

THERAPEUTICS

# Fluid resuscitation with albumin or saline in the intensive care unit did not affect 28-day mortality rates

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.

**QUESTION**

In patients in the intensive care unit (ICU), what is the effect of resuscitation with albumin versus normal saline fluid on 28-day mortality?

**METHODS**

**Design:** Randomized controlled trial (Saline versus Albumin Fluid Evaluation [SAFE] Study).

**Allocation:** Concealed.\*

**Blinding:** Blinded (clinicians, patients, outcome assessors, biostatisticians, and {data collectors}†).\*

**Follow-up period:** 28 days.

**Setting:** 16 academic tertiary care medical-surgical ICUs in Australia and New Zealand.

**Patients:** 6997 patients ≥ 18 years of age (mean age 59 y, 60% men) in ICUs who were judged by their clinician to require fluid resuscitation to increase intravascular volume. Patients were excluded if they were admitted to the ICU after cardiac surgery, liver transplantation, or treatment for burns.

**Intervention:** Patients were stratified by center and diagnosis of trauma, and were allocated to fluid resuscitation with 4% albumin (Albumex, CSL, Melbourne, Victoria, Australia) ( $n = 3497$ ) or normal saline

( $n = 3500$ ). Treating clinicians determined the amount and rate of fluid administration and other management decisions.

**Outcomes:** All-cause mortality within 28 days of randomization. Secondary outcomes were organ failure and duration of renal-replacement therapy, mechanical ventilation, and ICU and hospital stay. The study had 90% power to detect a 3% absolute difference between groups for all-cause mortality.

**Patient follow-up:** 6933 patients (99%) (intention-to-treat analysis).

**MAIN RESULTS**

Albumin and saline groups did not differ for all-cause mortality within 28 days (Table). New organ failure (47.3% vs 46.7%,  $P = 0.85$ ), duration of renal-replacement therapy (0.48 vs 0.39 d,  $P = 0.41$ ), mechanical ventilation (4.5 vs 4.3 d,  $P = 0.74$ ), length of ICU stay (6.5 vs 6.2 d,  $P = 0.44$ ), and hospital stay (15.3 vs 15.6 d,  $P = 0.30$ ) were similar between groups.

**CONCLUSION**

In patients in the intensive care unit, 28-day mortality and other clinical outcomes did not differ following fluid resuscitation with 4% albumin versus normal saline.

*Sources of funding:* Auckland District Health Board; Middlemore Hospital; Health Research Council of New Zealand; Australian Commonwealth Department of Health and Aged Care; CSL; Australian National Health and Medical Research Council; Health Department of Western Australia; New South Wales Health Department; Northern Territory Health Services; Queensland Health Services Department; Royal Hobart Hospital; South Australian Department of Human Services; Victorian Department of Human Services.

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\*See Glossary.

†Information provided by author.

**Albumin vs normal saline for fluid resuscitation in the intensive care unit at 28 days‡**

Outcome	Albumin	Saline	RRR (95% CI)	NNT
All-cause mortality	20.9%	21.1%	1% (-9 to 9)	Not significant

‡Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

**COMMENTARY**

Interpretation of previous fluid resuscitation trials has been difficult, in part because of their focus on physiologic rather than clinical outcomes and their small sample size. The debate about colloids versus crystalloids to resuscitate seriously ill patients has existed for decades. A Cochrane meta-analysis suggesting increased mortality associated with albumin (1) was the catalyst for this randomized, stratified, concealed, and blinded multicenter trial conducted in Australia and New Zealand by the SAFE Study Investigators.

Resuscitation achieved similar hemodynamic endpoints in the 2 groups. Baseline characteristics and co-interventions were comparable, compliance was excellent, and contamination was minimal. Normal saline versus albumin resuscitation resulted in similar clinical outcomes, including 28-day mortality. These results apply to a wide variety of critically ill patients similar to those enrolled. Fluid choices henceforth will reflect how clinicians interpret the point estimate from SAFE, the

confidence limits, previous studies, patient-specific conditions, clinician preferences, availability, and cost (2).

SAFE is a landmark trial addressing a fundamental question about one of the most common interventions in the ICU. This trial will stimulate additional research evaluating oncotic pressure modification with different albumin preparations and comparisons of alternative colloids and crystalloids in specific ICU populations.

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**References**

1. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *Cochrane Injuries Group Albumin Reviewers.* *BMJ.* 1998;317:235-40.
2. Cook D. Is albumin safe? *N Engl J Med.* 2004;350:2294-6.