin group (9.0±4.7 mm Hg, vs. 8.6±4.6 mm Hg in the saline group; P=0.03). The baseline characteristics of the 6997 patients are summarized in Table 1, and their progress through the study is summarized in Figure S1 of the Supplementary Appendix.

Study fluid was administered to all but 197 patients (2.8 percent), including 90 in the albumin group and 107 in the saline group. Resuscitation fluids in addition to the allocated study fluid were administered to 309 patients in the albumin group (8.8 percent) and 375 in the saline group (10.7 percent). The most common reason for the administration of nonstudy resuscitation fluid was error (in 189 patients in the albumin group [5.4 percent] and 190 in the saline group [5.4 percent]). Clinicians' preference for a specific nonstudy resuscitation fluid was the reason for its administration in 68 patients in the albumin group (1.9 percent) and 103 in the saline group (2.9 percent). At the completion of the trial, information on vital status 28 days after randomization was unavailable for 67 patients (1.0 percent), including 26 in the albumin group and 41 in the saline group. In 56 of these 67 cases, vital status was missing because the patient or his or her legal surrogate had withheld or withdrawn consent.

#### FLUIDS ADMINISTERED AND TREATMENT EFFECTS

On each of the first three study days, the patients who had been randomly assigned to receive albumin received significantly less study fluid than did those assigned to saline, resulting in a significantly greater net positive fluid balance in the saline group on each of those days (Table 2). The ratios of the volume of albumin to the volume of saline administered during the first four days were as follows: 1:1.3 on day 1, 1:1.6 on day 2, 1:1.3 on day 3, and 1:1.2 on

**Table 2. Fluids Administered and Physiological Effects of Treatment.\***

Variable	Albumin Group		Saline Group		P Value†
	No. of Patients	Value	No. of Patients	Value	
Study fluid (ml)					
Day 1	3410	1183.9±973.6	3418	1565.3±1536.1	<0.001
Day 2	3059	602.7±892.7	3068	954.0±1484.4	<0.001
Day 3	2210	268.0±554.5	2202	348.3±753.5	0.03
Day 4	1686	192.3±427.0	1664	228.6±642.6	0.57
Nonstudy fluid (ml)					
Day 1	3392	1459.4±1183.2	3405	1505.6±1254.3	0.30
Day 2	3051	2615.9±1372.5	3057	2707.3±1435.7	0.009
Day 3	2199	2618.5±1346.5	2191	2660.9±1319.3	0.15
Day 4	1680	2691.5±1228.7	1656	2707.7±1255.4	0.36
Packed red cells (ml)					
Day 1	3411	97.8±360.7	3415	71.7±296.8	<0.001
Day 2	3066	106.5±321.4	3074	61.1±235.2	<0.001
Day 3	2217	59.8±225.5	2210	49.5±190.8	0.30
Day 4	1692	43.6±167.5	1668	46.0±189.0	0.77
Net positive fluid balance (ml)					
Day 1	3363	1543.6±1619.7	3382	1990.5±2061.7	<0.001
Day 2	3044	1015.3±1826.9	3052	1505.1±2215.9	<0.001
Day 3	2190	422.1±1633.3	2182	553.0±1732.3	0.007
Day 4	1671	137.2±1491.0	1649	155.7±1650.6	0.70
Mean arterial pressure (mm Hg)					
Day 1	3406	81.4±14.4	3408	80.9±14.5	0.14
Day 2	3068	84.4±15.1	3075	84.2±15.7	0.49
Day 3	2215	87.2±15.3	2209	86.9±16.1	0.62
Day 4	1688	88.3±15.9	1666	88.4±16.3	0.87
Heart rate (beats/min)					
Day 1	3398	88.0±20.2	3406	89.7±20.8	<0.001
Day 3	3071	88.5±19.5	3075	89.5±19.2	0.06
Day 3	2216	88.8±19.1	2213	89.7±18.8	0.10
Day 4	1691	89.5±18.9	1668	89.9±18.5	0.52
Central venous pressure (mm Hg)					
Day 1	2204	11.2±4.8	2270	10.0±4.5	<0.001
Day 2	2095	11.6±4.9	2135	10.4±4.3	<0.001
Day 3	1531	11.4±4.8	1589	10.7±4.4	<0.001
Day 4	1221	11.1±4.8	1230	10.5±4.4	<0.001
Serum albumin (g/liter)					
Day 1	2081	28.7±7.0	2061	24.7±6.5	<0.001
Day 2	2708	30.8±6.4	2703	24.5±5.9	<0.001
Day 3	1921	30.0±6.4	1905	23.6±5.6	<0.001
Day 4	1498	29.0±6.2	1478	23.1±5.5	<0.001

\* Plus-minus values are means ±SD.

† P values are for the comparison between the two means for each variable at each time point.

day 4. The overall ratio of the volume of albumin to the volume of saline administered during the first four days was approximately 1:1.4. Patients in the two groups received similar volumes of other fluids during the first four days, except on days 1 and 2, when the patients in the albumin group received a greater volume of packed red cells than did those in the saline group; on average, during the first four days, patients assigned to receive albumin received 71.0 ml more packed red cells than those assigned

to receive saline. On day 2, patients in the saline group received a greater volume of nonstudy fluids than did those in the albumin group (Table 2). After day 4, there were no differences between the two groups in the volume of study fluids administered. There were no significant differences between the groups in the mean arterial pressure measured at the end of each of the first four days of the study. The patients assigned to receive albumin had a lower heart rate at the end of the first day than those as-

signed to receive saline. Central venous pressure was significantly higher in the albumin group than in the saline group at all time points during the first four days, and the serum albumin concentration was higher in the albumin group throughout the study period (Table 2).

**OUTCOMES**

Within 28 days after randomization, 726 of 3473 patients in the albumin group (20.9 percent) and 729 of 3460 patients in the saline group (21.1 percent) had died. For the albumin group as compared with the saline group, the absolute difference in mortality was -0.2 percent (95 percent confidence interval, -2.1 to +1.8 percent). The relative risk of death among patients assigned to receive albumin as

compared with those assigned to receive saline was 0.99 (95 percent confidence interval, 0.91 to 1.09; P=0.87). At 28 days, 111 patients in the albumin group (3.2 percent) and 87 patients in the saline group (2.5 percent) remained in the ICU (relative risk, 1.27; P=0.09); 793 (22.8 percent) and 848 (24.5 percent), respectively, remained in the hospital (relative risk, 0.93; 95 percent confidence interval, 0.86 to 1.01; P=0.10) (Table 3). There was no significant difference in survival times between the two groups (Fig. 1).

The number of patients who had new single-organ or multiple-organ failure, assessed according to their SOFA scores, was similar in the two groups (P=0.85 by Fisher's exact test) (Table 3). During the 28-day study period the mean length of stay in the

**Table 3. Primary and Secondary Outcomes.\***

Outcome	Albumin Group	Saline Group	Relative Risk (95% CI)	Absolute Difference (95% CI)	P Value
Status at 28 days — no./total no. (%)					
Dead	726/3473 (20.9)	729/3460 (21.1)	0.99 (0.91 to 1.09)		0.87
Alive in ICU	111/3473 (3.2)	87/3460 (2.5)	1.27 (0.96 to 1.68)		0.09
Alive in hospital†	793/3473 (22.8)	848/3460 (24.5)	0.93 (0.86 to 1.01)		0.10
Length of stay in ICU — days	6.5±6.6	6.2±6.2		0.24 (-0.06 to 0.54)	0.44
Length of stay in hospital — days†	15.3±9.6	15.6±9.6		-0.24 (-0.70 to 0.21)	0.30
Duration of mechanical ventilation — days	4.5±6.1	4.3±5.7		0.19 (-0.08 to 0.47)	0.74
Duration of renal-replacement therapy — days	0.48±2.28	0.39±2.0		0.09 (-0.0 to 0.19)	0.41
New organ failure — no. (%)‡					0.85§
No failure	1397 (52.7)	1424 (53.3)			
1 organ	795 (30.0)	796 (29.8)			
2 organs	369 (13.9)	361 (13.5)			
3 organs	68 (2.6)	75 (2.8)			
4 organs	18 (0.7)	17 (0.6)			
5 organs	2 (0.1)	0			
Death within 28 days according to subgroup — no./total no. (%)					
Patients with trauma	81/596 (13.6)	59/590 (10.0)	1.36 (0.99 to 1.86)		0.06
Patients with severe sepsis	185/603 (30.7)	217/615 (35.3)	0.87 (0.74 to 1.02)		0.09
Patients with acute respiratory distress syndrome	24/61 (39.3)	28/66 (42.4)	0.93 (0.61 to 1.41)		0.72

\* Plus-minus values are means ±SD. CI denotes confidence interval, and ICU intensive care unit.

† The data include the numbers of patients in the ICU or the length of stay in the ICU.

‡ Data were available for 2649 patients in the albumin group and 2673 patients in the saline group. New organ failure was defined as a Sequential Organ-Failure Assessment score<sup>13</sup> of 0, 1, or 2 in any individual organ system at baseline, followed by an increase in the score to 3 or 4 in the same system.

§ The P value pertains to the comparison between the albumin and saline groups in the numbers of patients who had no new organ failure or new failure of one, two, three, four, or five organs.

ICU was  $6.5 \pm 6.6$  days in the albumin group and  $6.2 \pm 6.2$  days in the saline group ( $P=0.44$ ). The mean length of stay in the hospital was  $15.3 \pm 9.6$  days and  $15.6 \pm 9.6$  days, respectively ( $P=0.30$ ). The numbers of days of mechanical ventilation and days of renal-replacement therapy were similar in the two groups (Table 3).

#### SUBGROUP ANALYSES

During the 28-day study period, the relative risk of death among patients with trauma in the albumin group as compared with such patients in the saline group was 1.36; the corresponding relative risk of death among patients without trauma was 0.96 ( $P=0.04$  by the test for a common relative risk). This difference in the relative risk of death was due to the greater number of patients with trauma and an associated brain injury who died after random assignment to albumin as opposed to saline: 59 of 241 such patients in the albumin group died (24.5 percent), as compared with 38 of 251 such patients in the saline group (15.1 percent) (relative risk, 1.62; 95 percent confidence interval, 1.12 to 2.34;  $P=0.009$ ). Among patients who had trauma without brain injury, there was no difference between the groups in terms of mortality: 22 such patients in the albumin group (6.2 percent) and 21 in the saline group (6.2 percent) died (relative risk, 1.00; 95 percent confidence interval, 0.56 to 1.79;  $P=1.00$ ). Among all the patients who had trauma (596 in the albumin group and 590 in the saline group), there were 81 (13.6 percent) deaths in the albumin group and 59 (10.0 percent) in the saline group (relative risk, 1.36; 95 percent confidence interval, 0.99 to 1.86;  $P=0.06$ ) (Fig. 2 and Table 3).

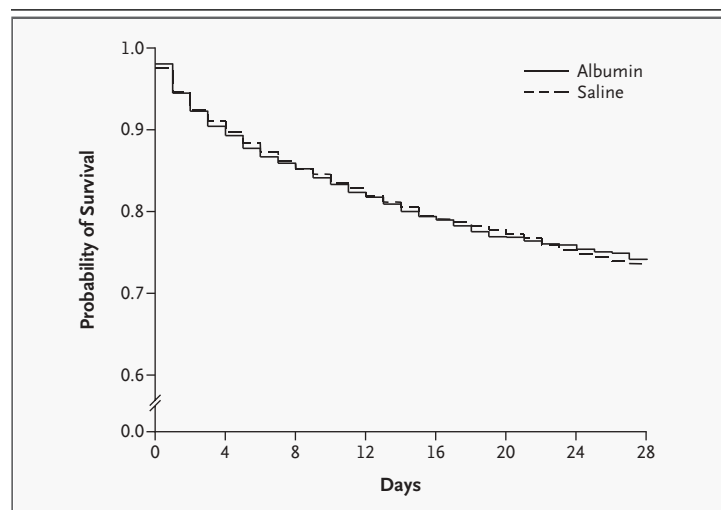
In a subgroup analysis of patients with severe sepsis, the relative risk of death during the 28-day study period among those randomly assigned to receive albumin as opposed to saline was 0.87, as compared with a corresponding relative risk of 1.05 among patients without severe sepsis ( $P=0.06$  by the test for a common relative risk). Of the 603 patients with severe sepsis who had been assigned to receive albumin, 185 (30.7 percent) died, and of the 615 patients with severe sepsis who had been assigned to receive saline, 217 (35.3 percent) died (relative risk, 0.87; 95 percent confidence interval, 0.74 to 1.02;  $P=0.09$ ) (Table 3). In a subgroup analysis of patients with the acute respiratory distress syndrome, the relative risk of death among those assigned to receive albumin as opposed to saline was 0.93; the corresponding relative risk among patients

without this syndrome was 1.00 ( $P=0.74$  by the test for a common relative risk).

#### DISCUSSION

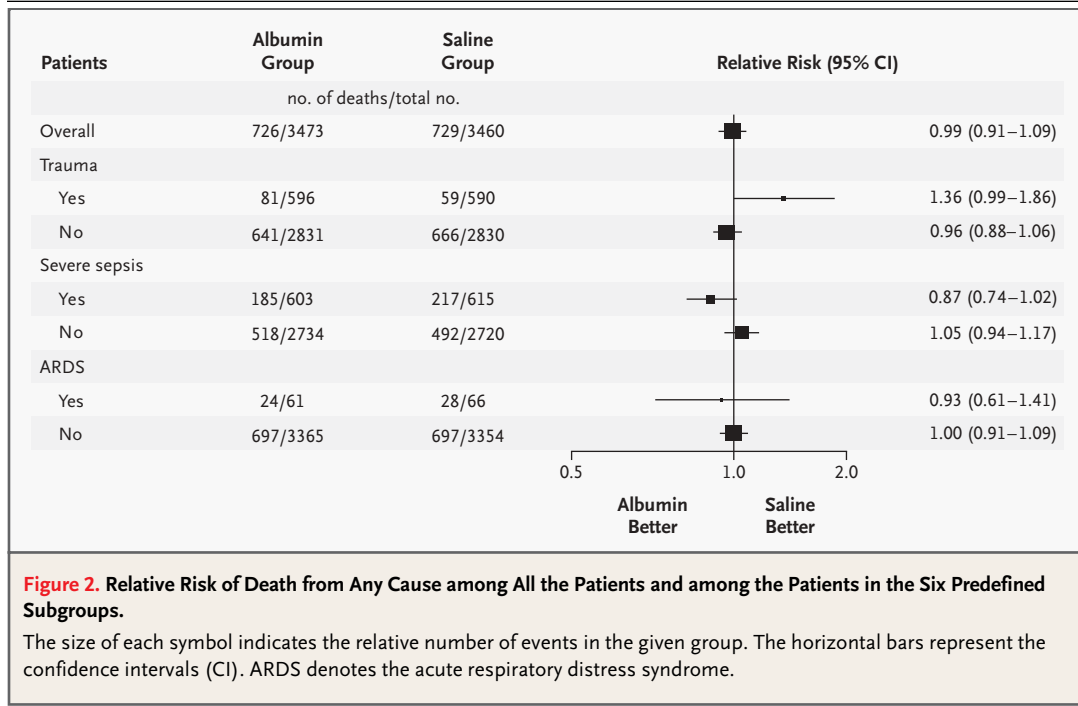
In this randomized trial, we found that the use of 4 percent albumin or normal saline for intravascular volume resuscitation in a heterogeneous population of patients in the ICU resulted in equivalent rates of death from any cause during the 28-day study period. Requirements for mechanical ventilation and renal-replacement therapy, time spent in the ICU and in the hospital during the 28-day study period, and the time until death (among the patients who died) were also equivalent. The proportion of patients in the two groups in whom new single-organ or multiple-organ failure developed were similar. Our findings do not support the results of the Cochrane Injuries Group Albumin Reviewers' meta-analysis, which suggested that the use of albumin was associated with an increased mortality rate among critically ill patients.<sup>1</sup>

Our study was conducted as a double-blind, randomized trial. Albumin and saline are not considered equipotent intravascular volume expanders, but their relative potencies have not previously been examined in an adequately powered, blinded trial. In our study, patients who were resuscitated with albumin received less fluid than those who were resuscitated with saline. During the first four days,



**Figure 1. Kaplan-Meier Estimates of the Probability of Survival.**

$P=0.96$  for the comparison between patients assigned to receive albumin and those assigned to receive saline.



the ratio of albumin administered to saline administered was approximately 1:1.4. However, there was no significant difference in mean arterial pressure between the groups, and the differences in central venous pressure and heart rate were small. Thus, we believe that the patients in the two groups were resuscitated to similar and acceptable end points.

Our study was also a large, pragmatic study in a population of patients subject to a large number of concurrent interventions. We did not collect information on all concurrent interventions performed in the ICU. However, randomization was stratified according to participating institution, so that each institution treated equal numbers of patients assigned to saline or to albumin. As a result, we do not believe that an imbalance in concurrent interventions could have influenced the results.

Patients who were assigned to albumin received a significantly greater volume of packed red cells during the first two days of the study. The reasons for this difference remain speculative but may include greater hemodilution with albumin than with saline or increased blood loss with albumin due to transient alterations in coagulation. In a study of transfusion requirements in critically ill patients conducted by Hébert and colleagues, a liberal transfusion policy resulted in the administration of an

excess of 3.0 units of packed red cells. This was associated with an increase in in-hospital mortality of 5.9 percentage points.<sup>15</sup> During the first four days of our study, the excess volume of fluid transfused in the albumin group averaged 71.0 ml per patient (less than one quarter of a unit). Accordingly, we do not believe this small excess in transfused volume influenced the results.

Given that our study had insufficient power to detect small but important differences in mortality among the predefined subgroups, the results provide only limited evidence that the treatment effects varied among these subgroups. The finding that patients with trauma might benefit more from resuscitation with saline than patients without trauma appears to be consistent with the results of a meta-analysis by Choi et al., who suggested that colloid resuscitation was associated with increased mortality in patients with trauma.<sup>2</sup> In our study, however, the increased relative risk of death among patients with trauma as compared with those without trauma resulted from a small excess number of deaths among patients who had trauma with brain injury, whereas the meta-analysis by Choi et al. did not include studies in patients with brain injury.<sup>2</sup>

In our study, the difference in mortality between the albumin and saline groups among patients with trauma involving brain injury should be interpreted

with caution. Patients with traumatic brain injury constituted only 7 percent of the study population, and the excess number of deaths in the albumin group was only 21. In large studies, such subgroup differences frequently occur by chance.<sup>16</sup> In addition, the rate of death from any cause over a 28-day period is not considered the most appropriate outcome measurement with which to assess treatment effects in patients with brain injury. Assessment of mortality and functional neurologic status at least six months after injury is recommended.<sup>17</sup> In contrast with our findings in patients with trauma, the comparison of the relative risk of death among patients with severe sepsis and those without severe sepsis provides limited evidence of a treatment effect that favors albumin in patients with severe sepsis. It should be noted that such differences between subgroups frequently occur by chance and that only specifically designed and appropriately powered studies can determine whether any such treatment effects are real.

In conclusion, our study provides evidence that albumin and saline should be considered clinically equivalent treatments for intravascular volume re-

suscitation in a heterogeneous population of patients in the ICU. Whether either albumin or saline confers benefit in more highly selected populations of critically ill patients requires further study. According to the current state of knowledge, factors that may influence the choice of resuscitation fluid for a critically ill patient include the individual clinician's preference, the tolerability of the treatment, its safety, and its cost.

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Dr. A. Davies and Dr. D. Stephens report owning shares in CSL.

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#### APPENDIX

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#### REFERENCES

1. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ* 1998; 317:235-40.
2. Choi PT, Yip G, Quinonez LG, Cook DJ. Crystalloids vs. colloids in fluid resuscitation: a systematic review. *Crit Care Med* 1999;27:200-10.
3. Wilkes MM, Navickis RJ. Patient survival after human albumin administration: a meta-analysis of randomized, controlled trials. *Ann Intern Med* 2001;135:149-64.
4. Cook D, Guyatt G. Colloid use for fluid resuscitation: evidence and spin. *Ann Intern Med* 2001;135:205-8.
5. Whether albumin therapy improves or worsens survival of critically ill patients is not known. *Ann Intern Med* 2001;135:S-25.
6. Boldt J. New light on intravascular volume replacement regimens: what did we learn from the past three years? *Anesth Analg* 2003;97:1595-604.
7. Bunn F, Alderson P, Hawkins V. Colloid solutions for fluid resuscitation. *Cochrane Database Syst Rev* 2003;1:CD001319.
8. ANZICS Clinical Trials Group, Institute for International Health SAFE Study Investigators. The Saline vs. Albumin Fluid Evaluation (SAFE) Study (ISRCTN76588266):

- design and conduct of a multi-centre, blinded randomised controlled trial of intravenous fluid resuscitation in critically ill patients. London: BMJ Publishing, 2004. (Accessed May 3, 2004, at <http://bmj.com/cgi/content/full/326/7389/559/DC1>.)
9. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; 13:818-29.
  10. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest* 1992;101:1644-55.
  11. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994;149: 818-24.
  12. Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. *Lancet* 1974;2:81-4.
  13. Vincent JL, de Mendonca A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. *Crit Care Med* 1998;26: 1793-800.
  14. Woodward M. Epidemiology: study design and data analysis. Boca Raton, Fla.: Chapman & Hall/CRC Press, 1999.
  15. Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999;340:409-17. [Erratum, 1999;340:1056.]
  16. Collins R, MacMahon S. Reliable assessment of the effects of treatment on mortality and major morbidity. I. Clinical trials. *Lancet* 2001;357:373-80.
  17. Narayan RK, Michel ME, Ansell B, et al. Clinical trials in head injury. *J Neurotrauma* 2002;19:503-57.

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