

# Resuscitation fluids in critical care

**John A Myburgh**

MBBCh PhD FCICM

Professor of Critical Care Medicine  
The George Institute for Global Health  
University of New South Wales  
St George Hospitals, Sydney

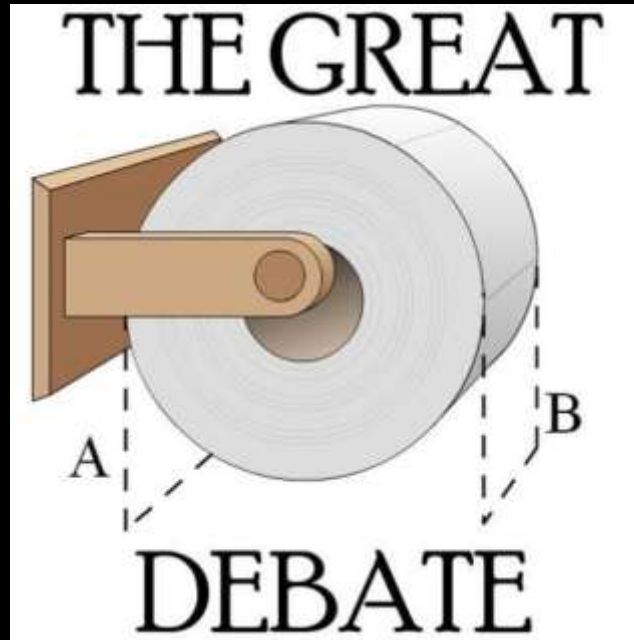
UNSW







# The Great Fluid Debate



I don't care if you use dog's piss, as long as you use it carefully."

Malcolm Fisher AO

# Human albumin administration in critically ill patients: systematic review of randomised controlled trials

Cochrane Injuries Group Albumin Reviewers

## Abstract

**Objective:** To quantify effect on mortality of administering human albumin or plasma protein fraction during management of critically ill patients.

**Design:** Systematic review of randomised controlled trials comparing administration of albumin or plasma protein fraction with no administration or with administration of crystalloid solution in critically ill patients with hypovolaemia, burns, or hypoalbuminaemia.

**Subjects:** 30 randomised controlled trials including 1419 randomised patients.

**Main outcome measure:** Mortality from all causes at end of follow up for each trial.

ing a direct protective effect.<sup>1</sup> Partly as a result of the association between serum albumin and mortality, human albumin solutions are now used in the management of a diverse range of medical and surgical problems. Licensed indications for human albumin solution are the emergency treatment of shock and other conditions in which restoration of blood volume is urgent, the acute management of burns, and clinical situations associated with hypoproteinaemia.<sup>2</sup>

Compared with other colloidal solutions and with crystalloid solutions, human albumin solutions are expensive.<sup>3</sup> Volume for volume, human albumin solution is twice as expensive as hydroxyethyl starch and over 30 times more expensive than crystalloid

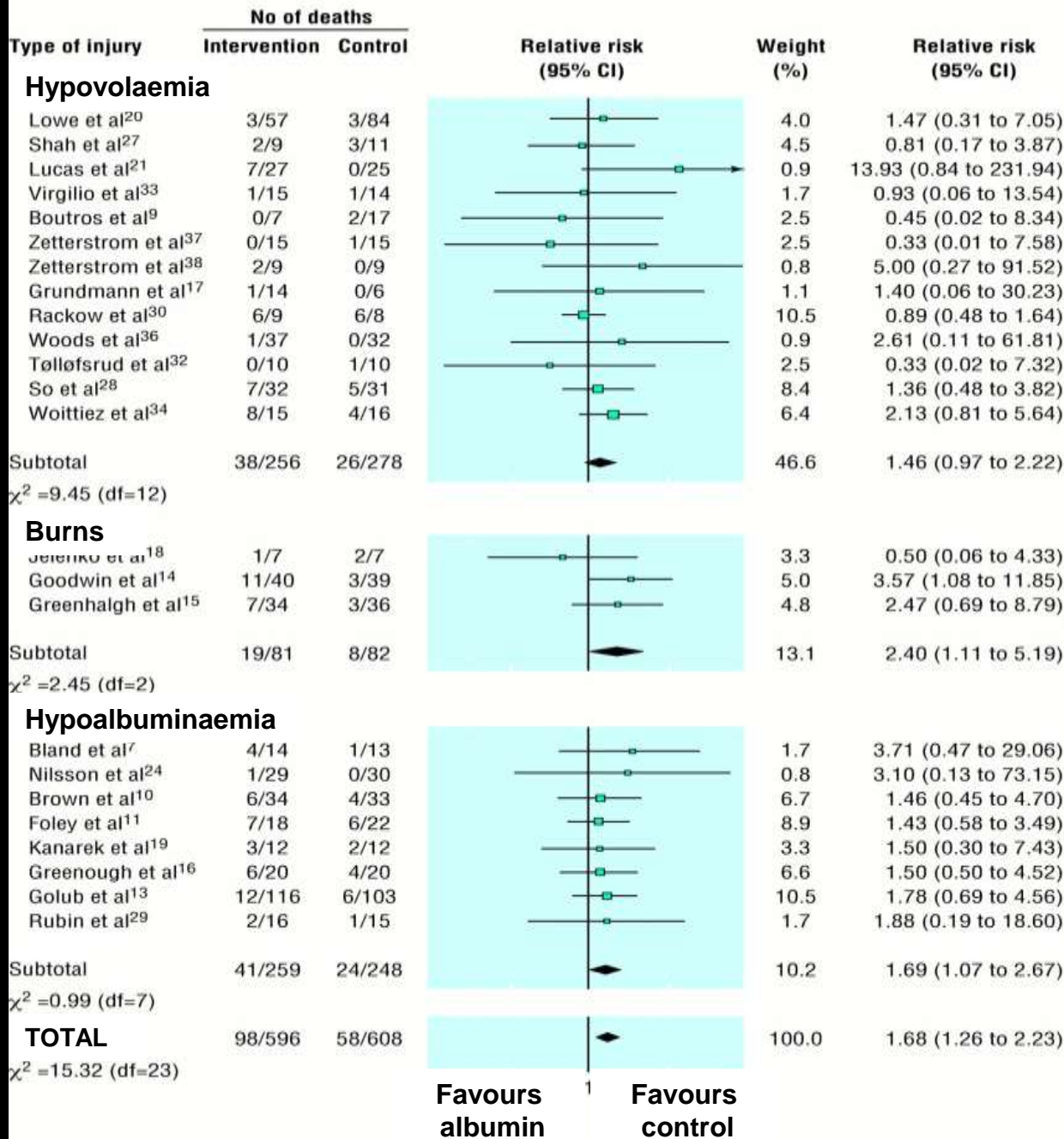
*Editorial  
by Offringa and  
Letters p 277*

Cochrane Injuries  
Group, Department  
of Epidemiology  
and Public Health,  
Institute of Child  
Health, London  
WC1N 1EH

Ian Roberts,  
director, child health  
monitoring unit

Ian.Roberts@ich.ucl.  
ac.uk

BMJ 1998;317:235-40



24/30 studies  
n=1104/1419

RRD 1.68 (1.25 – 2.23)

Overall excess mortality  
of 6%  
(95% C.I. 3 - 9%)

Favours albumin 1 Favours control

# Burns treatment 'kills thousands'

By Cella Hall, Medical Editor

A STANDARD treatment for adults and children with severe burns and suffering from shock and blood loss might have caused thousands of deaths, a report says today.

Doctors who have carried out research into the use of soluble human albumin, a blood protein, want the treatment stopped for any patient not included in a strict research programme.

They estimate that there is one extra death for every 17 patients given it. The effect was strongest in burns patients, they found.

As a result of the research, published in the *British Medical Journal*, the Committee on Safety of Medicines has convened an expert group, which met for the first time yesterday.

"They are studying the findings in detail," a spokesman for the Health Depart-

ment said. Albumin is given to about 100,000 patients a year. The treatment, which has been used for 50 years, helps to increase blood and fluid volume in accident and burns victims.

But it is feared that it makes tissue "waterlogged", which, in the lungs, stops people breathing.

The research was carried out by a team led by Dr Ian Roberts, the director of the child health monitoring unit at the Institute of Child Health, London.

Dr Roberts is also a member of the Cochrane injuries group, an international collaboration in which doctors systematically assess the value of established and new treatments.

He said: "I would not want to be treated with albumin. This is an established treatment and we were quite surprised by the results."

## Doctors advised to take special care with human albumin

Richard Woodman, London

The Committee on Safety of Medicines has advised doctors to restrict the use of, and take special care when using, human albumin after concerns that far from saving life the preparation may actually increase mortality.

A systematic review by the Cochrane Group published last year (*BMJ* 1998;317:253-40) of 23 randomised controlled trials, including 1419 critically ill patients with hypovolaemia, burns, and hypoalbuminaemia, found that the risk of death in the group treated with albumin was significantly higher than in patients who received either crystalloids or no treatment.

The relative risk of death was 1.46 (confidence interval 0.97 to 2.22) for hypovolaemia, 2.40 (1.11 to 5.19) for burns, and 1.69 (1.07 to 2.67) for hypoalbuminaemia. The pooled difference in the risk of death with albumin was 6% (3% to 9%).

Ian Roberts of the Institute of Child Health, London, who

carried out the review, which attracted numerous protests, emphasised at the time that the results must be interpreted with caution because the trials were relatively small and involved only a limited number of deaths. But he also pointed out that 100 000 patients receive human albumin in the United Kingdom each year and warned: "The really worrying thing is that if these results apply to just 10% of these patients, six deaths per 100 would work out at 600 deaths a year. This could be one of the biggest medical disasters in a long time."

An expert working group set up by the Committee on Safety of Medicines to examine the findings has now concluded, however, that there is "insufficient evidence of harm to warrant withdrawal of albumin products from the market" and that the effect of albumin on mortality can "only be answered by conducting large, purpose designed, randomised, con-



Albumin: possible association with increased mortality

trolled clinical trials."

Nevertheless, it has recommended that the indication for human albumin solutions should focus on the use of albumin to replace lost fluids rather than the underlying illness resulting in hypovolaemia and that hypoalbuminaemia in itself is not an appropriate indication.

The working group's recommendations—published on 11 June in *Current Problems in Pharmacovigilance*—add that product information should contain warnings about the risks of hypervolaemia and cardiovascular overload and emphasise that monitoring in patients receiving albumin should be undertaken. □

“...I would attempt to sue anyone who gave me an albumin infusion.

And, as for any attempt to secure my informed consent to take part in a randomised trial . . . forget it !”

Chalmers BMJ:1998

# The SAFE study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

The SAFE Study Investigators\*



ANZICS  
Clinical Trials Group



THE GEORGE INSTITUTE  
*for International Health*

# The SAFE study

Double-blind, randomised trial

4% albumin vs 0.9% saline for all volume resuscitation in the Intensive Care Unit

16 Intensive Care Units in Australia and New Zealand

Powered to detect 3% difference in absolute mortality from an estimated baseline of 15% ( $\beta=0.1$ ,  $\alpha=0.05$ )

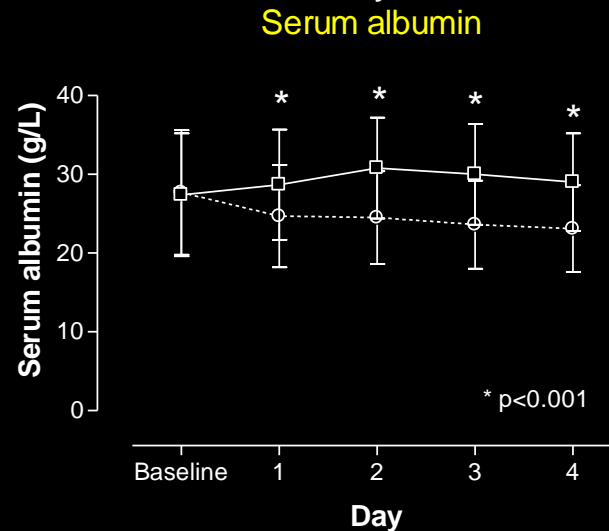
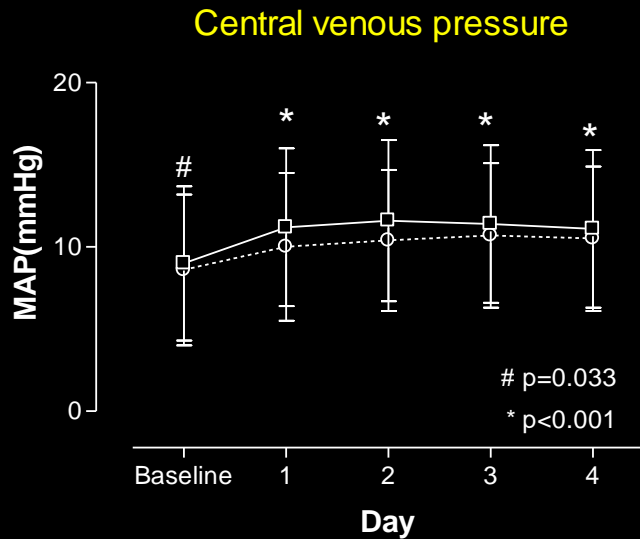
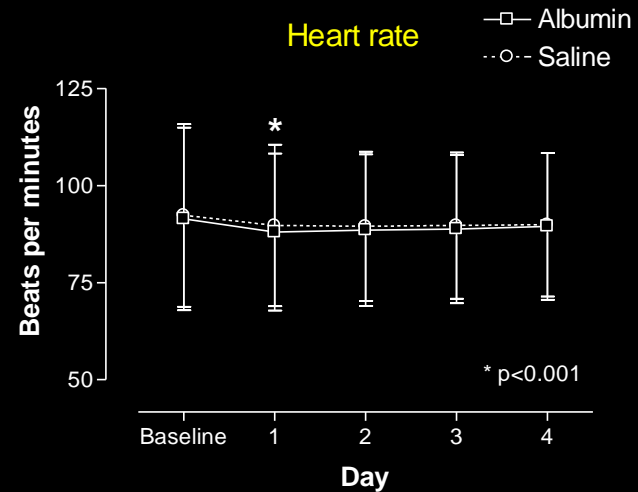
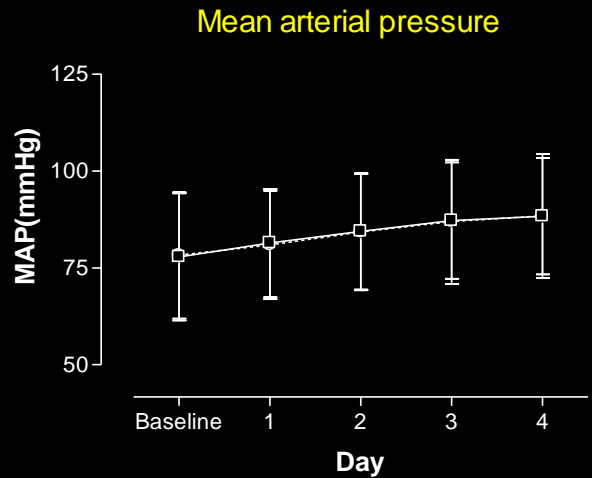
n=7000

Stratified by an admission diagnosis of trauma

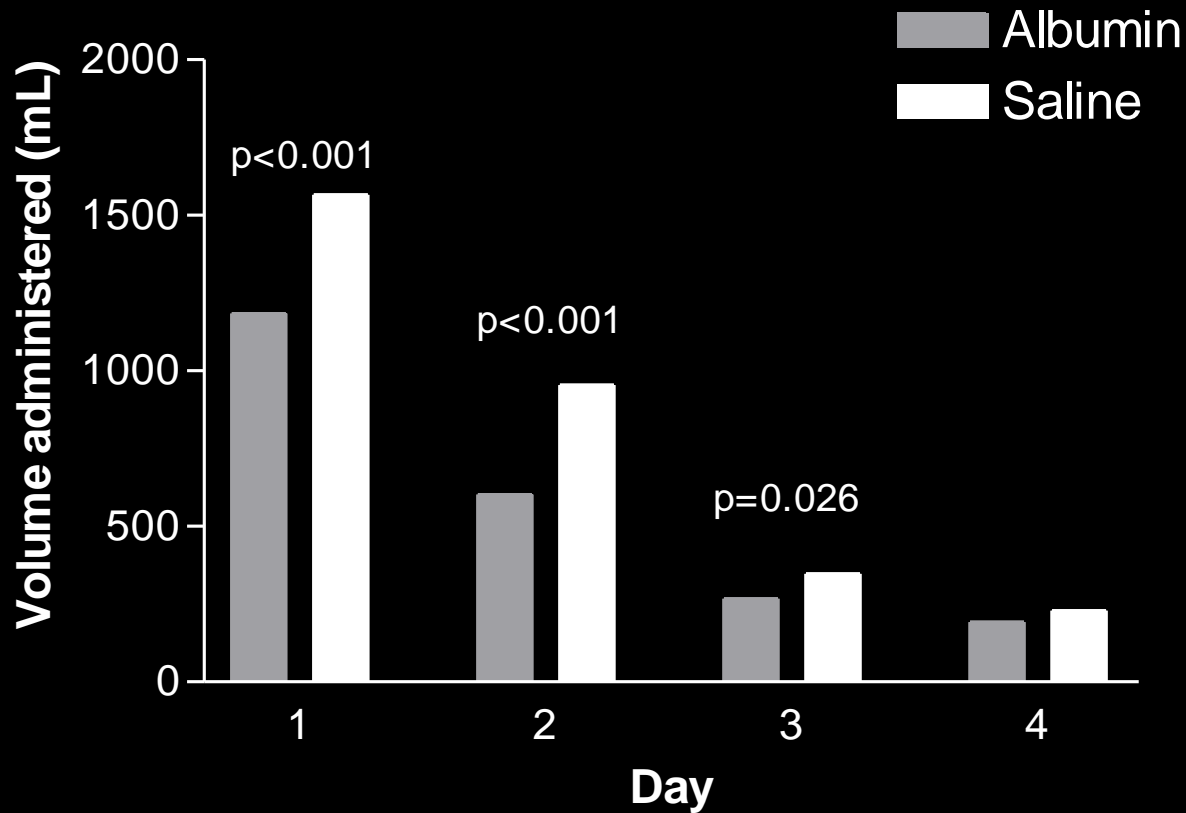
# Methodology



# Resuscitation endpoints



# Fluid volumes



Ratio of albumin to saline for first four days = 1:1.4

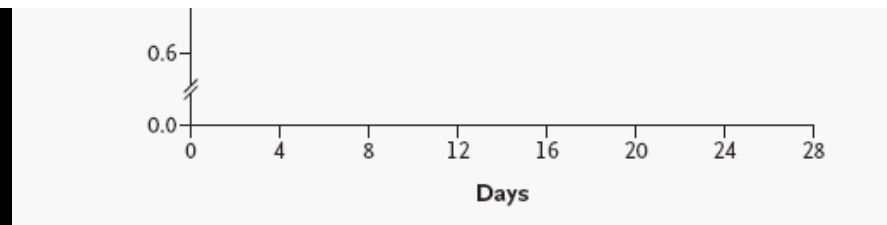
# Outcomes

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



## CONCLUSIONS

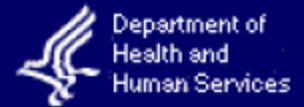
In patients in the ICU, use of either 4 percent albumin or normal saline for fluid resuscitation results in similar outcomes at 28 days.



# Should you change practice?



U.S. Food and Drug Administration



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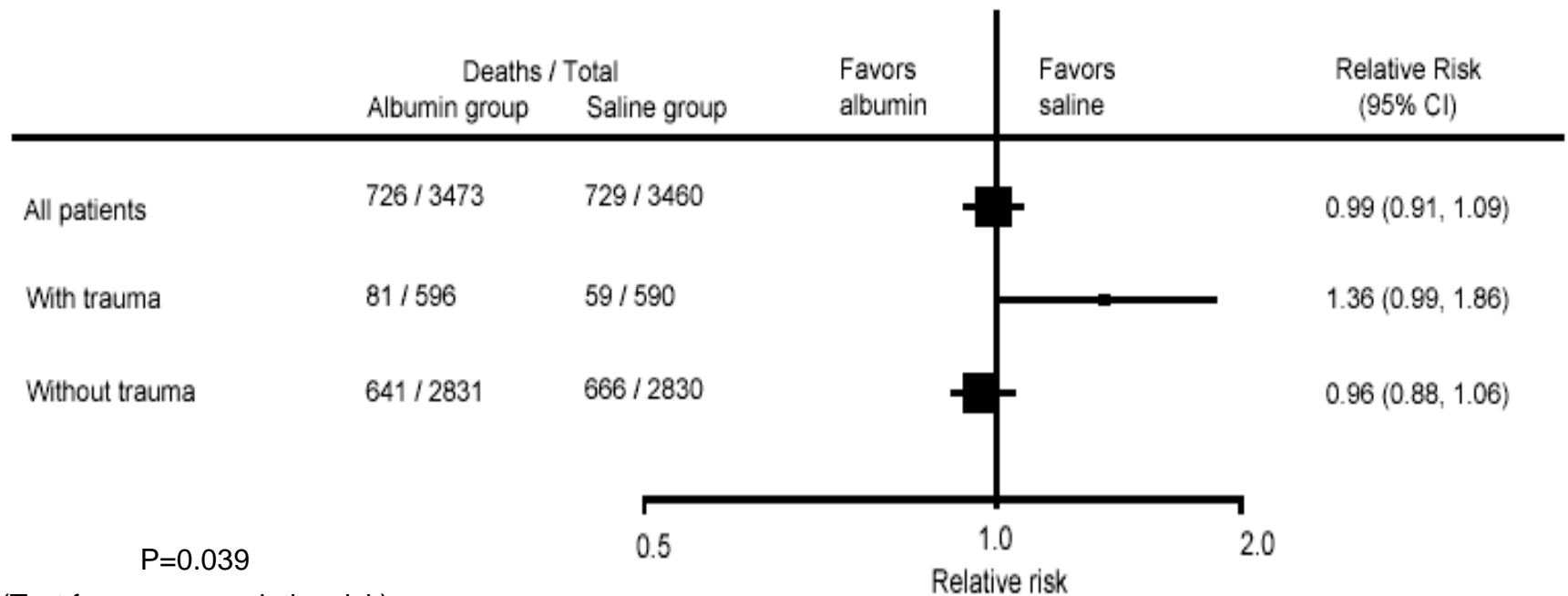
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## Safety of Albumin Administration in Critically Ill Patients

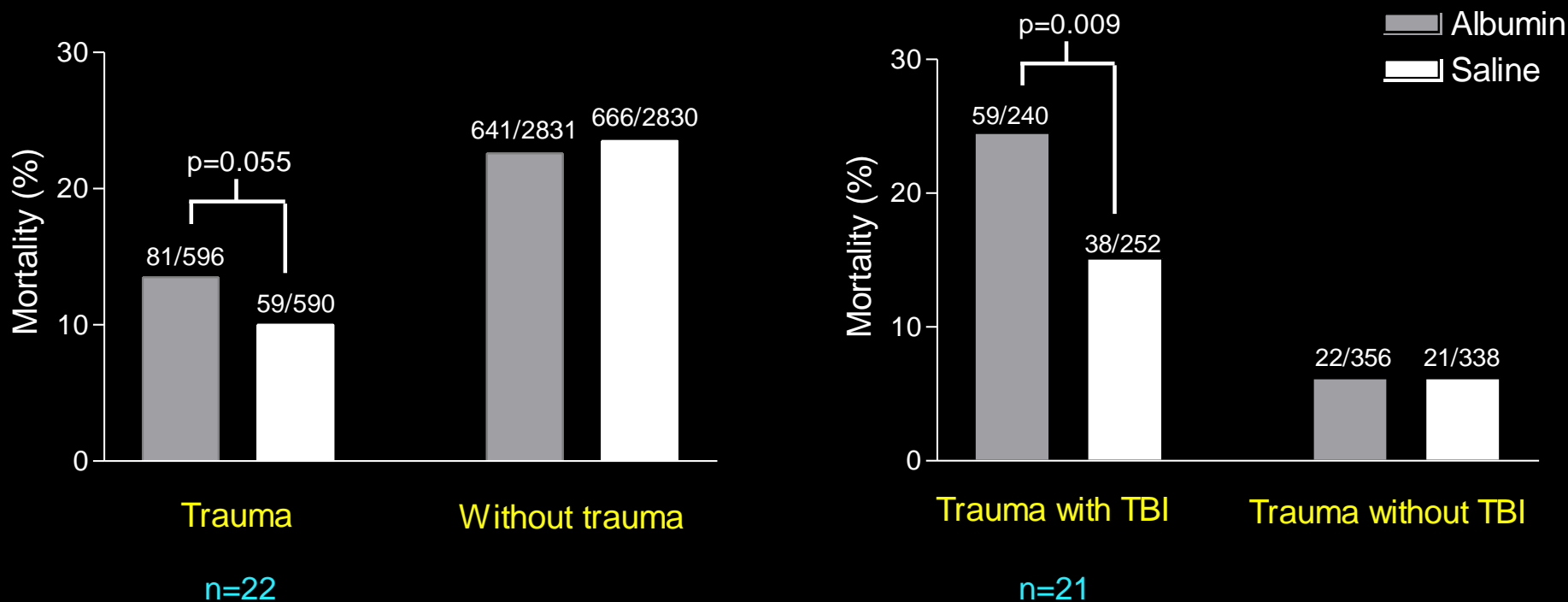
May 16, 2005

Based on these data, the BPAC voted unanimously that the SAFE study had resolved the prior safety concerns raised by the Cochrane Injuries Group in 1998. However, the relative safety of albumin for use in patients with burns cannot be determined at this time as this group was excluded from the SAFE study. Additionally, further evaluation of albumin in patients with traumatic brain injury and septic shock will have to be performed to ascertain the safety of albumin administration in these patient populations.

# SAFE: trauma subset



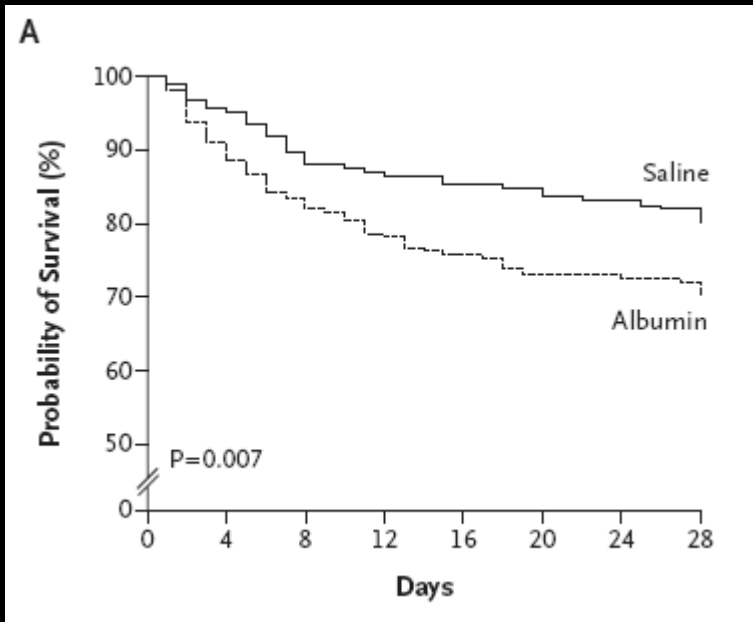
# Trauma and traumatic brain injury



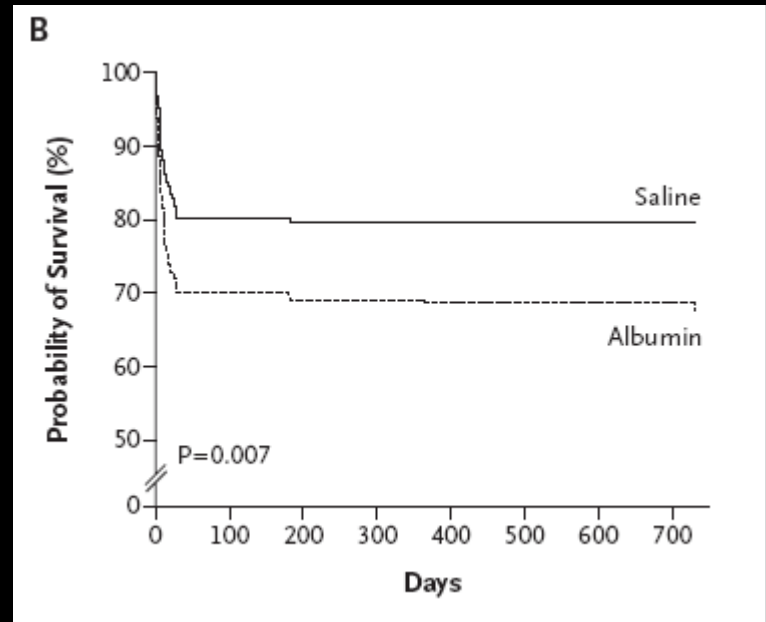
ORIGINAL ARTICLE

# Saline or Albumin for Fluid Resuscitation in Patients with Traumatic Brain Injury

The SAFE Study Investigators\*



Mortality at 28 days



Mortality at 2 years

# Albumin and sepsis

Intensive Care Med (2011) 37:86–96  
DOI 10.1007/s00134-010-2039-6

ORIGINAL

The SAFE Study Investigators

**Impact of albumin compared to saline  
on organ function and mortality of patients  
with severe sepsis**

*The NEW ENGLAND JOURNAL of MEDICINE*

ORIGINAL ARTICLE

**Mortality after Fluid Bolus in African Children  
with Severe Infection**

Kathryn Maitland, M.B., B.S., Ph.D., Sarah Kiguli, M.B., Ch.B., M.Med.,  
Robert O. Opoka, M.B., Ch.B., M.Med., Charles Engoru, M.B., Ch.B., M.Med.,

# What about synthetic colloids?



# Colloids v crystalloids

Colloid	Trials	n	RR	95%CI
Albumin	23	7754	1.01	0.92 to 1.10
HES	16	637	1.05	0.63 to 1.75
Gelatin	11	506	0.91	0.49 to 1.72
Dextran	9	834	1.24	0.94 to 1.65

## Authors' conclusions

There is no evidence from RCTs that resuscitation with colloids reduces the risk of death, compared to resuscitation with crystalloids, in patients with trauma, burns or following surgery. As colloids are not associated with an improvement in survival, and as they are more expensive than crystalloids, it is hard to see how their continued use in these patients can be justified outside the context of RCTs.

# Colloids for resuscitation

Colloid	Trials	n	RR	95%CI
Albumin v HES	25	1234	1.14	0.91 to 1.43
Albumin v gelatin	7	636	0.97	0.68 to 1.39
Albumin v dextran	4	360	3.75	0.42 to 33.09
Gelatin v HES	18	1337	1.00	0.80 to 1.25

## Authors' conclusions

From this review, there is no evidence that one colloid solution is more effective or safe than any other, although the confidence intervals are wide and do not exclude clinically significant differences between colloids. Larger trials of fluid therapy are needed if clinically significant differences in mortality are to be detected or excluded.

# SAFE TRIPS

Finfer et al. *Critical Care* 2010, **14**:R185  
<http://ccforum.com/content/14/5/R185>



RESEARCH

Open Access

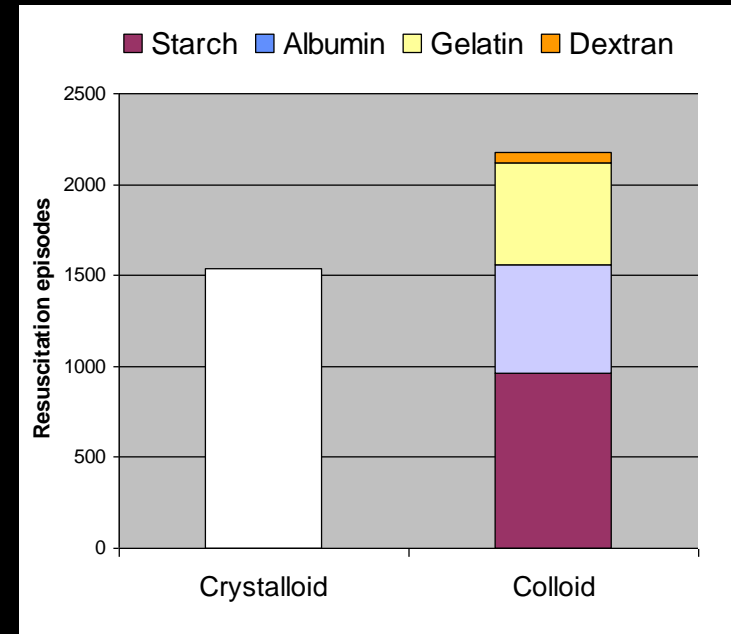
## Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units

Simon Finfer<sup>1\*</sup>, Bette Liu<sup>1,2</sup>, Colman Taylor<sup>1</sup>, Rinaldo Bellomo<sup>3</sup>, Laurent Billot<sup>1</sup>, Deborah Cook<sup>4</sup>, Bin Du<sup>5</sup>, Colin McArthur<sup>6</sup>, John Myburgh<sup>1</sup> for the SAFE TRIPS Investigators<sup>1</sup>

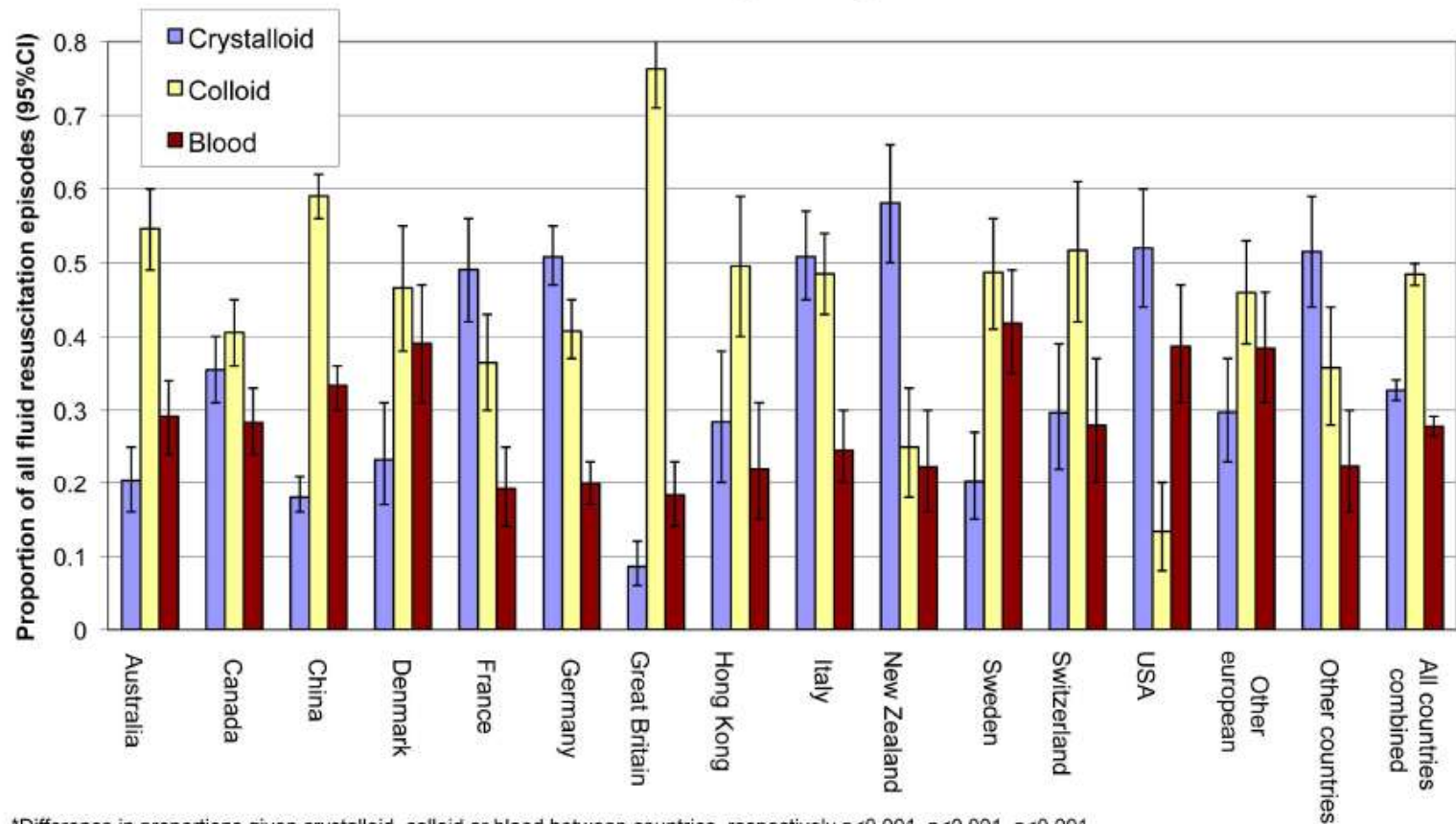
# SAFE TRIPS



24 Countries, 391 Intensive Care Units – single day in 2007  
1970 / 5339 (36.8%) patients received fluid resuscitation

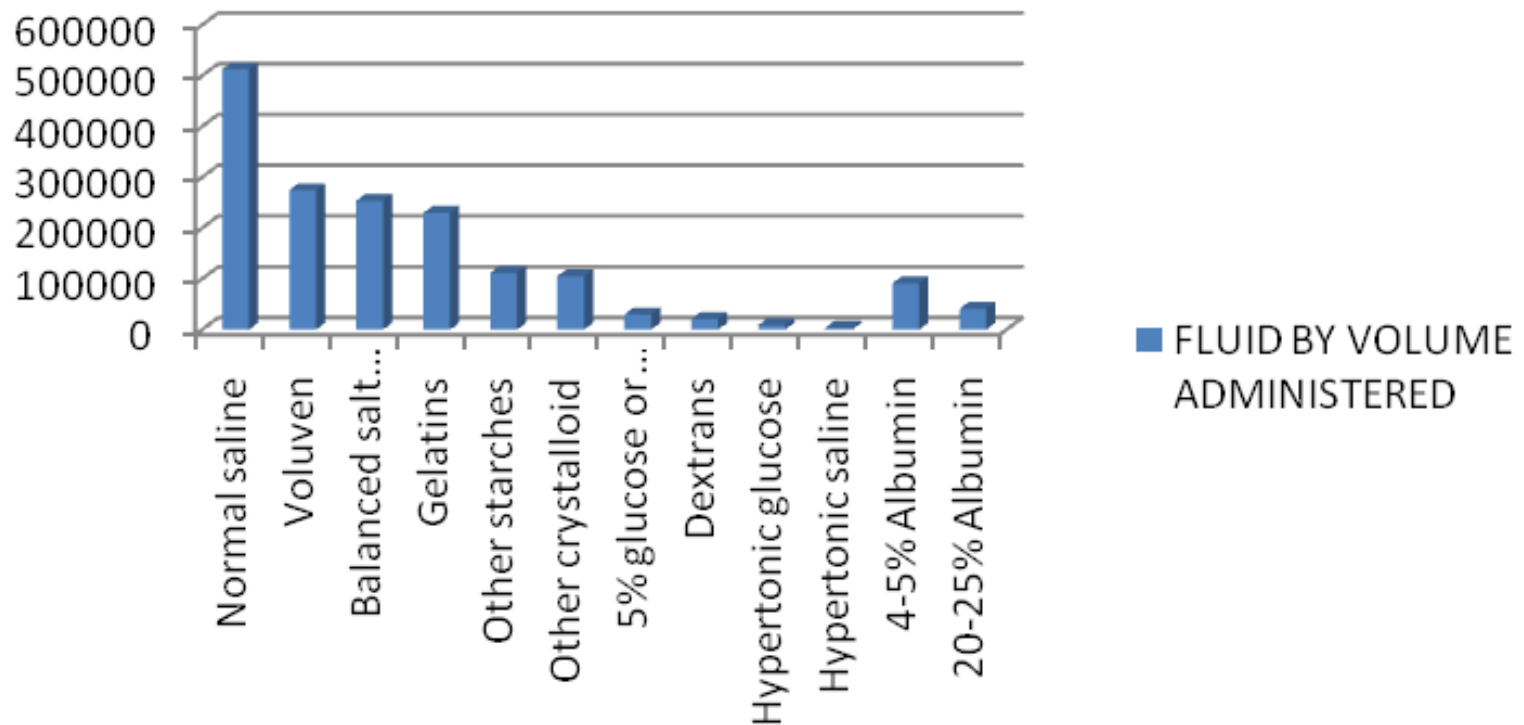


# Fluid type by country / region

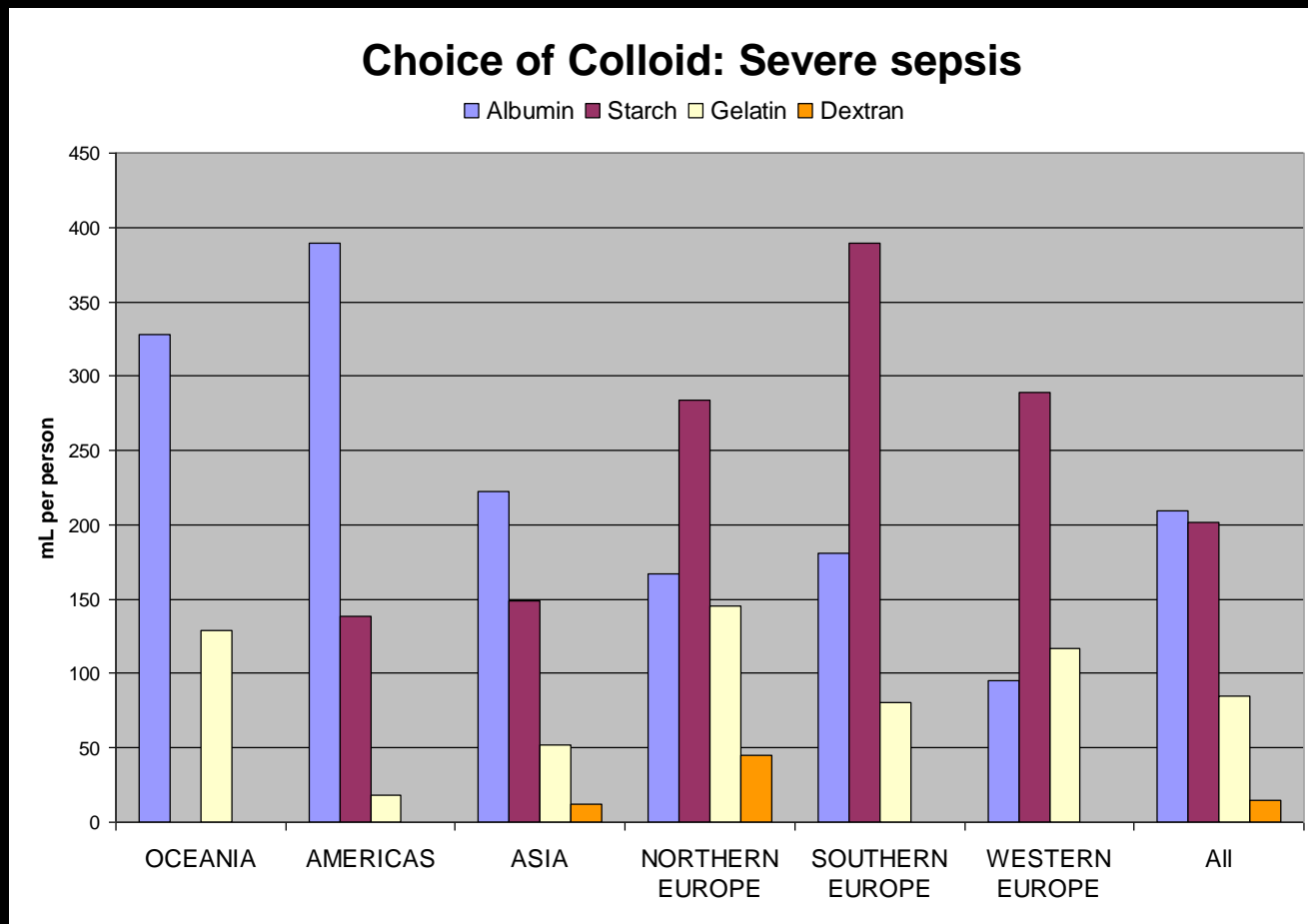


# Fluid volumes

## FLUID BY VOLUME ADMINISTERED

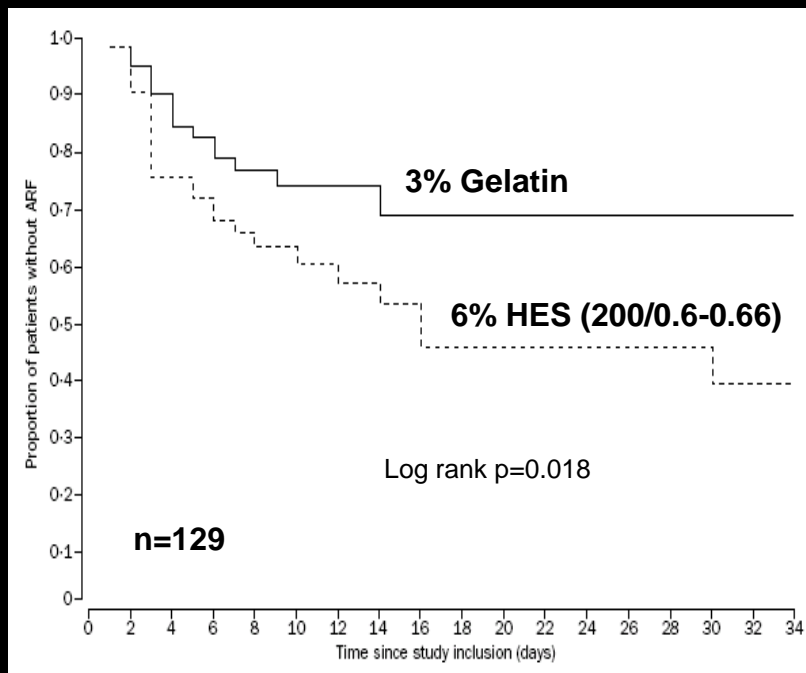


# Colloid use in severe sepsis

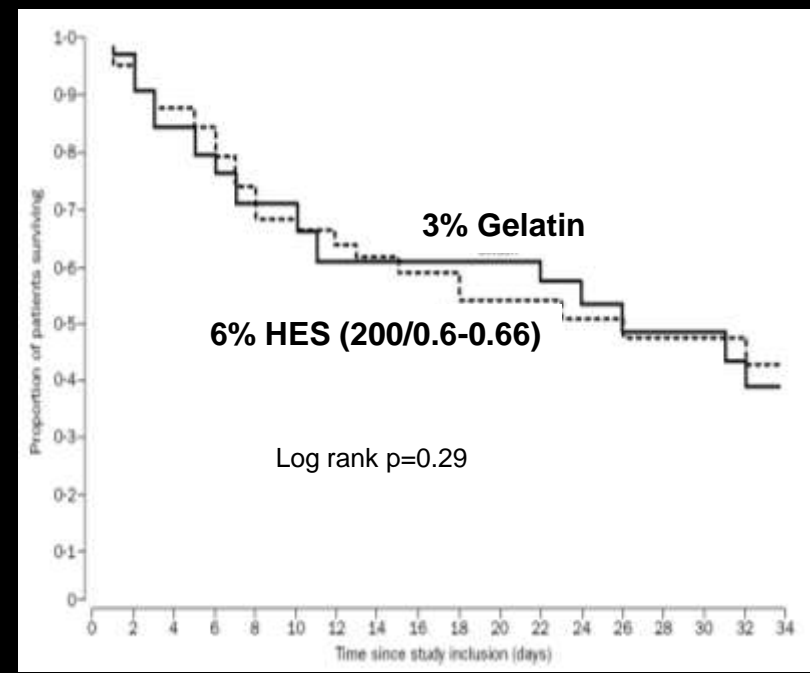


# Starch and nephrotoxicity

**Effects of hydroxyethylstarch and gelatin on renal function in severe sepsis: a multicentre randomised study**



Proportion without ARF



Proportion survival

ORIGINAL ARTICLE

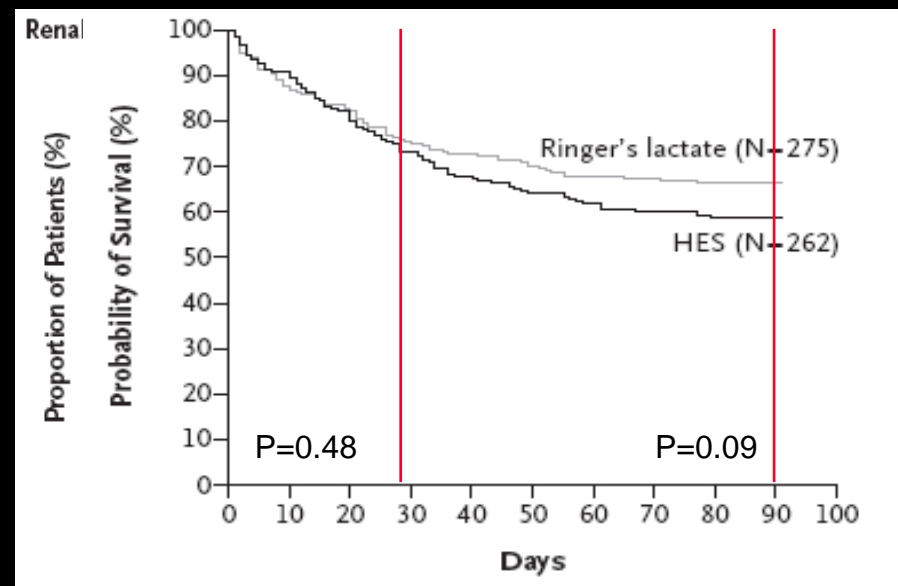
# Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis

## Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP)

10% Pentastarch  
(200/0.5)

		YES	NO
Intensive insulin therapy	YES	IIT + PS	IIT
	NO	PS	Neither

Open label, RCT:  
10% ARR in 28d mortality  
N=600+600 (adaptive design)



Renal replacement therapy: 31.0 v 18.8% p=0.001



# HES: effects on renal function

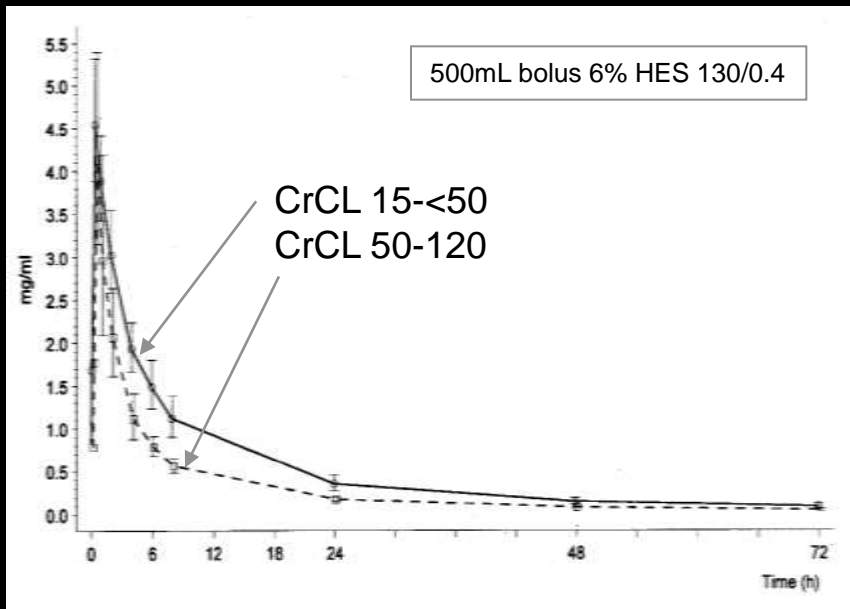
Outcome	Trials	n	RR	95%CI
Renal replacement therapy	34	1236	1.38	0.89 to 2.16
RRT : sepsis	3	702	1.59	1.2 to 2.1
Author-defined ARF	34	1199	1.50	1.12 to 1.87
Author-defined ARF: sepsis	4	832	1.55	1.22 to 1.96

## Authors' conclusions

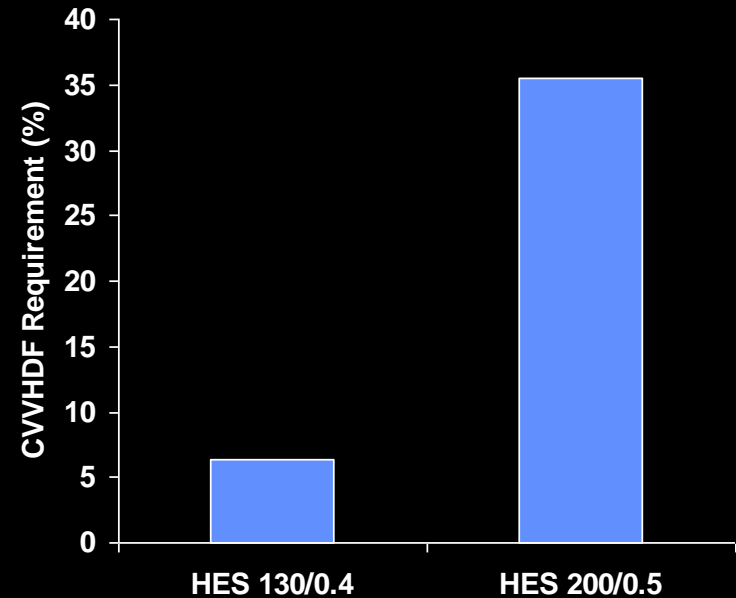
Potential for increased risk of AKI should be considered when weighing the risks and benefits of HES for volume resuscitation, particularly in septic patients. Large studies with adequate follow-up are required to evaluate the renal safety of HES products in non-septic patient populations. RIFLE criteria should be applied to evaluate kidney function in future studies of HES and, where data is available, to re-analyse those studies already published. There is inadequate clinical data to address the claim that safety differences exist between different HES products.

# Are 'newer' starches different?

## Evidence of safety?



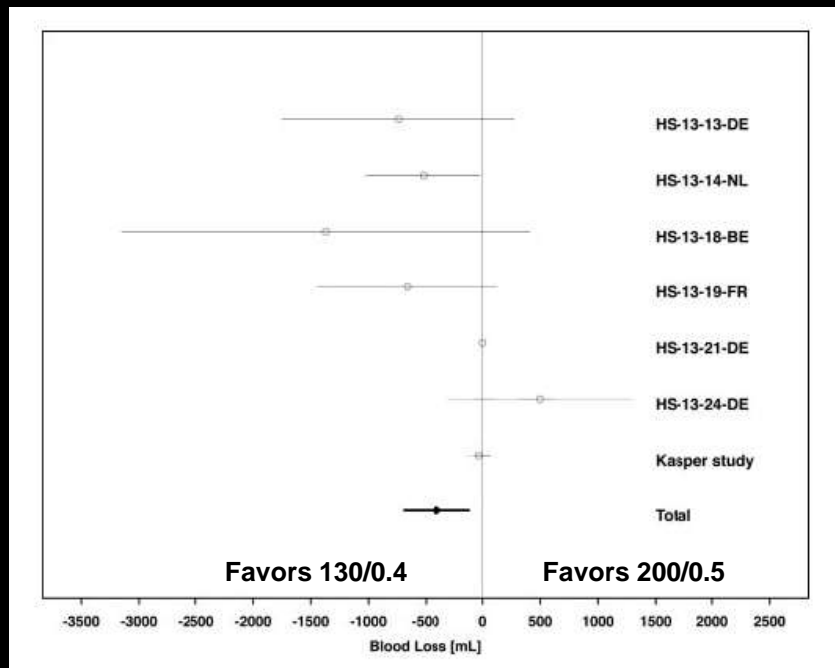
Reduced accumulation in renal dysfunction  
Jungheinrich Anesth Analg 2002



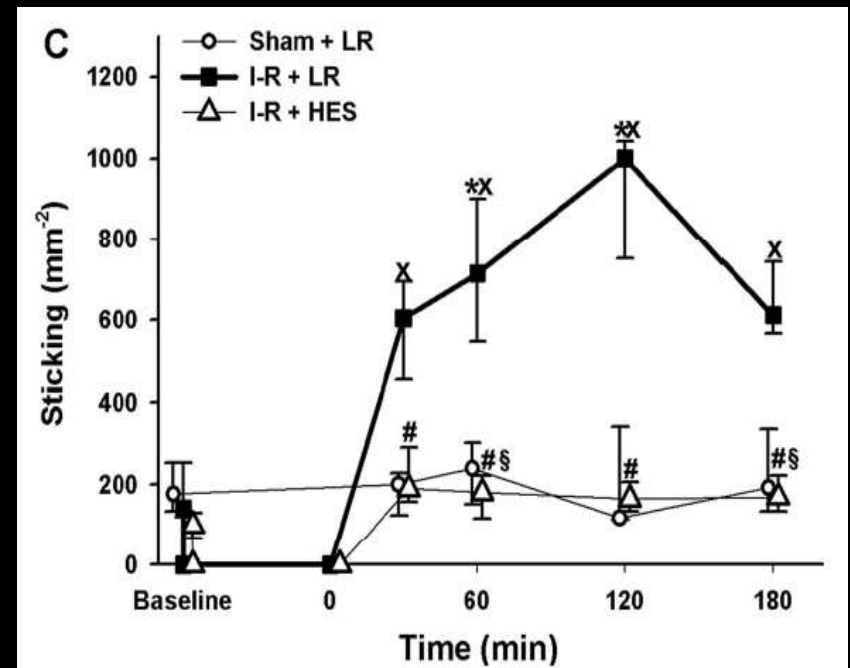
Renal function in ICU  
Retrospective observational study: n=8408 (4yrs)  
Brimer: abstract ESICM 2008

# Are 'newer' starches different?

## Evidence of benefit?



Blood loss in high risk surgery  
Kozek: Anes Analg 2008



Immunomodulation in ischaemia-reperfusion injury  
Varga: Crit Care Med 2008



# C.H.E.S.T

Crystalloid Hydroxy-Ethyl Starch Trial



THE GEORGE INSTITUTE  
*for International Health*



ANZICS  
Clinical Trials Group



The University of Sydney

# Design and outcomes

Intensive Care Med  
DOI 10.1007/s00134-010-2117-9

ORIGINAL

The Crystalloid versus  
Hydroxyethyl Starch Trial  
(CHEST) Management Committee

**The Crystalloid versus Hydroxyethyl Starch Trial: protocol for a multi-centre randomised controlled trial of fluid resuscitation with 6% hydroxyethyl starch (130/0.4) compared to 0.9% sodium chloride (saline) in intensive care patients on mortality**

[Clinicaltrials.gov](http://Clinicaltrials.gov) : [GI-CCT24378](https://clinicaltrials.gov/ct2/show/study/GI-CCT24378)

# CHEST

## Aim

To determine the effects of intravenous fluid resuscitation with 6% hydroxyethyl starch (130/0.4) in 0.9% sodium chloride solution compared to 0.9% sodium chloride alone on all-cause mortality in critically ill patients.

## Design

Blinded, multicentred, randomised-controlled trial

## Power

N=7000

To detection ARR 3.5% from baseline mortality of 21% ( $\alpha=0.05$ ;  $\beta 0.9$ )

To detect RRI in renal failure by 1.3 from baseline of 6%.

## Outcomes

All-cause mortality at 90 days

Incidence of acute renal injury/acute renal failure

Interval mortality rates

Organ failures (respiratory, cardiovascular, coagulation and hepatic)

Quality of life and functional outcome assessments

Cost-effectiveness analysis

# Joachim Boldt



# Shadow of Doubt

Steven L. Shafer, MD

ing committee to determine the integrity of the research. I received their report on November 25, 2010. Notable findings by the investigating committee include the following:

1. There are no original patient data or laboratory data to support the findings in the study.
2. According to the head of the perfusionist team, no albumin has been used as a priming solution since 1999.
3. According to the pharmacy, no albumin has been delivered to the cardiac operating rooms for many years.
4. All laboratory measurements, including IL-6, IL-10, intercellular adhesion molecule, neutrophil gelatinase-associated lipocalin, and  $\alpha$ -glutathione-S-transferase, would have been performed in the clinical laboratory at the Klinikum Ludwigshafen. These assays have only been performed on patients receiving hydroxyethyl starch priming solutions. The laboratory could identify no assays from patients receiving albumin priming solutions.
5. Professor Boldt has admitted forging the signatures of the coauthors on the copyright transfer form submitted to *Anesthesia & Analgesia*.
6. The coauthors denied participation in the fabrication.
7. There is no convincing evidence that this study was performed at all.

In other words, the study is fabricated.

**Editors-in-Chief Statement Regarding Published Clinical Trials  
Conducted without IRB Approval by Joachim Boldt**

March 4, 2011

Acta Anesthesiologica Scandinavica :3  
Anaesthesia: 6  
Anesthesiologie Intensivmedizin Notfallmedizin Schmerztherapie: 6  
Anesthesia and Analgesia: 22  
Anesthesiology: 1  
Annals of Thoracic Surgery: 2  
British Journal of Anaesthesia: 11  
Canadian Journal of Anaesthesia: 5  
Critical Care Medicine: 2  
Der Anesthesist: 2  
European Journal of Anaesthesiology: 8  
Intensive Care Medicine: 5  
Journal of Cardiothoracic and Thoracic Anaesthesia: 12  
Journal of Cranio-Maxillary-Facial Surgery: 1  
Medical Science Monitor: 2  
Minerva Anesthesiologica: 1  
The Thoracic and Cardiovascular Surgeon: 1  
Vox Sanguinis: 1



# 6% HES (130/0.4) systematic review

Confidential Galley Proof. Not For Distribution.

## Fluid Resuscitation with 6% Hydroxyethyl Starch (130/0.4) in Acutely Ill Patients: An Updated Systematic Review and Meta-Analysis

David J. Gattas, MB BS, MMed, FCICM,\*† Arina Dan, MB BS, FCICM,\*‡  
John Myburgh, MBBCh, PhD, FCICM,§|| Laurent Billot, MSc, DEA, AStat,¶|| Serigne Lo, PhD, AStat,¶||  
Simon Finfer,§# and The CHEST Management Committee

**CONCLUSIONS:** Published studies are of poor quality and report too few events to reliably estimate the benefits or risks of administering 6% HES 130/0.4. This same conclusion is reached with or without the retracted studies. Given the widespread use of 6% HES 130/0.4, high-quality trials reporting a large number of events are urgently required. (Anesth Analg 2011; X:●●●–●●●)



# Cochrane updates 2011

## **Colloids versus crystalloids for fluid resuscitation in critically ill patients (Review)**

Perel P, Roberts I

## **Colloid solutions for fluid resuscitation (Review)**

Bunn F, Trivedi D, Ashraf S

# What about crystalloids?



“Abnormal” saline vs “Balanced” salt solutions

# Guidelines .....

## British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients

### GIFTASUP

Jeremy Powell-Tuck (chair)<sup>1</sup>, Peter Gosling<sup>2</sup>, Dileep N Lobo<sup>1,3</sup>, Simon P Allison<sup>1</sup>, Gordon L Carlson<sup>3,4</sup>, Marcus Gore<sup>3</sup>, Andrew J Lewington<sup>5</sup>, Rupert M Pearse<sup>6</sup>, Monty G Mythen<sup>6</sup>

*On behalf of <sup>1</sup>BAPEN Medical - a core group of BAPEN, <sup>2</sup>the Association for Clinical Biochemistry, <sup>3</sup>the Association of Surgeons of Great Britain and Ireland, <sup>4</sup>the Society of Academic and Research Surgery, <sup>5</sup>the Renal Association and <sup>6</sup>the Intensive Care Society.*



28 evidence- based, consensus recommendations

Fluid resuscitation

Peri-operative fluid management

Intra-operative fluid management

Post-operative fluid and nutritional management

Fluid management in acute renal injury

# Fluid resuscitation

## Recommendation 1

*Because of the risk of inducing hyperchloraemic acidosis in routine practice, when crystalloid resuscitation or replacement is indicated, balanced salt solutions e.g. Ringer's lactate/acetate or Hartmann's solution should replace 0.9% saline, except in cases of hypochloraemia e.g. from vomiting or gastric drainage.*

Evidence level 1b<sup>1-7</sup>

Seven references – all pre date SAFE:

- 3 volunteer studies

- 2 review articles

- 2 “randomised” trials:

  - n=68

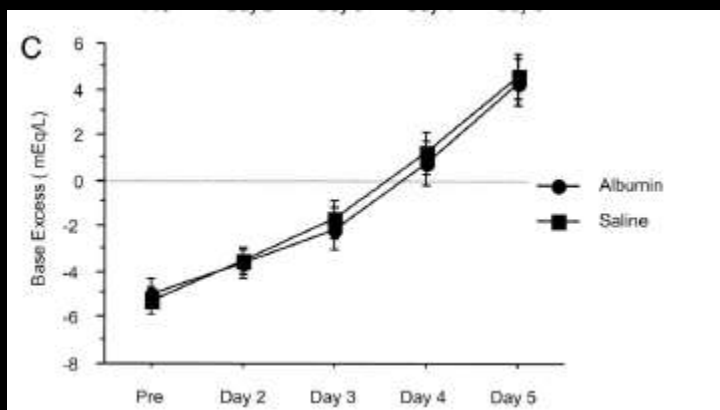
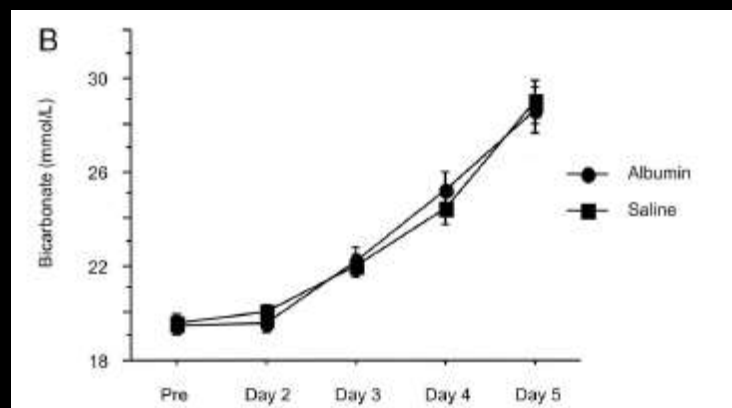
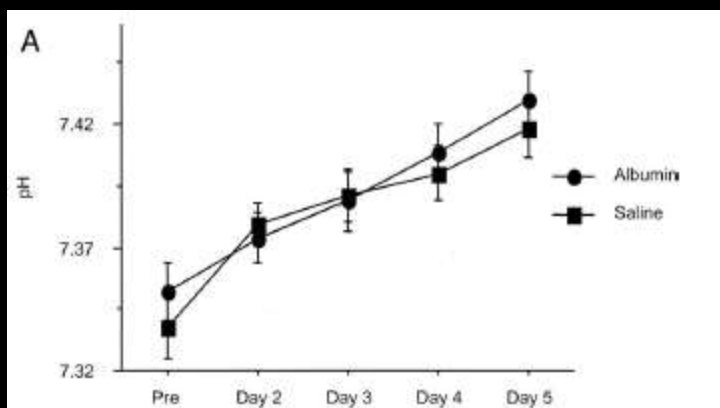
  - Secondary outcomes

**NOT** level “1”

Sensible maybe, “but eminence” based

# SAFE and acid base

Nested, cohort study within the SAFE study  
N=691, 3 general ICUs



Volume of fluid is predictor of acid base change  
Changes are minor – alkalosis predominates  
Influenced by disease severity and time

# Conclusions

The crystalloid – colloid debate continues unabated ...

Apart from the SAFE study, there is little high-quality evidence to guide the prescription and administration of the majority of resuscitation fluids given to critically ill patients in Australia and globally.

# So, which fluid should I use??

On the weight of published, high-quality evidence, crystalloid, specifically normal saline, is the resuscitation fluid of choice for critically ill patients.

There is no evidence of benefit of one crystalloid over another in terms of improving patient-centred outcomes.

# So, which fluid should I use??

With respect to colloids, albumin should not be used for the resuscitation of patients with traumatic brain injury.

Whether albumin confers a benefit in patients with severe sepsis requires further study.

There is no justification for the use of synthetic colloids for resuscitation outside the context of randomised-controlled trials.

# And so ....

There is an intellectual and ethical imperative to continue to conduct high-quality studies about one of the most common interventions in acute medicine.

Australian and New Zealand researchers continue to lead the field in this area through the ANZICS Clinical Trials Group and collaborators.

← Visitors Lounge

Intensive Care Unit

FIRE  
EXTINGUISHER

NOTICE  
This Area is Under  
24 Hour Camera  
Surveillance

TURN OFF MOBILE PHONES  
& TWO WAY RADIOS



MOBILE DEVICES MUST NOT  
BE USED IN THIS AREA.  
TO AVOID INTERFERENCE,  
PLEASE SWITCH OFF ALL  
MOBILE DEVICES.

**WARNING**  
**Shit**  
**Happens!!**

Intensive Care Unit

