Synthetic colloids still have a role in the ICU-Con!

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Friedrich-Schiller-University Jena, Germany
# i.v. fluids

## Crystalloids

<table>
<thead>
<tr>
<th>Year</th>
<th>Fluid Type</th>
<th>Inventor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1832</td>
<td>hypotonic NaCl</td>
<td>Thomas Latta</td>
</tr>
<tr>
<td>1883</td>
<td>Ringer Solution</td>
<td>Sydney Ringer</td>
</tr>
<tr>
<td>1885</td>
<td>isotonic NaCl</td>
<td>H. J. Hamburger</td>
</tr>
<tr>
<td>1934</td>
<td>Ringer’s lactate</td>
<td>Alexis Hartmann</td>
</tr>
<tr>
<td>1970</td>
<td>Ringer’s acetate</td>
<td></td>
</tr>
</tbody>
</table>

## Synthetic colloids

<table>
<thead>
<tr>
<th>Year</th>
<th>Fluid Type</th>
<th>Inventor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1916</td>
<td>Gum acacia</td>
<td>W. Bayliss</td>
</tr>
<tr>
<td>1939</td>
<td>Polyvinyl pyrrolidone</td>
<td>G. Hecht, H. Weese</td>
</tr>
<tr>
<td>1947</td>
<td>Oxypolygelatin</td>
<td>L. Pauling</td>
</tr>
<tr>
<td>1952</td>
<td>Succinylated Gelatin</td>
<td>D. Tourtelotte</td>
</tr>
<tr>
<td>1962</td>
<td>Urea-linked Gelatin</td>
<td>M. Lindner, J. Schmidt-Thomé</td>
</tr>
<tr>
<td>1944</td>
<td>Dextran</td>
<td>A. Grönwall, B. Ingelmann</td>
</tr>
<tr>
<td>1972</td>
<td>HES 450/0.7</td>
<td>W.L. Thompson</td>
</tr>
<tr>
<td>1999</td>
<td>HES 130/0.4</td>
<td></td>
</tr>
</tbody>
</table>

## Human albumin

<table>
<thead>
<tr>
<th>Year</th>
<th>Fluid Type</th>
<th>Inventor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1940</td>
<td>Human albumin</td>
<td>E. Cohn</td>
</tr>
<tr>
<td>1940</td>
<td>Human albumin</td>
<td>E. Cohn</td>
</tr>
</tbody>
</table>
Drug approval

This legislation was created in the late 1970ies.
Synthetic colloids were introduced into the market in an era where eminence based medicine over evidence based medicine
Synthetic colloids are widely used.

Fluid volumes delivered

Finfer et al crit Care 2011
“[t]here 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. …it is hard to see how their continued use in these patients can be justified outside the context of RCTs.”

Perel et al., Cochrane Sys. Review 2013
VISEP: HES 200/0.5 vs. Ringer’s for fluid therapy in sepsis - 90 day survival

Cumulative dose 70ml/kgBW

Brunkhorst FM et al. NEJM, 2008
Cumulative dose:
Renal replacement therapy and 90-day mortality

Brunkhorst FM et al. NEJM, 2008
6S: 6% HES 130/042 vs. Ringer’s for fluid therapy in sepsis - 90 day survival

Cum. dose 44ml/kgBW

A. Perner et al 6S Trial, NEJM 2012
Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

John A. Myburgh, M.D., Ph.D., Simon Finfer, M.D., Rinaldo Bellomo, M.D.,

7000 patients
Low dose – 17 mL/Kg of 6% HES (130/0.4)
No significant difference in mortality
Significant more need for RRT
Significant more itching
No subgroup where HES better

DOI: 10.1056/NEJMo1209759
Impact of HES on need for RRT

OR 1.32 (1.15-1.50) p= 0.001
Impact of HES on mortality

OR 1.09 (1.02-1.17) p= 0.02
According to Fresenius Voluven and Volulyte world wide is the most used hydroxyethyl starch preparation, which since 1999 has been administered to more than 30 Million patients. There is a data base of more than 180 publications that covers numerous patient populations including children.

Source: Fresensius Advertisement Journal of DIVI 2010
Fresenius Blood Volumizer Linked to Deaths in Study

By Naomi Kresege - Feb 19, 2013 10:00 PM GMT+0100

A product made by Fresenius SE to boost blood volume in critically ill patients increases the risk of death and kidney damage, according to an analysis of previous studies that excluded data from a discredited researcher.
Millions of surgery patients at risk in drug research fraud scandal

Millions of NHS patients have been treated with controversial drugs on the basis of "fraudulent research" by one of the world's leading anaesthetists, The Daily Telegraph can disclose.
“[t]here 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. Furthermore, the use of hydroxyethyl starch might increase mortality…..it is hard to see how their continued use in these patients can be justified outside the context of RCTs.”
Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function

• 42 studies (11,399 patients)
• Significant increase in the need for RRT with HES (RR 1.31, 95% CI 1.16 to 1.49;)
• No differences between sepsis versus non-sepsis patients,
• High molecular weight (MW) and degree of substitution (DS) versus low MW and DS or
• High versus low dose treatments (i.e. ≥ 2 L versus < 2 L).

Mutter TC, Ruth CA, Dart AB
Authors` conclusions:
The current evidence suggests that all HES products increase the risk in AKI and RRT in all patient populations and a safe volume of any HES solution has yet to be determined.

Mutter TC, Ruth CA, Dart AB 2013
Hydroxyethyl-starch solutions (HES) should no longer be used in patients with sepsis or burn injuries or in critically ill patients – CMDh endorses PRAC recommendations

25/10/2013

Hydroxyethyl-starch solutions (HES) should no longer be used in patients with sepsis or burn injuries or in critically ill patients – CMDh endorses PRAC recommendations
FDA Recommendations for Health Professionals

- Do not use HES solutions in critically ill adult patients including those with sepsis, and those admitted to the ICU.
- Avoid use in patients with pre-existing renal dysfunction.
- Discontinue use of HES at the first sign of renal injury.
- Need for renal replacement therapy has been reported up to 90 days after HES administration. Continue to monitor renal function for at least 90 days in all patients.
- Avoid use in patients undergoing open heart surgery in association with cardiopulmonary bypass due to excess bleeding.
- Discontinue use of HES at the first sign of coagulopathy.
Balanced crystalloid compared with balanced colloid solution using a goal-directed haemodynamic algorithm

Table 3 Descriptive postoperative data. Data are shown as median (25%; 75%) quartiles or as n (%). For grade and number of complications according to the Clavien classification and mortalities, excluded patients were included as it reflects a safety analysis. P-values calculated using the exact Wilcoxon–Mann–Whitney test or the exact χ² test in contingency tables as appropriate.

<table>
<thead>
<tr>
<th></th>
<th>Balanced crystalloid (n=24)</th>
<th>Balanced colloid (n=24)</th>
<th>Balanced starch (n=24)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital length of stay (dd/hh)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of stay in post-anaesthesia care unit or high dependency care unit (dd/hh)</td>
<td>13/21 (10/24; 15/24)</td>
<td>01/18 (00/18; 02/19)</td>
<td></td>
<td>0.401†</td>
</tr>
<tr>
<td>Need for postoperative ventilator therapy [n (%)]</td>
<td>5 (20.8)</td>
<td>5 (20.8)</td>
<td></td>
<td>1.000‡</td>
</tr>
<tr>
<td>Sequential Organ Failure Assessment (SOFA) score, postoperatively</td>
<td>1.0 (0; 2.0)</td>
<td>2.0 (1.0; 4.0)</td>
<td></td>
<td>0.093†</td>
</tr>
<tr>
<td>Highest grade of complication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clavien grade 0 [n (%)]</td>
<td>5 (20.8)</td>
<td>3 (11.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clavien grade 1, n (%)</td>
<td>0 (0)</td>
<td>6 (23.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clavien grade II [n (%)]</td>
<td>15 (62.5)</td>
<td>9 (34.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clavien grade IIIa [n (%)]</td>
<td>1 (4.2)</td>
<td>1 (3.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clavien grade IIIb [n (%)]</td>
<td>3 (12.5)</td>
<td>5 (19.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clavien grade IVa [n (%)]</td>
<td>0 (0)</td>
<td>2 (7.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of complication per patient according to Clavien classification (number)</td>
<td>2.0 (1.0; 3.8)</td>
<td>2.0 (1.0; 4.3)</td>
<td></td>
<td>0.201†</td>
</tr>
<tr>
<td>Intrahospital mortality [n (%)]</td>
<td>0 (0)*</td>
<td>1 (3.8)*</td>
<td></td>
<td>1.000‡</td>
</tr>
<tr>
<td>Mortality 3 months after surgery [n (%)]</td>
<td>0 (0)*</td>
<td>5 (19.2)*</td>
<td></td>
<td>0.051†</td>
</tr>
</tbody>
</table>

90 day mortality rate HES 19.2% vs 0% crystalloids p = 0.051
Increased risk of AKI and RRT after HES and after gelatin in cardiac surgery

Peri-operative data from 6478 consecutive patients from 3 fluid periods (1. HES, 2. Gelatin, 3. only crystalloids)

Risk for AKI

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gelatin</td>
<td>1.85</td>
<td>1.31, 2.62</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HES</td>
<td>2.55</td>
<td>1.76, 3.69</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Risk for RRT

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Multiple Logistic Regression</th>
<th>Propensity Score Stratification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HES, mainly 6% 130/0.4</td>
<td>2.29 (1.47, 3.60)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gelatin 4%</td>
<td>2.75 (1.84, 4.16)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Observational trials: 
HES volume and acute kidney injury (AKI)

44,176 adults who had noncardiac, nonurological inpatient surgery at the Cleveland Clinic between January 2005 and September 2012

Propensity matching →14,680 colloid [predominantly Hextend] and 14,680 non-colloid patients

OR 1.21 (1.06–1.38)

Kashy et al, Anesthesiology 2014
Increased risk of AKI after HES in surgery

1129 patients with lung resection surgery – retrospective analysis - intraoperative HES was dose-dependent risk factor for postoperative AKI  OR 1.5 (95% CI: 1.1–2.1)

Ishikawa et al, Anaesth & Analg 2012

174 patients with liver transplantation – before-and-after change from 5% albumin to 6% HES - adjusted hazard ratio for AKI  2.97, 1.13–7.7, P = 0.027)

Hand et al, Anaesth & Analg 2014
Postoperative renal replacement therapy after hydroxyethyl starch infusion: a meta-analysis of randomised trials

M.M. Wilkes, R.J. Navickis

**Figure 2.** RR for RRT. Error bars indicate 95% CI. Data points scaled according to meta-analytic weight.

<table>
<thead>
<tr>
<th>Trial</th>
<th>RRT (n)</th>
<th>RR (95% CI)</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>London et al., 1989(^{24})</td>
<td>1 (50)</td>
<td>0.88 (0.06-13.7)</td>
<td>1.8</td>
</tr>
<tr>
<td>Cittanova et al., 1996(^{25})</td>
<td>9 (27)</td>
<td>6.67 (0.92-48.4)</td>
<td>2.0</td>
</tr>
<tr>
<td>Bennett-Guerrero et al., 2001(^{26})</td>
<td>4 (95)</td>
<td>2.21 (0.41-11.8)</td>
<td>3.3</td>
</tr>
<tr>
<td>Mahmood et al., 2007(^{27})</td>
<td>2 (42)</td>
<td>0.32 (0.06-1.75)</td>
<td>7.0</td>
</tr>
<tr>
<td>Godet et al., 2008(^{28})</td>
<td>0 (32)</td>
<td>0.34 (0.01-8.13)</td>
<td>2.6</td>
</tr>
<tr>
<td>Mukhtar et al., 2009(^{30})</td>
<td>1 (20)</td>
<td>1.00 (0.07-14.9)</td>
<td>1.7</td>
</tr>
<tr>
<td>Lee et al., 2011(^{32})</td>
<td>1 (53)</td>
<td>3.00 (0.12-72.0)</td>
<td>0.9</td>
</tr>
<tr>
<td>Myburgh et al., 2012(^{10})</td>
<td>61 (1425)</td>
<td>1.38 (0.94-2.01)</td>
<td>77.4</td>
</tr>
<tr>
<td>Skhirtladze et al., 2014(^{36})</td>
<td>1 (81)</td>
<td>0.96 (0.09-10.4)</td>
<td>2.4</td>
</tr>
<tr>
<td>Yates et al., 2014(^{37})</td>
<td>3 (106)</td>
<td>6.61 (0.35-126)</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>83 (1931)</td>
<td>1.44 (1.04-2.01)</td>
<td>100.0</td>
</tr>
</tbody>
</table>

\(^{24}\) I^2 = 0% (CI, 0-57%); p = 0.54
Resuscitation with hydroxyethyl starch \underline{improves renal function and lactate clearance in penetrating trauma} in a randomized controlled study: the FIRST trial (Fluids in Resuscitation of Severe Trauma)

M. F. M. James\textsuperscript{1*}, W. L. Michell\textsuperscript{2}, I. A. Joubert\textsuperscript{1}, A. J. Nicol\textsuperscript{2}, P. H. Navsaria\textsuperscript{2} and R. S. Gillespie\textsuperscript{1}

\textsuperscript{1}Department of Anaesthetics and \textsuperscript{2}Department of Surgery, Groote Schuur Hospital and Faculty of Health Sciences, University of Cape Town, Anzio Road, Observatory, Cape Town, Western Cape 7925, South Africa
\* Corresponding author. E-mail: mike.james@uct.ac.za

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|}
\hline
 & HES 130 & NaCl \\
\hline
James et al. & 21.4\% & 11.3\% \\
\hline
\end{tabular}
\caption{Comparison of lactate clearance between HES 130 and NaCl in penetrating trauma patients.}
\end{table}

\textbf{Editor's key points}
- Opinions are divided
- Biochemical markers of resuscitation and renal function were better in those who received HES 130/0.4 after penetrating trauma.
- Study outcomes were similar after blunt trauma, although numbers in these subgroups were modest.

\textbf{Background.} The role of fluids in trauma resuscitation is controversial. We compared resuscitation with 0.9\% saline vs hydroxyethyl starch, HES 130/0.4, in severe trauma with respect to resuscitation, fluid volume, gastrointestinal recovery, renal function, and blood products [packed red blood cell volumes 2943 (1628) vs 1473 (1071) ml, \(P=0.005\)] and was more severely injured than the saline group (median injury severity score 29.5 vs 18; \(P=0.01\)). Haemodynamic data were similar, but, in the penetrating group, plasma lactate concentrations were lower over the first 4 h (\(P=0.029\)) and on day 1 with HES than with saline [2.1 (1.4) vs 3.2 (2.2) mmol litre\(^{-1}\); \(P=0.017\)]. There was no difference between any groups in time to recovery of bowel function or mortality. In penetrating trauma, renal injury occurred more frequently in the saline group than the HES group (16\% vs 0\%; \(P=0.018\)). In penetrating trauma, maximum sequential organ function scores were lower with HES than with saline (median 2.4 vs 4.5, \(P=0.012\)). No differences were seen in safety measures in the blunt trauma patients.

\textbf{Conclusions.} In penetrating trauma, HES provided significantly better lactate clearance and less renal injury than saline. No firm conclusions could be drawn for blunt trauma.
Acute kidney injury following severe trauma: Risk factors and long-term outcome

Mikael Eriksson, MD, Olof Brattström, MD, PhD, Johan Mårtensson, MD, PhD, Emma Larsson, MD, PhD, and Anders Oldner, MD, PhD, Stockholm, Sweden

Figure 2. Multivariable model for AKI risk. Odds ratio and 95% confidence interval. Admission refers to the admission to the trauma unit.
Authors conclusions:

• AKI in ICU-treated trauma patients is a common complication with significant mortality…..

• ….resuscitation with HES were also independently associated with postinjury AKI. This was not noted for pre-AKI sepsis, shock on admission, or radio contrast….

• Based on the current findings, volume resuscitation with HES should be avoided in trauma patients.
Why is benefit risk ratio of synthetic colloids so poor

- Potential beneficial volume effects have been grossly overrated
- Harmful effects have been neglected and belittled
Colloid efficacy - greatly overrated

- Textbooks state that colloids are severalfold more effective than crystalloids -> 4 : 1 ratio
- RCTs show a ratio of little more than 1 to 1
Synthetic colloids leak rapidly from the vasculature

FITC-HES, rat model of mild hemorrhage, in-vivo

Figure 1. Color image of leaking hydroxyethyl starch particles bound with fluorescein-isothiocyanate (FITC-HES), seen under the intravital microscope over time. A significant amount of FITC-HES was shown to have leaked out in a few seconds from the capillary blood vessels in the cremaster muscle.

Hitosugi et al, Anesth Analg 2007
Colloid efficacy - CHEST
**Table 4. Treatment Effects in the First 72 Hours**

<table>
<thead>
<tr>
<th></th>
<th>Colloids</th>
<th>Crystalloids</th>
<th>Mean difference (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC for mean blood pressure</td>
<td>1606</td>
<td>1598</td>
<td>17.9</td>
<td>0.85</td>
</tr>
<tr>
<td>during the first 24 hours</td>
<td>(898-1822)</td>
<td>(1058-1821)</td>
<td>(-1746;+1782)</td>
<td></td>
</tr>
<tr>
<td>Weight at 72 hours</td>
<td>0.5</td>
<td>0.5</td>
<td>-0.23</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>(0;+2.0)</td>
<td>(0;+2.4)</td>
<td>(-0.61;+0.15)</td>
<td></td>
</tr>
<tr>
<td>Chest X Ray score at 72 hours</td>
<td>0</td>
<td>0</td>
<td>-0.04</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>(0-0)</td>
<td>(0-0)</td>
<td>(-0.24;+0.16)</td>
<td></td>
</tr>
</tbody>
</table>

Reported data are medians with interquartile ranges into brackets; the figure under the table reports the histogram of AUC for mean blood pressure during the first 24 hours in both randomized arms, exhibiting the lack of difference between arms.
Peri-operative data from 6478 consecutive cardiac surgery patients Before-and-after study with 3 fluid periods (HES/gelatin/only crystalloids)

**Figure 2.** Hemodynamic stabilization. Results of volume resuscitation in patients during hydroxyethyl starch (HES), gelatin, or crystalloids only periods with patients calculated by this logistic model indicated are the proportions of patients without normalization of abnormal central venous saturation (A), abnormal central venous pressure (B), abnormal serum lactate (C), and ongoing vasopressor use (D). Bayer et al, CCM 2013.
Impact of type of fluid on time to reversal of septic shock
Jena UH 2006-2010 (patients n =1046)

Bayer, Reinhart et al CCM 2012
Fluid balance

b. Fluid balance (ml/kg) per hour

- HES
- Gelatin
- Crystalloid

Day: 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14

n (HES): 2110 2067 1877 725 499 355 279 235 168 171 159 149 141 129 120
n (Gelatin): 2002 2281 1822 884 497 375 312 243 204 193 159 159 145 123 121
Crystallloid: 2001 1604 803 422 313 234 106 173 157 144 135 122 110 60
Net fluid balance CHEST Trial

Net fluid balance
HES 921±1069 vs 982±1161 Saline
Mechanisms of HES toxicity

Kidney damage → „osmotic nephrosis-like lesions“, proximal tubular epithelial cells
Lyosomal pathway → uptake in RES → liver, spleen, bone marrow,

**Similar risk profile for gelatins and dextrans**

Impairment of coagulation and prolonged bleeding
→ depletion of fibrinogen and circulating coagulation factors (von Willebrand syndrome)
→ impairment of platelet function → reduction in clot strength and enhancement of fibrinolysis
→ impairment of viability of tubular cells
The kidney takes up most of HES

Autopsy of 12 Young Adults Who Died of Sepsis and Multi-Organ Failure after Repeated Infusions of HES 200/0.5

HS-13-26-EU: this controlled (5% glucose), randomized, double-blind, Phase 2 multicenter trial studied different doses for 6-day therapy of sudden hearing loss. Although no differences in hearing gain were noted, pruritus was clearly more frequent in the test groups (6%, 4%, and 2% HES 130/0.4).
Quality of life

- Pruritus impaired QoL for 89% of patients.
- Sleep disturbances 88%.
- Limitations on private life 89% of patients and work life for 68%.
- 6 patients: job loss, separation from partner, reduced capacity at work, inability to participate in sport, and depression

Ständer et al Acta Derm Venereol 2013
Molecular Size and Origin Do Not Influence the Harmful Side Effects of Hydroxyethylstarch on Human Proximal Tubule Cells (HK-2) In Vitro

Raphael R. Bruno, MD, * Winfried Neuhaus, PhD, † Norbert Roewer, MD, * Christian Wunder, MD, * and Martin A. Schick, MD*

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![Graph showing cell viability](image)

0% HES  | 0.1 ng TNF  | 1 ng TNF  | 10 ng TNF  | 100 ng TNF  | 10 ng + 1.5% HES  | 1.5% HES
--- | --- | --- | --- | --- | --- | ---
Cell viability [%]
1978 - FDA suspended Gelatin due to reduced blood clotting and prolonged bleeding time

Gelatin: All intravenous drug products containing gelatin. Gelatin for intravenous use, formerly marketed as Knox Special Gelatine Solution Intravenous-6 percent, was found not to be suitable as a plasma expander because the drug caused increased blood viscosity, reduced blood clotting, and prolonged bleeding time. Approval of the NDA for Knox Special Gelatine Solution Intravenous-6 percent was withdrawn on April 19, 1978 (see the Federal Register of April 7, 1978 (43 FR 14743)).
Renal failure after gelatin and 6% HES 130/0.4 (comparison of three sequential periods)

1046 Patients with severe sepsis

6478 Cardiac surgical patients

Bayer O et al, CCM 2011

Bayer O. et al.; CCM 2012
Osmotic nephrosis like lesions

A: GEL,
B: HES

C Human albumin
D NaCl 0.9%
Meta-Analysis Gelatin vs. albumin or crystalloids

Mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Gelatin Events</th>
<th>Gelatin Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stockwell 1992</td>
<td>50</td>
<td>249</td>
<td>45</td>
<td>229</td>
<td>49.7%</td>
<td>1.02 [0.71, 1.47]</td>
</tr>
<tr>
<td>Gondos 2010</td>
<td>12</td>
<td>50</td>
<td>26</td>
<td>100</td>
<td>18.3%</td>
<td>0.92 [0.51, 1.67]</td>
</tr>
<tr>
<td>Parker 2004</td>
<td>19</td>
<td>198</td>
<td>9</td>
<td>198</td>
<td>10.9%</td>
<td>2.11 [0.98, 4.55]</td>
</tr>
<tr>
<td>Upadhay 2005</td>
<td>9</td>
<td>29</td>
<td>9</td>
<td>31</td>
<td>10.8%</td>
<td>1.07 [0.49, 2.32]</td>
</tr>
<tr>
<td>Hejden 2009</td>
<td>3</td>
<td>12</td>
<td>5</td>
<td>24</td>
<td>4.1%</td>
<td>1.20 [0.34, 4.20]</td>
</tr>
<tr>
<td>Wu 2001</td>
<td>2</td>
<td>18</td>
<td>3</td>
<td>16</td>
<td>2.4%</td>
<td>0.59 [0.11, 3.11]</td>
</tr>
<tr>
<td>Akech 2006</td>
<td>7</td>
<td>44</td>
<td>1</td>
<td>44</td>
<td>1.5%</td>
<td>7.00 [0.90, 54.55]</td>
</tr>
<tr>
<td>Verheij 2006</td>
<td>1</td>
<td>16</td>
<td>1</td>
<td>34</td>
<td>0.9%</td>
<td>2.13 [0.14, 31.85]</td>
</tr>
<tr>
<td>Tollofsrud 1995</td>
<td>0</td>
<td>10</td>
<td>1</td>
<td>20</td>
<td>0.7%</td>
<td>0.64 [0.03, 14.36]</td>
</tr>
<tr>
<td>Himpe 1991</td>
<td>1</td>
<td>35</td>
<td>0</td>
<td>35</td>
<td>0.6%</td>
<td>3.00 [0.13, 71.22]</td>
</tr>
</tbody>
</table>

Total (95% CI) 661 731 100.0% 1.13 [0.88, 1.46]

Total events 104 100

Heterogeneity: Tau² = 0.00; Chi² = 7.78, df = 9 (P = 0.56); I² = 0%
Test for overall effect: Z = 0.93 (P = 0.35)

Thomas-Rueddel et al. (2012): ICM, 38:1134-1142
Meta-Analysis Gelatin vs. albumin or crystalloids

Exposure to allogeneic transfusion (7 RCT, n=672)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Gelatin Events</th>
<th>Total Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volta 2007</td>
<td>1</td>
<td>12</td>
<td>0</td>
<td>12</td>
<td>1.8%</td>
<td>3.00 [0.13, 67.06]</td>
<td></td>
</tr>
<tr>
<td>Boldt 1992</td>
<td>2</td>
<td>12</td>
<td>1</td>
<td>36</td>
<td>3.3%</td>
<td>6.00 [0.60, 60.44]</td>
<td></td>
</tr>
<tr>
<td>Mittermayr 2007</td>
<td>8</td>
<td>21</td>
<td>1</td>
<td>20</td>
<td>4.3%</td>
<td>7.62 [1.05, 55.55]</td>
<td></td>
</tr>
<tr>
<td>Fries 2004</td>
<td>2</td>
<td>20</td>
<td>2</td>
<td>20</td>
<td>4.9%</td>
<td>1.00 [0.16, 6.42]</td>
<td></td>
</tr>
<tr>
<td>Schramko 2010</td>
<td>4</td>
<td>15</td>
<td>3</td>
<td>15</td>
<td>9.0%</td>
<td>1.33 [0.36, 4.97]</td>
<td></td>
</tr>
<tr>
<td>Parker 2004</td>
<td>31</td>
<td>198</td>
<td>22</td>
<td>198</td>
<td>32.7%</td>
<td>1.41 [0.85, 2.35]</td>
<td></td>
</tr>
<tr>
<td>Scott 1995</td>
<td>18</td>
<td>29</td>
<td>40</td>
<td>64</td>
<td>43.9%</td>
<td>0.99 [0.71, 1.40]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>307</td>
<td>365</td>
<td>100.0%</td>
<td></td>
<td>1.35</td>
<td>[0.88, 2.08]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 66
Total events: 69

Heterogeneity: \( \tau^2 = 0.08; \chi^2 = 8.23, \text{df} = 6 \) (\( P = 0.22 \)); \( I^2 = 27\%

Test for overall effect: \( Z = 1.38 \) (\( P = 0.17 \))

Thomas-Rueddel et al. (2012): ICM, 38:1134-1142
V. We suggest not to use gelatin in ICU patients who are at increased risk for renal failure or bleeding outside the context of clinical trials (Grade 2 C).

The good news!
Note: Total HES Sales irrespective of bottle size and %
Source: IMS Colloids Q2 2014 Data

HES- Sales Analysis- EU5

Total HES Unit Sales- EU5

6S trial
Chest trial
1Reg Action- Jun’13
HES- Sales Analysis- Germany

Note: Total HES Sales irrespective of bottle size and %

Source: IMS Colloids Q2 2014 Data
HES- Sales Analysis- UK

Note: Total HES Sales irrespective of bottle size and ¹Reg- Regulatory
Source: IMS Colloids Q2 2014 Data
HES- Unit Sales Analysis - Poland

**Total HES Unit Sales - Poland**

<table>
<thead>
<tr>
<th>Quarter</th>
<th>HES Unit Sales (No. of packs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 2013</td>
<td>30683</td>
</tr>
<tr>
<td>Q2 2013</td>
<td>19485</td>
</tr>
<tr>
<td>Q3 2013</td>
<td>18194</td>
</tr>
<tr>
<td>Q4 2013</td>
<td>7772</td>
</tr>
<tr>
<td>Q1 2014</td>
<td>3529</td>
</tr>
<tr>
<td>Q2 2014</td>
<td>3997</td>
</tr>
<tr>
<td>Q3 2014</td>
<td>1420</td>
</tr>
<tr>
<td>Q4 2014</td>
<td>2412</td>
</tr>
</tbody>
</table>

Note: Units - # of Packs Sold

Source: IMS Colloids Q4 2014 (Mar 2015)
The bad news!
HES- Unit Sales Analysis - Russia

Note: Units - # of Packs Sold
Source: IMS Colloids Q4 2014 (Mar 2015)
HES- Sales Analysis- China

Note: Total HES Sales irrespective of bottle size and %
Source: IMS Colloids Q2 2014 Data
HES- Unit Sales Analysis- Turkey

Note: Units - # of Packs Sold
Source: IMS Colloids Q4 2014 (Mar 2015)
HES- Unit Sales Analysis - Austria

Note: Units - # of Packs Sold
Source: IMS Colloids Q4 2014 (Mar 2015)
For prophylaxis & treatment of hypovolemia

**Voluven®, always with you**

Efficacy and safety proven in surgical, trauma and critical ill adult and pediatric patients

- Effective in achieving hemodynamic stability
- Better fluid balance
- Good pro-inflammatory properties as a priming solution
- Decreased incidence of hypotension during C-section with less PONV
- Effective and safe in pediatrics
- Less transfusions (RBC, FFP, Platelets)
- Less hospital and ICU LOS
- Less use of mechanical ventilation
- Less infections
- Without difference in mortality, coagulation or renal function compared with other fluid alternatives
Use of synthetic colloids – a major lifethreatening misconception in the history of medicine
“When the facts change, I change my views. What do you do, Sir?”

John Maynard Keynes