Carbs and Protein: the role of starches and albumin

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Thank the organisers for inviting me today
• No conflict of interest

• No relationship with manufacturers of intravenous fluid products
Aims

• Determine which clinical situations are best treated with starch or albumin products
• Define the role of starch and albumin products in fluid management
• Prepare strategies to plan for the delisting of starch products
“Let’s face it - we’re not rocket scientists”
IV fluids is a HUGE subject

Focus on:
• Starches and Albumin
• Review properties
• Use in fluid resuscitation
• Use in ICU
• Adverse effects
• Impossible to give more than brief overview
Not focusing on:

- Pediatric uses
- Cardiac surgery
- Neurosurgery
- Burns resuscitation
- Liver disease and surgery

...ie highly specialised uses
Not attempting to cover whole subjects of:

• Fluid homeostasis and physiology in health and disease
• Perioperative and ICU fluid management

These could fill a textbook by themselves!
Crystalloids and Colloids
Crystalloids

- H2O with electrolytes approximating the composition and osmolality of plasma.
- Crystalloids redistribute through the extracellular fluids and, therefore, only about 20% of the volume administered will remain in the intravascular space.
- Aim to replace H2O and electrolyte losses throughout body fluid compartments
Colloids

- H2O, electrolytes and other particles (synthetic or natural) large enough to remain in the intravascular space for several hours.
- Used as artificial plasma volume expanders
- Albumin solutions are natural colloids
- Synthetic colloids are mainly starches or gelatin compounds.
The crystalloid/colloid controversy

• Controversial since the 1980s

• More recently also relates to type of colloid administered
Problems with many of the studies make comparison and analysis difficult:

- different species
- Choice of fluids and different regimens
- Type of injury or surgery
- Pre-existing illnesses
- Outcomes studied and complications studied
- Confounding use of whole blood
• Impossible to test every fluid regime and combination in every type of patient
• No clear consensus
• Difficult to keep score of every meta analysis favouring colloids and every meta analysis favouring crystalloids for resuscitation
Adding to the Controversy

- Dr Joachim Boldt
- Professor of Anesthesiology
- University of Giessen, Germany
- Arguably the biggest “name” in Colloid research and opinion

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Fraud
'Unethical' anaesthetics research is retracted

The editors of 16 medical journals have retracted "unethical" studies by an influential German anaesthetist.

Joachim Boldt carried out research into colloids, drugs used in surgery to boost fluid levels in the body.

But he did not get the necessary approval for 89 studies. He has been suspended, and is now being investigated for research fraud.

However, a UK expert said patients should not worry, as the work was not fundamental to how colloids are used.

Dr Boldt worked as chief anaesthetist at the Klinikum Ludwigshafen hospital in Rhineland.
• 89 articles retracted by multiple journals
• No ethics committee approval for studies
• Some say this does not effect validity of findings….but there are suspicions.
• Investigations ongoing
• However, investigation came about because readers of Anesthesia and Analgesia suspicious of “too perfect results”

• So..this presentation is a “Boldt free zone”
Accepted statements

- Crystalloids replace interstitial losses.
- Colloids are superior at replacing plasma volume deficits - more quickly and lasting longer - giving greater increases in plasma volume, cardiac output and organ blood flow.
- Crystalloid administration may also produce such increases but approximately three times as much will be needed with consequent delays in achieving goals of resuscitation.
• Crystalloids are cheap.
• Colloids are more expensive.
• Many centres in the US use crystalloids almost exclusively.
• In most situations eg routine surgery both potentially give excellent results if appropriate amounts are used.
• Much of those debates relate to how much fluid to give (and when) as much as to the type of fluid given.

• Limit discussion today to indications for, adverse effects of, and, effect on outcome of administration of intravenous starches and albumin.
International fluid use for resuscitation. 24hr period in 2007

Crit Care 2010 ; 14 : R185
Figure 2 Percentage of fluid resuscitation episodes given as crystalloid, colloid or blood product according to country*. Crystalloid; Colloid; Blood: *Difference in proportions given crystalloid, colloid or blood between countries, respectively $P < 0.001$, $P < 0.001$, $P < 0.001$.
Starches
Hydroxyethyl starch

Derived from corn

Different types starches described by:

• Average molecular weight, typically around 130 to 200 kDa (range of different-sized molecules in any given solution)

• Degree of molar substitution (what proportion of the glucose units on the starch molecule have been replaced by hydroxyethyl units)

• Concentration in % (i.e. grams per 100ml).

• For example, Voluven© is 6% HES 130 / 0.4
• Early starches had relatively high mean molecular weights (450-650 kDa) and high proportion of molar substitution (0.7 hence hetastarch).

• Significant adverse effects due to slow rate of degradation and persistence within plasma and tissues. For example: impaired coagulation, hyperoncotic renal failure, persistent pruritus
• Later, developed pentastarches (0.5)
• Latest generation 0.4 (tetrastarches)
• Extent of substitution determines breakdown by amylase
• Tetrastarches 20x plasma clearance of hetastarches
• Less adverse effects?
• Little dispute that older starches had significant adverse effects
• Concentrate, therefore, on newer tetrastarches
• Voluven (6% HES 130/0.4) max dose 50ml/kg/24hr
Potential benefits of starches

- Increased plasma volume quicker and for longer compared to crystalloids.
- Cardiac output increases less predictable in critically ill patients.
- Overall oxygen delivery to tissues may be reduced due to hemodilution.
- Useful as blood substitute eg Jehovah’s Witnesses.
Prevention of Hypotension eg spinal anesthesia

• Colloid preloading is more effective than crystalloid preloading for decreasing the incidence and severity of spinal-induced hypotension.
• However, neither were completely effective.
• The reduced incidence must be set against the increased costs and slightly increased risk of allergic reactions associated with colloids.

Can J Anaesth 2000; 47: 616-21
Resuscitation from hypovolemia

- Resuscitation from hypovolemia eg ER, OR, ICU may be improved (greater and earlier increases in cardiac output) and sustained compared with crystalloids.
- ‘J’ shaped curve – see later

Intensive Care Med 2006; 32: 1030-8
Intensive Care Med 2010; 36: 697-701
Eur J Anaesthesiol 2010; 27: 794-800
Pulmonary complications

• Type of fluid administered does not seem to influence pulmonary edema formation provided fluid overload is avoided.
• Fluid overload may be a polite term for drowning.

Br J Anaesth 2006 ; 96 : 21-30
Crit Care Med 2009 ; 37 : 1275-81
Coagulation
• Earlier generations of starches had significant detrimental effects on coagulation

• All colloids (and to a lesser extent, crystalloids) can interfere with coagulation at high doses eg due to hemodilution. Longer lasting = longer impairment of coagulation

• Beware of studies in vitro or in healthy volunteers eg no surgical “stress response” changes, blood loss, role of endothelium, administration of other drugs etc
HES causes decrease in Factor VIII and Von Willebrand factor even when used below suggested maximum doses.

Also speculation that HES molecules attach to platelets or are phagocytized by them.

In vitro studies: newer generation fluids lesser effects on coagulation.

Anesthesiology 2009: 111; 187-202
HES for pump prime for CABG

• HES 120 v HES 400 v Albumin for CPB pump prime
• Thromboelastographic assessment of speed of clot formation and strength of clot – reduced in both HES groups
• Blood loss in first 4hrs postop increased in both HES groups

• Problem is that most studies on coagulation compare one colloid with another!

• Few compare a new generation colloid with crystalloid
Colloids v crystalloids

- Elective cardiac surgery
- Coagulation assessed by thromboelastography
- HES 130 v Gelatin v Crystalloid postop
- Even a small dose of HES130/0 or gelatin impaired clot strength after cardiac surgery in a dose-dependent fashion, but neither colloid increased blood loss.
- Crystalloid slightly increased clot strength

Br J Anaesth 2010; 104: 691–7
So….it seems that even the newer generations of starches have the potential to adversely influence coagulation – certainly when compared with crystalloids
The kidney
Hyperoncotic colloids and the kidney

• May be adverse effect of hyperoncotic fluids including hyperoncotic Albumin (20 – 25%) and starches.

• Plasma colloid osmotic pressure may counteract opposing hydrostatic filtration pressure in the glomerulus.
• Prospective cohort study. 1013 patients
• Hyperoncotic fluids associated with renal complications and increased risk of ICU death (OR 2.79)

Intensive Care Med 2008; 34: 2157-68
Renal effects of HES

HES use in donors in the past shown to have deleterious effects on renal function in transplanted patients.

Most studies comparing HES and Gelatins in ICU and surgical patients show little difference in adverse renal effects.

Moderate cumulative doses of either are associated with a higher risk of acute renal failure.

Intensive Care Med 2009 ; 35 : 1539–1547
VISEP study

• Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP)
• Compared conventional versus intensive insulin therapy and HES (200/0.5) versus crystalloid in severe sepsis patients in ICU.
• Stopped early after 488 patients due to increased hypoglycemia in intensive insulin group.
• Data for fluid part of study stopped after 537 patients
• HES associated with increased rate of renal failure and trend to increased mortality

Cochrane Review 1

• 34 studies
• Relative risk of author-defined kidney failure was 1.50 (95% CI 1.20 - 1.87) and 1.38 for requiring renal replacement therapy (95% CI 0.89 - 2.16) with HES compared with other fluid therapies.
• Possible increased risk in septic patients compared to (surgical/trauma) patients.
Does use of colloids increase survival compared to the use of crystalloids for resuscitation?
Cochrane Review 2

- No evidence that one colloid is more effective or safe than any other
- There are still possibly significant differences between colloids.
- Larger trials of fluid therapy are needed if clinically significant differences in mortality are to be detected or excluded.
Cochrane Review 3

• No evidence from RCTs that resuscitation with colloids reduces mortality compared to crystalloids in patients with trauma, burns or following surgery.

• “it is hard to see how their continued use in these patients can be justified outside the context of RCTs.”
• Perhaps Cochrane reviewers are wrong?
• Perhaps adverse effects from earlier generations of starches “cancelled out” benefits of their administration?
• Perhaps later Cochrane reviews of studies using newer generation starches will reach different conclusions?
‘J’ shaped survival curve

- Most patients do well if given reasonable amounts of almost ANY fluid – so survival not influenced by choice of fluid type.
- Small group of patients who will die from their injuries regardless of which fluid is given – so survival not influenced by choice of fluid type.
- Perhaps small group of patients in whom choice of type of fluid crucial!
Are the new starches any safer?

There are some studies suggesting newer generations of HES (130) are associated with less adverse effects on the kidney – at least when compared with gelatins.

British Journal of Anaesthesia 2008; 100: 504–8
British Journal of Surgery 2007; 94: 427–433
“HES 130/0.4 was approved on the basis of equivalence studies, which focus on acute hypovolemia, mostly in the setting of elective surgery, use predominantly other synthetic colloids as comparators, have small sample sizes, use short-term and moderate-volume exposure, and are not suitable for assessing safety.”

Anesth Analg 2011; 112: 507-11
The curse of Boldt continues

“There are 56 randomized controlled trials (RCTs) on HES130/0.4. One-third of these RCTs were published by Boldt et al, all in the elective surgical setting.”

Anesth Analg 2011; 112: 507-11
“published clinical data are inadequate to support the conclusion that HES130/0.4 is safer than other HES solutions in surgical and critically ill patients.”

Anesth Analg 2011; 112: 507-11
Why are starches still used?

• Belief in ‘J’ shaped survival curve
• Belief in ‘Golden hour’
• Increases in cardiac output, oxygen delivery
• Blood substitute eg Jehovah’s Witnesses
• Habit?
Final word on starches?

“recent data from large clinical studies in various populations of critically ill patients show that colloid resuscitation provides no clinically relevant outcome benefit. Against this background, it is a concern that HES administration is associated with dose-related side effects that are not trivial”

Albumin
• Most abundant plasma protein
• 585 amino acid peptide chain
• Synthesised in liver. Approx 12-20g/day
• Maintains plasma oncotic pressure
• Carrier of molecules including hormones and drugs
• Anti oxidant and anti inflammatory properties
Safety of Albumin

- Human pooled plasma
- Low allergic potential
- Low virus transmission (heat treated)
- Potential for prion transmission (low?)
- Used for 60 years with good safety record
- (Expensive)
May be low in:

- Malignancy
- Liver disease
- Protein losing enteropathy
- Nephrotic syndrome
- Malabsorption
- Malnutrition
- ICU
Albumin in ICU

- Serum albumin reduced secondary to reduced synthesis, increased losses and loss from intravascular space.
- Not stored, so no albumin reserves.
- Correlates with both severity of illness and predictive of outcome in critically ill.
- Not markedly influenced by nutritional support
• Meta analysis of 90 cohort studies.
• Strong predictor of poor outcome
• Each 10g/dl fall in serum albumin increased mortality by 137%, morbidity by 89% and prolonged ICU stay by 28%

• Should we routinely replace albumin in ICU patients by giving albumin infusions?

• That’s what we do K, Hb, glucose etc

• So why not albumin?
• Is hypoalbuminemia in ICU responsible for worse outcome?

OR

• Is hypoalbuminemia in ICU just a marker for more severe illness?
Still considered controversial!

Some meta analyses have shown reductions in morbidity when albumin supplementation given. Often include non critically ill patients.

When patients’ underlying condition improves, albumin levels will arise and patients will have a spontaneous diuresis.
Best way to increase serum albumin in critically ill patients may be to treat the underlying cause, good supportive and nutritional care and treat sepsis.
% of patients in ICU study receiving Albumin during 15 day study period

Critical Care 2005, 9 : R745-R754
Does albumin administration improve outcome in critically ill patients?
Further confounding issues with albumin:

- Administered to correct hypoalbuminemia or for resuscitation of shock?
- Administered as hyperoncotic solution?
Albumin – 2 early meta-analyses

- Cochrane review
- ICU studies of albumin administration for hypovolemia, burns or hypoalbuminemia
- 30 RCTS including 1419 patients
- Relative risk of death 1.69 ie for every 17 critically ill patients treated with albumin there was 1 extra death

• 55 trials including 3054 patients
• Relative risk of death was 1.11
• Lower in larger trials, trials with blinding and mortality as end point
• Concluded that any effect of albumin on mortality was small

Ann Intern Med 2001; 135: 149-64
“C’mon, c’mon — it’s either one or the other.”
SAFE trial

- Saline versus Albumin Fluid Evaluation
- Multicentre trial of 6997 patients
- ICU patients received 4% Albumin or NS for intravascular fluid resuscitation as required for next 28 days

- No significant difference in any outcome measure (apart from cost)
- Concluded that Albumin safe in ICU
- Alternative conclusion would be….no benefit giving albumin!
• So….Albumin administration in ICU is probably safe.

BUT

• That’s hardly a ringing endorsement!
SAFE subgroup analyses
Baseline Albumin

<table>
<thead>
<tr>
<th>Deaths/Total</th>
<th>Albumin</th>
<th>Saline</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>644/3012</td>
<td>655/3028</td>
<td>0.99 (0.87 to 1.11)</td>
</tr>
<tr>
<td>Baseline serum albumin concentration ≤ 25 g/l</td>
<td>291/1228</td>
<td>321/1223</td>
<td>0.87 (0.73 to 1.05)</td>
</tr>
<tr>
<td>Baseline serum albumin concentration &gt; 25 g/l</td>
<td>353/1784</td>
<td>334/1805</td>
<td>1.09 (0.92 to 1.28)</td>
</tr>
</tbody>
</table>

Heterogeneity P=0.08

BMJ 2006; 333: 1044-6
Coagulation

- Both groups transient decreases in platelet count and no change in INR
- Small prolongation of APPT (of unlikely clinically significance) in Albumin group.
- Albumin administration and large volume of resuscitation associated with prolongation of APTT.

Crit Care Resusc 2009; 11: 250-6
Head Injury

- 460 patients
- Similar severity of head injury
- Followed up for 24 months

Sepsis and organ failure scores

<table>
<thead>
<tr>
<th>Severe sepsis</th>
<th>185/603</th>
<th>217/615</th>
<th>0.87 (0.74–1.02)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>518/2734</td>
<td>492/2720</td>
<td>1.05 (0.94–1.17)</td>
</tr>
</tbody>
</table>

ie trend towards greater survival in patients with severe sepsis resuscitated with Albumin compared to Saline

Intensive Care Med 2011 ; 37 : 86-96
SOAP (Sepsis Occurrence in Acutely ill patients)

- International trial across Europe
- 3147 patients
- 339 matched pairs
- Albumin associated with reduced 30 day survival

Critical Care 2005, 9: R745-R754
Cochrane Review 4

- Updated 2008.
- Concluded that no evidence that Albumin reduces mortality in critically ill patients, patients with burns or patients with hypoalbuminemia compared to cheaper alternatives such as Saline.
Albumin in ICU Conclusions

No clear benefits in ICU patients from correcting hypoalbuminemia on mortality, length of stay, duration of mechanical ventilations or renal support.

Crit Care Resusc 2009 ; 11 : 67–70
• Unclear role in sepsis but suggestion of decreased survival
• Probably should not be given in head injury patients
• Hyperoncotic albumin may increase renal failure
• Albumin is very expensive
• Shown are % of total ICU costs attributed to Albumin use for one US ICU.

Albumin in cirrhosis

- Albumin beneficial in patients with cirrhosis
- Also benefits seen in patients with spontaneous bacterial peritonitis, hepatorenal syndrome and post paracentesis of ascites

Journal of Hepatology 2010; 53: 397-417
Albumin in Burns

- Some centers use albumin as part of a fluid resuscitation strategy for patients with severe burns.
- Little evidence of increased efficacy compared to crystalloids.
- Most studies are small.
- Recent Cochrane reviews also cover burns patients.
• Albumin is also used during plasmapheresis (therapeutic plasma exchange)

• Used chiefly for autoimmune diseases
The future
“Given that pharmaceutical agents have to demonstrate safety and efficacy before they receive marketing approval, regulatory agencies should consider reviewing their criteria for granting marketing approval to resuscitation fluids. In particular they should require evidence from clinical trials that examine longer term patient-centred safety and efficacy outcomes.”

Critical Care 2010 ; 14 : R185
The CHEST trial

- **Crystalloid versus HydroxyEthyl Starch**
- 7000 patients planned
- N Saline v 6% HES 130 for fluid resuscitation
- 90 day mortality & other endpoints eg renal function
- Commenced April 10
The 6S - Scandinavian Starch for Severe Sepsis/Septic Shock trial

• Will randomize 800 patients with severe sepsis in 30 Scandinavian ICUs to masked fluid resuscitation using either 6% HES 130/0.4 in Ringer's acetate or Ringer's acetate alone.

• Primary outcomes: 90-day mortality or end-stage kidney failure.
If results are negative will anyone listen?
Some doctors are scientists—just as some politicians are scientists—but most are not. As medical students they were filled full with information on biochemistry, anatomy, physiology, and other sciences, but information does not a scientist make—otherwise, you could become a scientist by watching the Discovery channel. A scientist is somebody who constantly questions, generates falsifiable hypotheses, and collects data from well designed experiments—the kind of people who brush their teeth on only one side of their mouth to see whether brushing your teeth has any benefit. Most doctors follow familiar patterns and rules, often improvising around those rules. In their methods of working they are more like jazz musicians than scientists.

Questioning whether doctors are scientists may seem outrageous, but most doctors know that they are not scientists. I once asked a room of perhaps 150 medically trained educators which of them thought of themselves as scientists. About five put up their hands.
What should hospitals do to prepare for delisting?

Use as teachable moment to educate clinicians towards more rational (and restricted) use.
Conclusions

• IV Starch role is limited
• Probably should be used (if at all) for resuscitation of acute hypovolemic, as blood substitute or where rapid plasma volume expansion necessary
• IV Albumin role even more limited
• May still be subspecialised uses
Thank you