

Albumin reduces the risk of death in children with severe malaria and acidosis in a Phase II randomised controlled trial of volume expansion

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Severe malaria in African children



→ in-hospital fatality still ~ 20-30%

Improvements in outcome of severe falciparum malaria

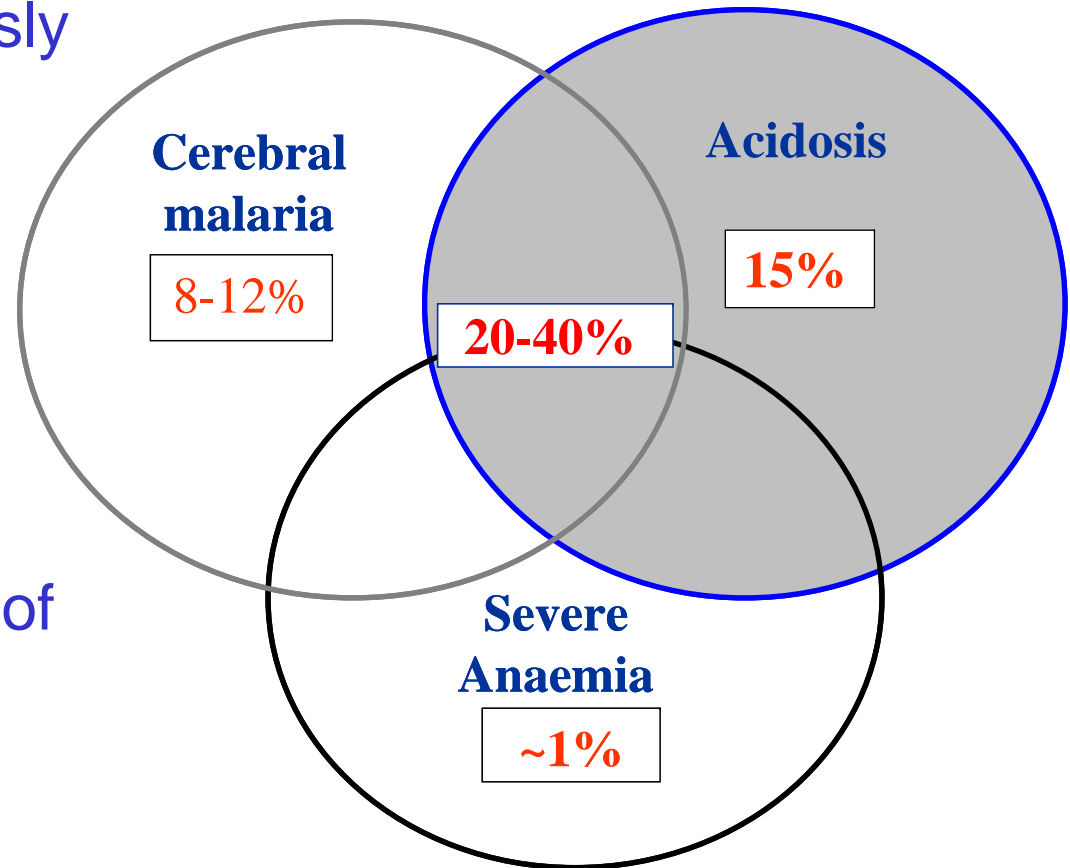


Two approaches:

- Antimalarial Rx
 - optimise doses
 - identify novel candidates
- Supportive treatments
 - treat complications
 - based upon a better understanding of physiology

Targeted interventions: metabolic acidosis

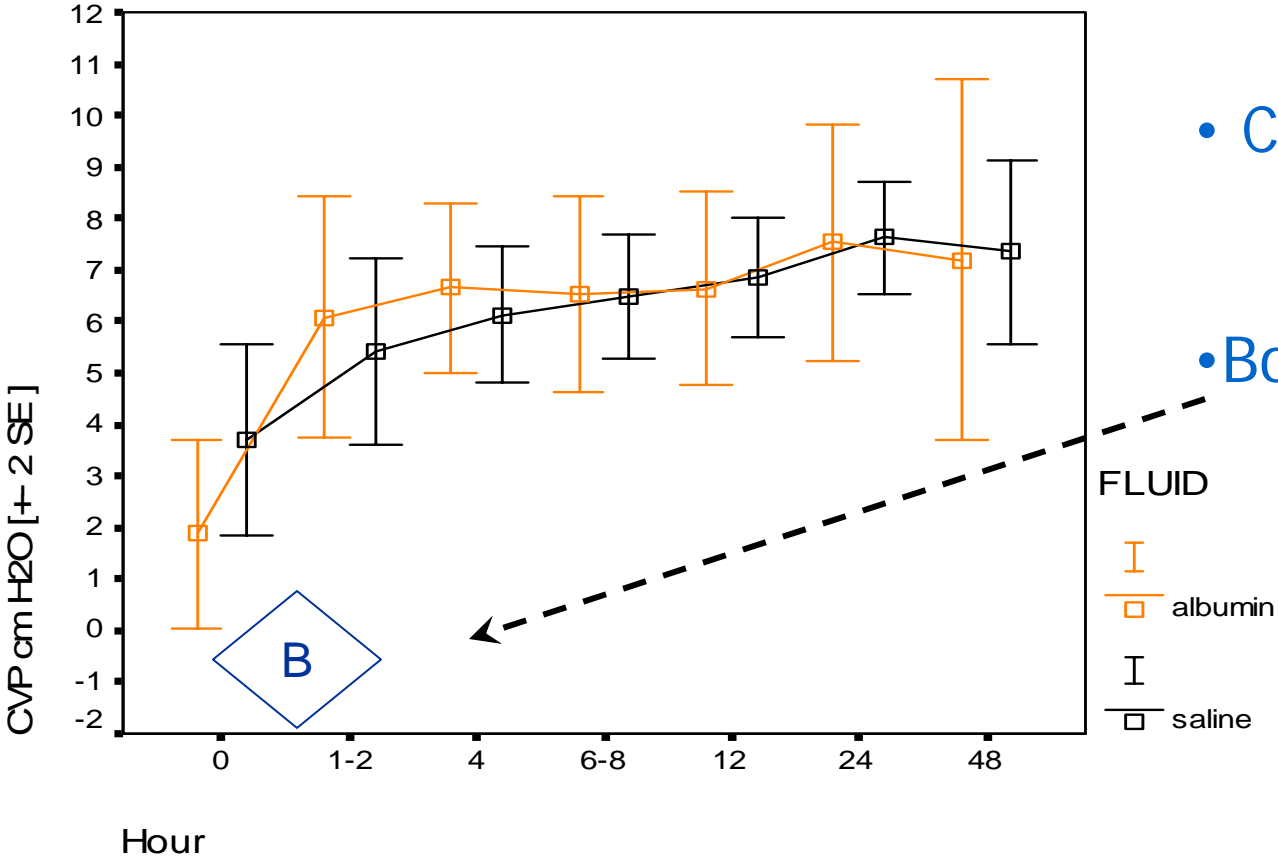
- More common than previously recognised ~60-80% cases
- Presents as respiratory distress
- Best independent predictor of a fatal outcome



Acidosis: in critically ill children

- Commonest cause of metabolic acidosis in children is hypovolaemia (shock)
- Often hypovolaemia not considered in absence hypotension
- *Standard management –volume resuscitation*

Phase I physiological studies



- CVP low at admission

- Bolus: saline or albumin 20-40mls/kg

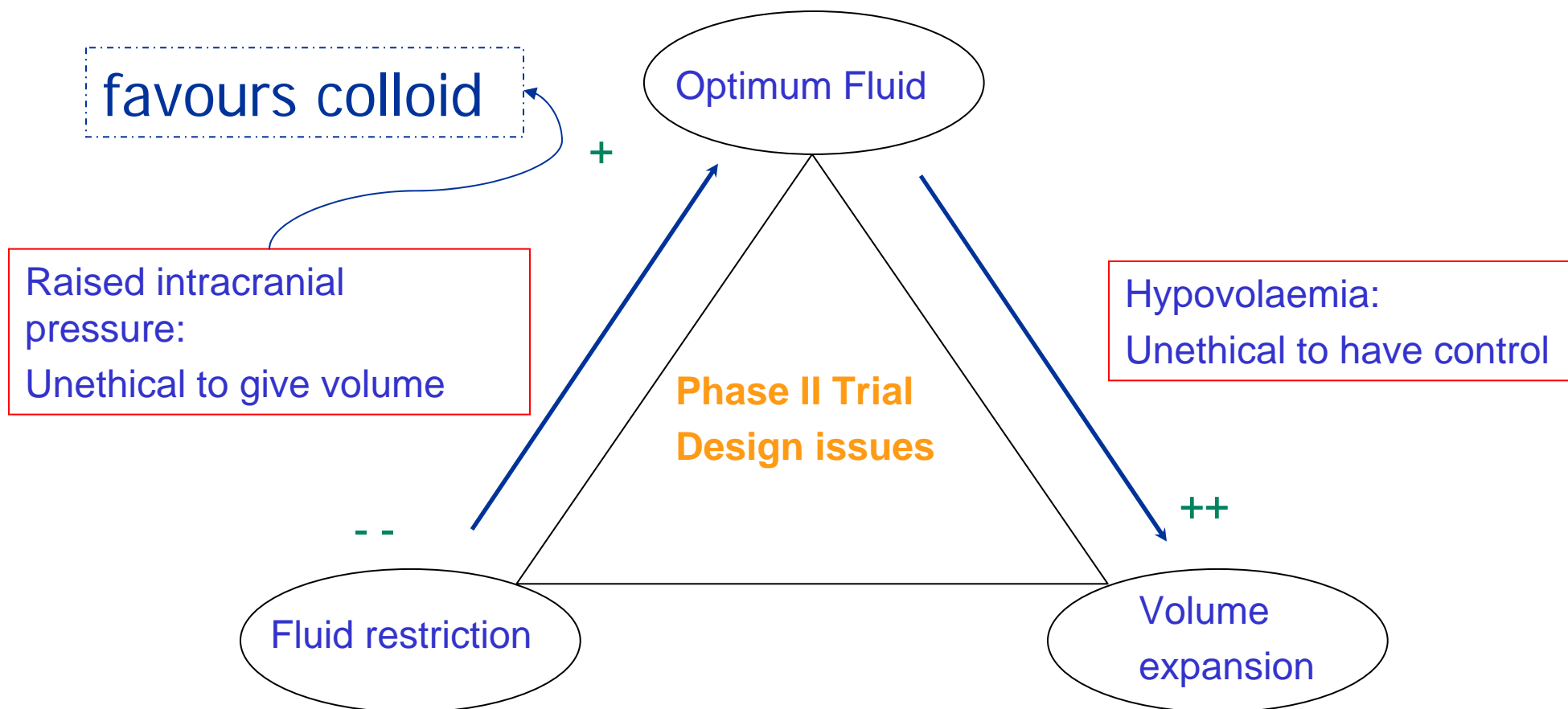
FLUID
I albumin
I saline

Summary of Phase I trials

- Evidence of hypovolaemia
- **Hypotension ~40% with severe acidosis**
- Hypovolaemia resolved with volume resuscitation
- Safety confirmed: 4 deaths (8%) no pulmonary oedema or evidence of raised intracranial pressure

Maitland *et al*. *Pediatr. Crit. Care Med.* 2003;4:426-431

Simple rules for volume resuscitation: lead to improved outcome ?

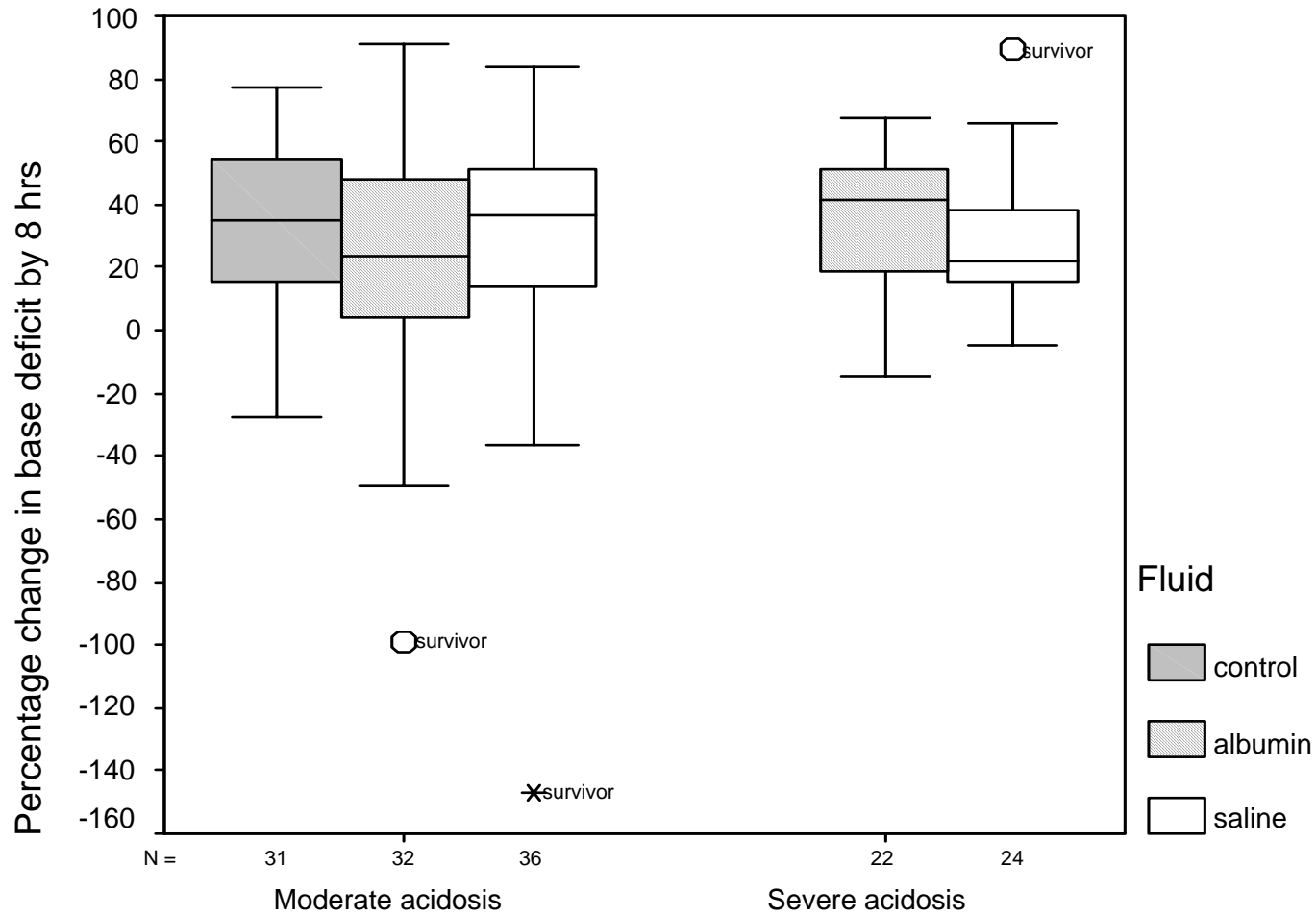


Compromised trial design

Trial considered two groups:

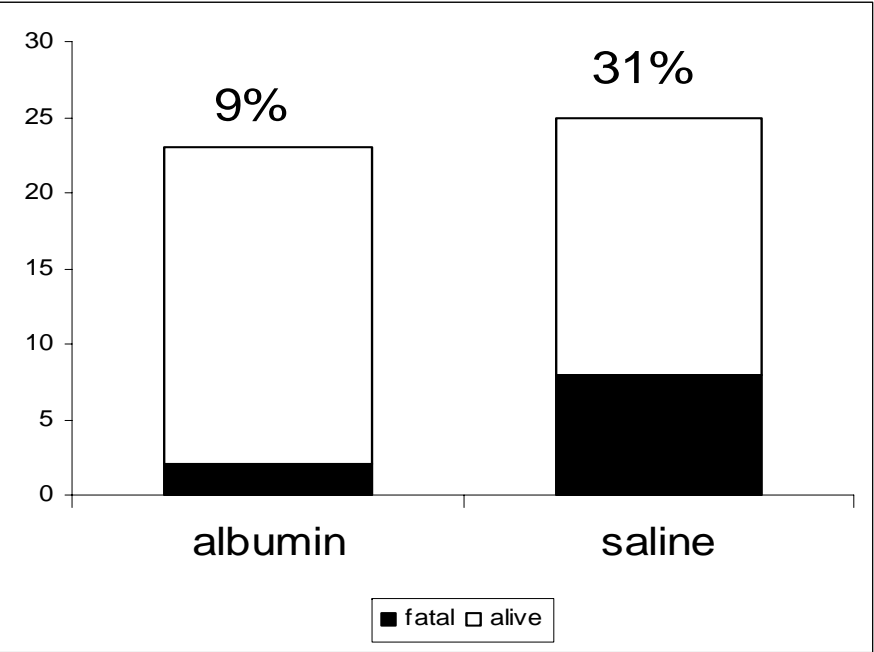
- Moderate acidosis group (base deficit 8-15)
Albumin, saline (20mls/kg bolus) or control (no bolus)
- Severe acidosis group (base deficit >15)
Albumin or saline (40mls/kg bolus)

Phase II trials 1^o endpoint: Resolution of acidosis by 8 hours

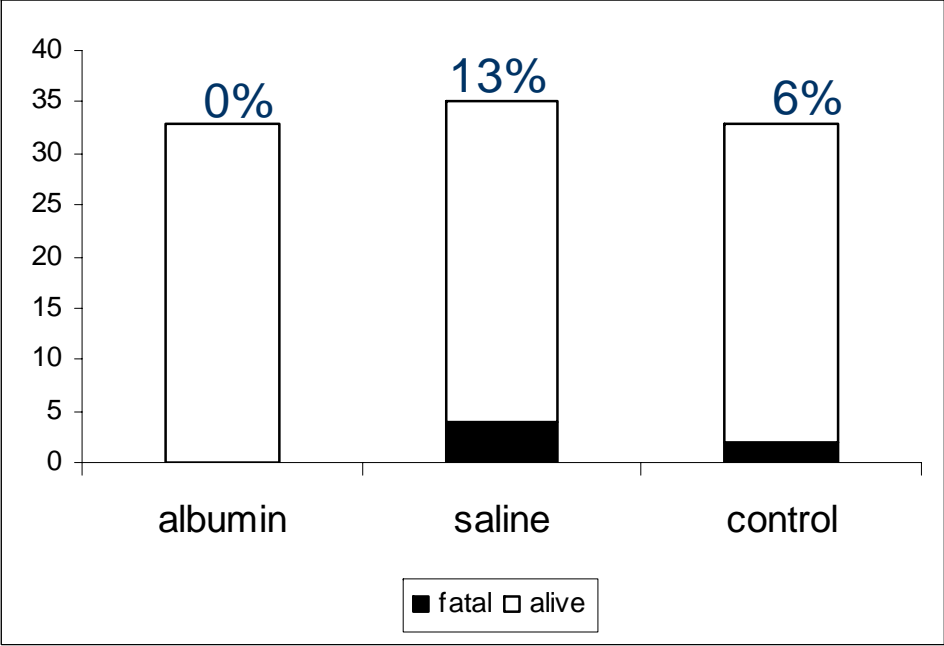


Mortality in both studies

Severe Acidosis

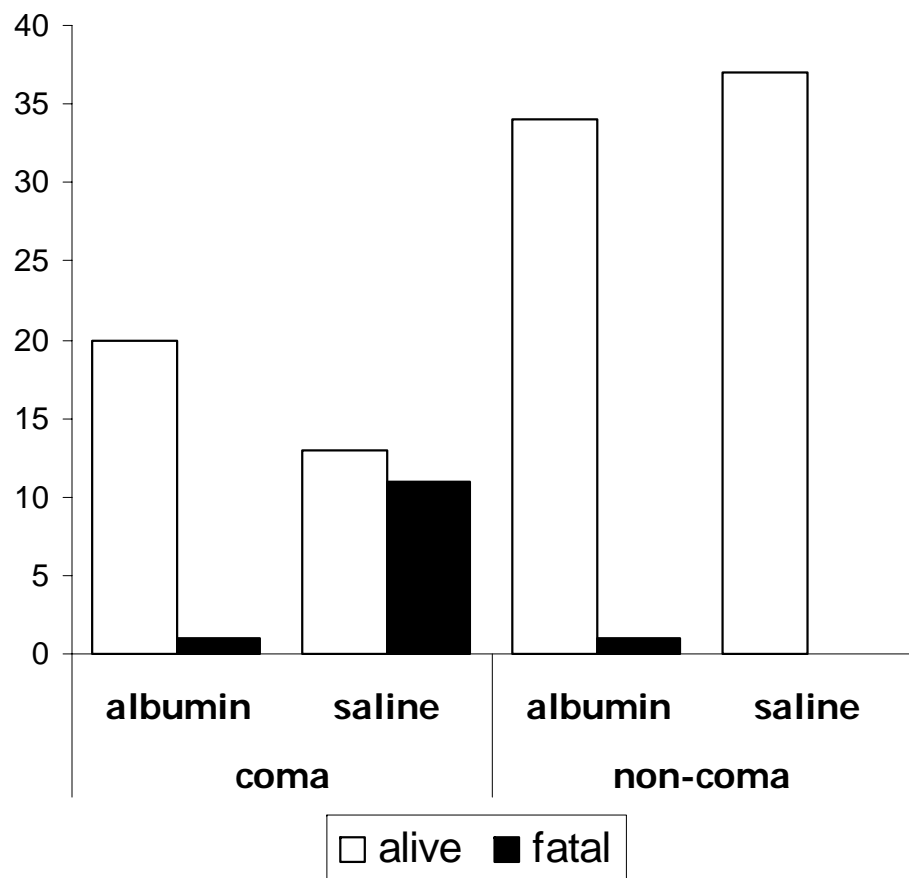


Moderate Acidosis



Saline vs albumin Relative Risk (95 % CI): 8.24 (1.1-60) $P < 0.001$

Mortality: Coma vs non-coma



Coma

Albumin 1/21 (5%)

Saline 11/24 (46%)

RR [95 % ci]: 9.6 [1.4 to 68];
P=0.002

Non-coma

Albumin 1/35 (3%)

Saline 0/37 (0%)

Maitland *et al* (2005) *Clin Infect Dis*; 40: 538-545

Albumin – a 'neuro-protective' therapy?

- Human albumin solution: improves colloid oncotic pressure, membrane stabiliser: BBB impairment has been demonstrated
- Saline: corrects shock but at risk of cerebral oedema (~80% deaths consistent with raised ICP)
- HAS expensive- need to examine other cheaper colloids (MIMCOM Poster Akech *et al* 425)

Summary

- Volume resuscitation corrects hypovolaemia
- Due to trial design and clinical withdrawals unable to address whether volume better than control
- Albumin improved outcome in high risk coma group: needs confirmation in larger trial with mortality as primary endpoint



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