Hypothesis: Safety differences exist among colloids widely used for fluid management in acutely ill patients, as judged according to the comparative incidence of adverse events.

Data Sources: Colloid safety data for human subjects were sought, without language or time period restrictions, by means of computer searches of bibliographic and clinical trial databases, hand searches of medical journals and Index Medicus, inquiries with investigators and colloid suppliers, and examination of reference lists. Search terms included “colloids”, “morbidity”, and “mortality”.

Study Selection: Controlled trials, cohort studies, pharmacovigilance studies, and prior meta-analyses were independently selected by 2 unblinded investigators. Of 189 candidate studies, 113 were included, with safety data encompassing $1.54 \times 10^6$ patients and $1.09 \times 10^6$ colloid infusions.

Data Extraction: Two unblinded investigators independently extracted data. Study limitations and confounding factors were tabulated.

Data Synthesis: With albumin as the reference colloid, the incidence rate ratio for anaphylactoid reactions was 4.51 (95% confidence interval, 2.06-9.89) after hydroxyethyl starch administration, 2.32 (95% confidence interval, 1.21-4.45) after dextran, and 12.4 (95% confidence interval, 6.40-24.0) after gelatin. Pruritus occurrence was significantly increased by hydroxyethyl starch exposure (odds ratio, 1.78; 95% confidence interval, 1.23-2.58). Artificial colloid administration was consistently associated with coagulopathy and clinical bleeding, most frequently in cardiac surgery patients receiving hydroxyethyl starch. On the basis of large-scale pharmacovigilance study results, albumin infusion resulted in a low rate of both total adverse events (3.1 to 8.6 per $10^5$ infusions) and serious adverse events (1.29 per $10^6$ infusions).

Conclusions: Significant safety differences exist among colloids. Therefore, conclusions regarding the clinical usefulness of colloids as a fluid class should be formed with caution.

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Colloids promote retention of fluid in the intravascular space, with concomitant reduction of the potential for edema that might compromise the function of organs such as the lungs, myocardium, and gastrointestinal tract. The chief colloids currently in routine clinical use worldwide are albumin, hydroxyethyl starch (HES), dextran, and gelatin. Clinically available albumin is a 69-kDa protein purified from human plasma. Hydroxyethyl starch is synthesized by partial hydrolysis of amylopectin plant starch and hydroxyethylateration at the C2, C3, and C6 positions of the constituent glucose molecules. Dextran is composed of naturally occurring glucose polymers synthesized by Leuconostoc mesenteroides bacteria growing in sucrose-containing media. Gelatin for clinical use is derived from hydrolysis of bovine collagen followed by being either succinylated or linked to urea. All 3 artificial colloids are polydisperse molecules in a range of sizes. Hydroxyethyl starch is clinically available in an array of forms differing on the basis both of average molecular weight and extent of molar substitution, although in the United States only the HES of high molecular weight (450 kDa) of 0.7 molar substitution ratio has been used in routine fluid management. In the United States, dextran is less extensively used for fluid management than is HES, and gelatin is unavailable for clinical use.

Clinically available colloids have generally exhibited similar effectiveness in maintaining colloid oncotic pressure. Thus, colloids have often been viewed as a class of essentially interchangeable in-
ert fluids, and selection of colloid has commonly been based on cost and convenience. Nevertheless, differences in safety profiles among colloids are well recognized.2,3 Such differences underlie, for example, the recommended 1500 mL (20 mL per kilogram of body weight) dose limitation for HES.4

The clinical importance of differences in colloid safety has been debated. Firm conclusions have been difficult to draw, in part because comparative colloid safety has not been systematically reviewed. We here present the results of such a review.

RESULTS

INCLUDED STUDIES

Of 189 candidate studies initially identified, 113 studies published from 1944 through 2002 were included.1-113 One RCT was excluded because of fluid overload in the albumin group.114 Numbers of study patients, which were reported in 107 of the included studies, totaled 1.54 × 10^6 patients. The median number of patients per study was 60, with an interquartile range of 29 to 200. In the remaining 6 studies, the numbers of infusions were reported, and these totaled 1.09 × 10^6 infusions. The median number of infusions per study was 8.5 × 10^3 (interquartile range, 1.20-74.0 × 10^3). Safety data about albumin, HES, dextran, and gelatin were available from 60, 75, 17, and 25 included studies, respectively.

Twenty-one of the included studies involved acute illness generally (Table 1), 35 cardiac surgery (Table 2), 19 noncardiac surgery (Table 3), 5 ascites, 4 sepsis, 13 brain injury, 3 dialysis, 6 plasma exchange, and 7 acute hearing loss. (Tables summarizing studies of ascites, sepsis, brain injury, dialysis, plasma exchange, and acute hearing loss are available from the authors.) Of the cardiac surgery studies, 14 were evaluations of extracorporeal circuit pump priming; 19, volume expansion; and 2, both.

The most frequently represented study design was the RCT, which accounted for 54 studies. Twenty-eight studies were NCTs, 22 were cohort studies, 6 were PVSs, and 3 were MAs.

ALL ADVERSE EVENTS

In large-scale PVSs, the reported incidence for adverse events of any severity in albumin recipients was 6.1 to 6.8 per 10^5 infusions of 5% albumin and 3.1 to 8.6 per 10^5 infusions of 20% to 25% albumin.7,28 For serious adverse events, an incidence of 1.29 per 10^5 infusions was reported.111 The PVSs are generally based on spontaneous adverse event reporting and are subject to underreporting. One of these PVSs also included data for gelatin, and the reported incidence of adverse events was similar to that for albumin.7 In a cohort study of 379 patients, the incidence of all HES-associated adverse effects was 4.5%.12

MORTALITY

One MA of RCTs indicated poorer survival in critically ill patients receiving albumin vs crystalloid or no albumin.59 However, authors of a subsequent MA110 considered RCT evidence approximately 3-fold more extensive than that of the first MA, and there was no evidence of increased albumin-associated mortality. Results of higher quality trials suggested a potential survival benefit of albumin.110 Thus, in a multivariate analysis of blinded larger RCTs, mortality was significantly reduced by albumin (odds ratio, 0.78; 95% CI, 0.70-0.81). A large-scale PVS provided evidence that deaths after albumin administration are rare (5.24 per 10^5 infusions).111 Hemodilution with HES was investigated in 1 RCT of patients with acute ischemic stroke.32 The trial was stopped...
prematurely because of a significant increase in mortality related to cerebral edema among HES recipients.

ANAPHYLACTOID REACTIONS

In 9 studies, data were reported on anaphylactoid reactions after 3.63 × 10⁶ total colloid infusions. 

The pooled incidence of anaphylactoid reactions after albumin administration was 9.44 per 10⁵ infusions (95% CI, 5.04-17.7 per 10⁵ infusions). Infusions of all 3 artificial colloids, as compared with albumin, were associated with significantly increased anaphylactoid reactions (Table 4).

PRURITUS

In 1 study, there was evidence of dextran-associated pruritus in some patients. Otherwise, however, reports of this adverse effect were restricted to HES exclusively. Pruritus associated with HES was reported in 14 studies involving a total of 2598 patients, of whom 2173 (83.6%) received HES and 425 (16.4%) did not.

The odds of pruritus associated with HES were compared with those of albumin, dextran, gelatin, or plasma. 

References 45, 52, 53, 55, 58, 59, 76, 84, 86, 93, 96, 99, 105, 106.

(continued)
ritus were significantly increased by HES exposure (Table 5). The effect of HES on pruritus occurrence depended on dose. Neither HES molecular weight nor HES molar substitution exerted a statistically significant effect on pruritus.

In 1 study of patients receiving intensive care, 44% of the patients developing pruritus experienced a severe, persistent, and refractory form of the condition. Pruritus associated with HES was typically delayed in onset and manifested as pruritic crises,52,99,105 prompting patients to seek medical attention and seriously detracting from their quality of life. Pruritus associated with HES is generally unresponsive to currently available forms of therapy.52

Table 5

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Design</th>
<th>No. of Patients</th>
<th>Setting</th>
<th>Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hedin and Ljungström,73 1997</td>
<td>PVS</td>
<td>$1.5 \times 10^4$</td>
<td>Spontaneously reported adverse events in Sweden from 1975 through 1997</td>
<td>Dextran with vs without prophylactic hapten inhibition</td>
<td>0.05% incidence of grade II-V dextran-induced anaphylactoid/anaphylactic reactions without and 0.0014% with prophylactic hapten inhibition</td>
</tr>
<tr>
<td>Cochrane Injuries Group Albumin Reviewers,84 1998</td>
<td>MA</td>
<td>1204</td>
<td>RCTs of hypovolemia, burns, and hypoalbuminemia</td>
<td>Albumin vs crystalloid, no albumin, or lower-dose albumin</td>
<td>Mortality increased by albumin in trials of burns and hypoalbuminemia and all trials combined; no effect in hypovolemia trials</td>
</tr>
<tr>
<td>Gröchenig et al.,98 1998</td>
<td>NCT</td>
<td>544</td>
<td>Hemodilution and volume substitution in general and vascular surgery, anaesthesiology, internal medicine, and otorhinolaryngology</td>
<td>HES of low (70/0.5) or medium (200/0.5) molecular weight, therapy according to standards of participating centers vs no HES; control group consisted of 47 otorhinolaryngology patients</td>
<td>Pruritus reported by 34% of patients and of these, 44% experienced severe pruritus that in many cases adversely affected quality of life, disturbed sleep, and was refractory to available remedies; in some patients pruritus persisted as long as 12 mo</td>
</tr>
<tr>
<td>Sharland et al.,95 1999</td>
<td>CS</td>
<td>73</td>
<td>Volume expansion in ICU patients</td>
<td>2 L median HES (200/0.5) volume administered</td>
<td>HES deposits observed in biopsy samples of liver, muscle, spleen, intestine, and skin; deposits persisted in skin as long as 54 mo after HES infusion, in muscle as long as 16 mo, and in intestine as long as 14 mo</td>
</tr>
<tr>
<td>Sirtl et al.,96 1999</td>
<td>NCT</td>
<td>26</td>
<td>Oncologic, orthopedic, plastic, or other surgery and vascular disease</td>
<td>≤2 g/kg HES (200/0.5 or 450/0.7) vs 3-15 g/kg HES (200/0.5-0.6)</td>
<td>Incidence of all spontaneously reported serious adverse events 1.29 per 10^6 infusions; no deaths probably attributable to albumin; incidence of fatal serious adverse events possibly related to albumin 5.24 per 10^6 infusions</td>
</tr>
<tr>
<td>von Hoegen and Waller,111 2001</td>
<td>PVS</td>
<td>$100 \times 10^6$</td>
<td>Albumin doses distributed worldwide by 9 major suppliers from 1990 through 1997</td>
<td>Albumin</td>
<td>Hepatic dysfunction worsened after HES infusion; biopsy results revealed diffuse microvacuolization of Kupffer cells; 8 patients died</td>
</tr>
<tr>
<td>Christidis et al.,101 2001</td>
<td>CS</td>
<td>9</td>
<td>Patients referred for refractory ascites or anicteric cholestasis</td>
<td>Repeated infusions of 6% HES of medium molecular weight (200/0.5) for large-volume paracentesis, maintenance hemodialysis, or plasma exchange</td>
<td>Hepatitis type or dose</td>
</tr>
<tr>
<td>Murphy et al.,108 2001</td>
<td>NCT</td>
<td>159</td>
<td>Two ICUs in the United Kingdom</td>
<td>HES (200/0.45 or 450/0.7) vs different plasma expanders</td>
<td>12.6% pruritus incidence in HES recipients not significantly greater than 4% in control group; no difference in incidence related to HES type or dose</td>
</tr>
<tr>
<td>Wilkes and Navickis,110 2001</td>
<td>MA</td>
<td>2958</td>
<td>RCTs of surgery or trauma, burns, hypoalbuminemia, high-risk neonates, ascites, and other indications</td>
<td>Albumin vs crystalloid, no albumin, or lower-dose albumin</td>
<td>No effect of albumin on survival in any category of indications or across all trials combined</td>
</tr>
</tbody>
</table>

Abbreviations: aPTT, activated partial thromboplastin time; CI, confidence interval; CS, cohort study; HES, hydroxyethyl starch; ICU, intensive care unit; MA, meta-analysis; NCT, nonrandomized controlled trial; OR, odds ratio; PVS, pharmacovigilance study; RCT, randomized controlled trial.

*Number of infusions.
†HES molecular weight in kilodaltons and molar substitution ratio indicated (eg, 200/0.5 for 200 kDa HES of 0.5 molar substitution).
### Table 2. Cardiac Surgery

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Design</th>
<th>No. of Patients</th>
<th>Setting</th>
<th>Treatment</th>
<th>Results</th>
</tr>
</thead>
</table>
| Palazzo et al,
1982 | NCT          | 79              | CAGB    | 3% HES vs 4% albumin | Decline in platelet count during bypass greater in HES group (P<.001) and postbypass platelet count lower (P=.02); postbypass platelet count in HES group (136 000 ± 36 600 mL⁻¹) below normal range (140 000 to 340 000 mL⁻¹). |
| Saunders et al,
1983 | RCT          | 20              | CAGB    | 1000 mL 6% HES (3% final concentration) in total 2000 mL vs 200 mL 25% albumin (2.5% final concentration) | In HES group, levels of liver enzymes were higher during and after bypass; mean platelet count and antithrombin III level after bypass were lower (P=.019 and P=.006, respectively) in HES than albumin group. |
| Sade et al,
1985 | RCT          | 54              | CABG-valve procedures, and CABG-valve procedures | 800 mL/m² 6% HES vs 800 mL/m² 5% albumin (0.6% final concentration); 5% albumin postoperatively in all groups to maintain stable hemodynamics | Intraoperative platelet count lower in HES than albumin group (P<.01) and pulmonary shunt fraction higher (P<.05); at 24 h postoperatively, HES group PT prolonged (P<.005) |
| Lumb,
1987 | RCT          | 20              | CAGB    | 500 mL 6% HES (1% final concentration) vs 150 mL 25% albumin (1.4% final concentration) | Need for bicarbonate during bypass higher in urea-linked gelatin than other groups (P<.05); intraoperative urine output lower in succinyl-linked gelatin group (P<.05); serum creatinine level elevated in both gelatin groups vs albumin group (P<.05). |
| Boldt et al,
1992 | RCT          | 48              | CAGB    | 250 mL 5% albumin (0.6% final concentration) vs 400 mL 20% albumin (3.6% final concentration) vs 500 mL 10% HES (2.2% final concentration) vs 500 mL 3.5% gelatin (0.8% final concentration); 5% albumin postoperatively in all groups | ADP-induced maximum platelet aggregation greater intraoperatively in 0.6% albumin and gelatin than other groups (P<.05) and greater in 0.6% albumin than all other groups at 24 h postoperatively (P<.05); collagen-induced maximum platelet aggregation greater in 0.6% albumin than other groups intraoperatively and postoperatively (P<.05). |
| London et al,
1992 | RCT          | 60              | CAGB and valve procedures | 750 mL 10% HES and 1250 mL RL (3.8% final concentration) vs 300 mL 25% albumin and 1700 mL RL (3.8% final concentration); postoperative albumin in both groups | Intraoperative aPTT prolonged (P<.05) and platelet count reduced (P<.05) in HES vs albumin group. |
| Videm et al,
1993 | RCT          | 63              | Coronary bypass operations | 6% dextran 70 with vs without 0.8% albumin | Platelet decline greater at both 4 h (P=.05) and 48 h (P<.001) postoperatively in dextran only group; blood loss during first 12 h higher by 52% in dextran only group (P=.05). |
| Tabuchi et al,
1995 | RCT          | 60              | Elective CABG | 400 mL 20% albumin and 1500 mL RL vs 2000 mL oxypolygelatin | Postoperative blood loss reduced by aprotinin in albumin (P<.05) but not oxypolygelatin group. |
| Schneider et al,
1996 | NCT          | 267             | Elective CABG | Gelatin, crystallloid prime, gentamycin, and fluocoxaclin vs gelatin, crystallloid, albumin prime, and cephalothin vs crystallloid prime, gentamycin, and fluocoxaclin vs crystallloid, albumin prime, and cephalothin | Incidence of acute renal failure in gelatin group receiving gentamycin and fluocoxaclin (31%) higher (P=.002) than in corresponding crystallloid group (7%); acute renal failure more frequent (P=.005) in gelatin group with cephalothin (12%) than corresponding crystallloid group (2%). |
| Tighelaar et al,
1997 and 1998 | RCT          | 36              | CAGB    | 400 mL 20% albumin and 1600 mL RL (4% final concentration) vs 500 mL 10% HES and 1500 mL RL (2.5% final concentration) vs 2000 mL 3% gelatin | On-bypass factor V-Von Willebrand factor complex levels decreased in gelatin compared with albumin group (P=.002). |
| Herwaldt et al,
1998 | NCT          | 511             | Cardiorthoracic operations | 6-15 mL/kg HES vs no HES | Odds of hemorrhage 37% higher in patients exposed to HES; effects of HES on bleeding dose-dependent; added costs due to hemorrhage greater than savings from lower HES acquisition cost. |
| Keyser et al,
1999 | NCT          | 200             | Consecutive adults undergoing first-time aortocoronary bypass | 750 mL 10% HES and 1000 mL RL (4.3% final concentration) in prospective series of 100 patients vs 200 mL 25% albumin and 1500 mL RL (2.9% final concentration) in retrospective series of 100 similar patients | Mean mediastinal blood loss in first 18 h postoperatively for HES group (834 ± 499 mL) greater (P=.002) vs albumin group (640 ± 388 mL). |
### Table 2. Cardiac Surgery (cont)

<table>
<thead>
<tr>
<th>Source</th>
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<th>No. of Patients</th>
<th>Setting</th>
<th>Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canver and Nichols,²⁶ 2000</td>
<td>NCT</td>
<td>887</td>
<td>Primary CABG</td>
<td>50 mL 25% albumin and 2150 mL crystalloid (0.6% final concentration) vs 500 mL 6% HES and 1700 mL crystalloid (1.4% final concentration) vs 50 mL 25% albumin and 500 mL 6% HES and 1650 mL crystalloid (final albumin and HES concentrations of 0.6% and 1.4%, respectively)</td>
<td>No differences in blood product use, length of stay, or mortality; however, (1) CPB duration in albumin only and albumin and HES groups longer, respectively, by 33% and 43% vs HES only group (P&lt;.00005 for both comparisons), (2) 3% observed power to detect 25% mortality difference, and (3) length of stay set by Veterans Administration policy</td>
</tr>
<tr>
<td>Dietl et al,² 1982</td>
<td>RCT</td>
<td>60</td>
<td>CABG</td>
<td>6% HES vs 5% albumin during first postoperative 24 h</td>
<td>No differences in clotting parameters, hepatic and renal function, or alveolar-arterial oxygen gradient</td>
</tr>
<tr>
<td>Moggio et al,²² 1983</td>
<td>RCT</td>
<td>47</td>
<td>CABG, valve procedures, or CABG-valve procedures</td>
<td>6% HES in 0.9% saline solution vs 5% albumin postoperatively to maintain cardiac index and PAWP at preoperative levels</td>
<td>Platelet count declined in HES (P&lt;.05) but not albumin group</td>
</tr>
<tr>
<td>Kirklin et al,¹⁷ 1984</td>
<td>RCT</td>
<td>30</td>
<td>CABG</td>
<td>6% HES vs 5% albumin to maintain left atrial pressure of 6-12 mm Hg and cardiac index &gt;2.0 L · min⁻¹ · m⁻²</td>
<td>Cumulative 24 h urine output lower in HES group (P&lt;.05); PT and aPTT prolonged at 12 h, and fibrinogen level lower at 7 d in HES recipients (P&lt;.05 for all comparisons)</td>
</tr>
<tr>
<td>Gallagher et al,²⁰ 1993</td>
<td>RCT</td>
<td>10</td>
<td>CABG</td>
<td>6% HES vs 5% albumin to maintain PAWP of 12-18 mm Hg postoperatively; prime of 1000 mL 5% albumin and 1000 mL RL for all groups; all groups received mean of 5.3 L RL intraoperatively</td>
<td>No differences in EVLW, PAWP, respiratory parameters, or weight gain; postoperative COP higher in albumin than crystalloid group (P&lt;.05); in both groups, colloid accounted for less than half of total postoperative fluid volume</td>
</tr>
<tr>
<td>Boldt et al,²³ 1986</td>
<td>RCT</td>
<td>42</td>
<td>CABG</td>
<td>300 mL 20% albumin vs 500 mL 3% HES vs 500 mL 3.5% gelatin intraoperatively after bypass; prime of 250 mL 3.5% plasma protein solution and 1500 mL crystalloid in all groups; 400 mL 5% glucose and 100 mL 20% albumin in cases of decreased blood and filling pressure</td>
<td>No differences in EVLW or pulmonary shunt</td>
</tr>
<tr>
<td>London et al,⁴ 1989</td>
<td>RCT</td>
<td>94</td>
<td>Primary or repeat CABG or valve replacement or CABG-valve procedures</td>
<td>10% HES in 0.9% saline solution vs 5% albumin for volume expansion during first 24 h postoperatively to maintain cardiac index ≥2.0 L · min⁻¹ · m⁻² and MAP within 10% of preinduction value</td>
<td>No differences in respiratory and coagulation parameters</td>
</tr>
<tr>
<td>Villarino et al,⁴⁹ 1992</td>
<td>RCT</td>
<td>468</td>
<td>Cardiac surgery</td>
<td>Outbreak of postoperative nonsurgical bleeding</td>
<td>Patients with bleeding received more intraoperative and postoperative HES per kilogram of body weight (19.4 mL/kg vs 14.1 mL/kg; P=.02) for volume expansion and larger total volume of HES (1492 mL vs 875 mL; P=.012)</td>
</tr>
<tr>
<td>Boldt et al,⁶¹ 1993</td>
<td>RCT</td>
<td>30</td>
<td>Assorted cardiac defect repair procedures in children younger than 3 y</td>
<td>6% HES vs 20% albumin to stabilize intraoperative hemodynamics; in both groups prime of 250 mL 5% albumin and 600 mL crystalloid</td>
<td>Urine output during bypass in HES group lower by 57% than that of albumin group (P&lt;.05); no differences in clotting parameters</td>
</tr>
<tr>
<td>Boldt et al,⁶¹ 1993</td>
<td>RCT</td>
<td>60</td>
<td>CABG</td>
<td>5% albumin vs 6% HES of high molecular weight (450/0.5) vs 6% HES of medium molecular weight (200/0.5) vs 3.5% gelatin to double reduced baseline PAWP intraoperatively; 250 mL 5% albumin (0.6% final concentration) in prime for all groups</td>
<td>Blood loss in first 24 h postoperatively higher in HES 450/0.5 than other groups (P&lt;.05); maximum platelet aggregation and gradient induced by ADP, collagen, and epinephrine lower intraoperatively in HES 450/0.5 than other groups (P&lt;.05); maximum platelet aggregation and gradient in HES 450/0.5 group correlated with blood loss (P&lt;.04 and P&lt;.01, respectively)</td>
</tr>
<tr>
<td>Mastroianni et al,³ 1994</td>
<td>RCT</td>
<td>29</td>
<td>CABG or valve procedures</td>
<td>10% HES vs 5% albumin during first 24 h postoperatively to achieve and maintain cardiac index ≥2.0 L · min⁻¹ · m⁻² and SBP &gt;100 mm Hg with PAWP &lt;20 mm Hg</td>
<td>Mediastinal blood loss in first 24 h postoperatively 22% higher in HES than albumin group (P&lt;.05); no differences in coagulation parameters</td>
</tr>
<tr>
<td>Tellefsrud et al,⁶³ 1995</td>
<td>RCT</td>
<td>30</td>
<td>CABG</td>
<td>4% albumin vs 6% dextran 70 vs 3.5% gelatin to maintain heart-lung machine reservoir and stabilize postoperative hemodynamics</td>
<td>No differences in respiratory function or blood loss</td>
</tr>
</tbody>
</table>

(continued)
Table 2. Cardiac Surgery (cont)

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Design</th>
<th>No. of Patients</th>
<th>Setting</th>
<th>Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brutocao et al,16 1996</td>
<td>RCT</td>
<td>47</td>
<td>Assorted cardiac defect repair procedures in children</td>
<td>6% HES vs 5% albumin to maintain adequate CVP, perfusion, and urine output</td>
<td>Prolongation of PT in patients receiving &gt;20 mL/kg HES (P = .006); no differences in chest tube drainage or urine output</td>
</tr>
<tr>
<td>Wahba et al,17 1996</td>
<td>RCT</td>
<td>20</td>
<td>CABG</td>
<td>5% gelatin vs 5% albumin to maintain MAP &gt;70 mm Hg, PAWP &gt;10 mm Hg, and cardiac index &gt;2.5 L · min⁻¹ · m⁻²</td>
<td>Intrathoracic blood volume index lower in gelatin group at 4 h postoperatively (P&lt;.05); ventilation time not different</td>
</tr>
<tr>
<td>Cope et al,18 1997</td>
<td>NCT</td>
<td>189</td>
<td>Cardiac surgery</td>
<td>Outbreak of bleeding after CPB surgery during hospital-wide albumin shortage necessitating preferential use of HES</td>
<td>Rate of blood loss during first 8 h postoperatively higher (P = .004) in patients exposed to intraoperative HES (50 mL/h) vs no HES (59 mL/h); hemoestatic agent use more frequent (P = .007) with intraoperative HES (35%) than no HES (14%)</td>
</tr>
<tr>
<td>Saxena et al,19 1997</td>
<td>RCT</td>
<td>50</td>
<td>CABG</td>
<td>6% HES vs 5% albumin after induction of anesthesia and removal of 10 mL/kg blood before bypass surgery Intraoperative HES vs albumin or crystalloid</td>
<td>No differences in urine output, blood loss, or blood product use</td>
</tr>
<tr>
<td>Knutson et al,14 2000</td>
<td>NCT</td>
<td>444</td>
<td>Cardiotoracic operations</td>
<td>Postoperative blood loss higher (P&lt;.001) in HES recipients; HES use independent predictor of bleeding (P = .011); postoperative use of blood products greater in HES recipients</td>
<td></td>
</tr>
<tr>
<td>Morgan and Berridge,15 2000</td>
<td>CS</td>
<td>85</td>
<td>Consecutive unselected cardiac surgery patients</td>
<td>HES vs saline solution, gelatin, or blood products</td>
<td>Pruritus in 22% of HES patients but none receiving other fluids (P = .007); pruritus classified as severe in 46% of cases; median HES volume 1400 mL in mild and 1500 mL in severe cases; median time of pruritus onset 4 wk; longest observed duration of pruritus ≥9 mo</td>
</tr>
<tr>
<td>Howard et al,16 2001</td>
<td>NCT</td>
<td>71</td>
<td>ICU care after cardiac surgery</td>
<td>Rapid infusion of 250-500 mL 4% albumin vs 0.9% saline solution across 10-30 min</td>
<td>Four cases of hypotension in albumin group vs none in crystalloid group (P = .12); however, effect correlated with use of angiotensin-converting enzyme inhibitors (P = .04)</td>
</tr>
<tr>
<td>Petroni et al,17 2001</td>
<td>RCT</td>
<td>28</td>
<td>Elective cardiac surgery requiring CPB</td>
<td>6% HES in RL vs 5% albumin for intraoperative and postoperative volume expansion as long as 24 h after surgery</td>
<td>No differences in thromboelastographic results, chest tube output, or blood product use</td>
</tr>
<tr>
<td>Tabuchi et al,18 1995</td>
<td>NCT</td>
<td>71</td>
<td>Elective CABG</td>
<td>Both Pump Priming and Volume Expansion</td>
<td>Postoperative blood loss linearly correlated (P&lt;.002) with volume of gelatin administered</td>
</tr>
<tr>
<td>Wilkes et al,19 2001</td>
<td>MA</td>
<td>653</td>
<td>RCTs of cardiac surgery</td>
<td>Gelatin-primed circuit and no perioperative limit on total gelatin use with vs without aprotinin</td>
<td>Increased postoperative bleeding with use of HES for either pump priming (P&lt;.05) or volume expansion (P&lt;.05)</td>
</tr>
</tbody>
</table>

Abbreviations: ADP, adenosine diphosphate; aPTT, activated partial thromboplastin time; CABG, coronary artery bypass graft; COP, colloid onotic pressure; CPB, cardiopulmonary bypass; CS, cohort study; CVP, central venous pressure; EVLW, extravascular lung water; HES, hydroxyethyl starch; ICU, intensive care unit; MA, meta-analysis; MAP, mean arterial pressure; NCT, nonrandomized controlled trial; PAWP, pulmonary arterial wedge pressure; PT, prothrombin time; RCT, randomized controlled trial; RL, Ringer lactate; SBP, systolic blood pressure.

*HES molecular weight in kilodaltons and molar substitution ratio indicated (eg, 200/0.5 for 200 kDa HES of 0.5 molar substitution).
†Mean ± SD.

COAGULOPATHY

Results of numerous studies indicate that HES administration can lead to reduction in circulating factor VIII and von Willebrand factor levels, impairment of platelet function, prolongation of partial thromboplastin time and activated partial thromboplastin time, and increase in bleeding complications.† Coagulopathy and hemorrhage associated with HES are often encountered in cardiac surgery, a setting in which susceptibility to such complications is heightened by transient acquired platelet dysfunction resulting from the procedure. Thus, in cardiac surgery studies with albumin as the control, HES has resulted in platelet depletion and dysfunction, prothrombin time and activated partial thromboplastin time prolongation, and increased postoperative bleeding.† One NCT of 444 patients revealed significant increases in blood product use, as well as postoperative blood loss, in patients receiving HES.

†References 27, 29, 34, 40, 61, 62, 69, 78, 80, 82, 94, 103, 104.
‡References 3, 11, 13, 15, 17, 46, 48, 50, 65, 92.
for volume expansion.\textsuperscript{96} The effects of HES on clinical bleeding in cardiac surgery patients depend on dose; however, excessive postoperative bleeding has been reported with HES doses less than the recommended maximum.\textsuperscript{87}

Results of 1 RCT suggested that postoperative bleeding might be greater in patients receiving HES of high rather than medium molecular weight.\textsuperscript{50} This result was not supported, however, by results of 1 NCT of 200 patients showing postoperative blood loss significantly greater after pump priming with HES of medium molecular weight than with albumin.\textsuperscript{92} Furthermore, in 1 MA of RCTs, bleeding was increased by HES, as compared with albumin, and the effects of HES of high and medium molecular weight were similar.\textsuperscript{109}

Dextran, as compared with albumin, has been shown to reduce platelets and increase postoperative bleeding in cardiac surgery patients.\textsuperscript{92} Postoperative blood loss was linearly correlated with the volume of gelatin used to prime the extracorporeal circuit.\textsuperscript{60}

\section*{RENAL FAILURE}

All 3 artificial colloids have been associated with renal impairment, and HES has been demonstrated to increase sensitive markers of renal tubule damage in surgical patients.\textsuperscript{74,95} In 1 RCT of sepsis patients, HES exposure was recently shown to be an independent risk factor for acute renal failure.\textsuperscript{108}

In the renal transplantation setting, HES reduced urinary output, increased creatinine levels and dopamine requirement, and increased the need for hemodialysis or hemodiafiltration.\textsuperscript{59,60} By contrast, in 1 NCT, no significant difference was evident in delayed graft function after renal transplantation with administration of HES to the donor.\textsuperscript{89}

In a cohort study of patients with acute ischemic stroke, 4.7\% experienced acute renal failure associated with dextran infusion.\textsuperscript{72} Gelatin, as compared with albumin as pump prime in cardiac surgery, elevated creatinine levels.\textsuperscript{91}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
Source & Study Design & No. of Patients & Setting & Treatment & Results \\
\hline
Schönöing and 
Lorenz,\textsuperscript{4} 
1980 & RCT & 450 & Orthopedic surgery & Preoperative gelatin without vs with H\textsubscript{1} receptor vs H\textsubscript{2} receptor antagonist premedication & No anaphylactoid reaction in any group \\
\hline
Schönöing 
et al,\textsuperscript{7} 1984 & RCT & 300 & Orthopedic surgery & 10\% HES (200/0.5) vs 6\% dextran 70 & Cardiac arrest occurred in 1 of 116 patients (0.9\%; 95\% CI, 0.02\%-4.96\%) randomized to dextran despite hapten inhibition \\
\hline
Harris et al,\textsuperscript{21} 
1985 & RCT & 154 & Total hip replacement & 10 mL/kg 10\% dextran of low molecular weight during operation and 7.5 mL/kg for 2 days postoperatively plus pneumatic compression vs 1.2 g/d aspirin vs 0.3 g/d aspirin & Excessive bleeding on day of operation in 3 dextran recipients during early part of study prompted dextran dose reduction to maximum of 500 mL intraoperatively for remaining patients \\
\hline
Davidson et al,\textsuperscript{2} 1987 & RCT & 17 & Kidney transplants from living related donors & 0.5 g/kg albumin vs dextran 40 during surgery & Postoperative urine volume and serum creatinine level not different between groups \\
\hline
Paul,\textsuperscript{4} 1987 & CS & 5745 & Major gynecological surgery or cesarean section & 1000 mL dextran 70 in first 24 h and 500 mL per 24 h thereafter until removal of intravenous cannula & 0.26\% (95\% CI, 0.22\%-0.30\%) incidence of dextran-induced anaphylactoid reactions \\
\hline
Gold et al,\textsuperscript{26} 
1990 & RCT & 40 & Abdominal aortic aneurysm surgery & 1 g/kg 5\% albumin vs 6\% HES before completion of vascular anastomoses & No differences in coagulation parameters, blood loss, or RBC use \\
\hline
Prien et al,\textsuperscript{9} 1990 & RCT & 18 & Abdominal surgery & 10\% HES vs 20\% albumin to maintain CVP at preoperative level & Intraoperative intestinal edema greater in HES recipients (P < .05) \\
\hline
Heilmann 
et al,\textsuperscript{59} 1991 & RCT & 207 & Consecutive women undergoing cesarean section & 3 × 500 mL 6\% HES of medium molecular weight (200/0.62) vs 3 × 5000 IU/d heparin & No differences in blood loss, bleeding complications, transfusion requirements, or reoperation \\
\hline
Bernard et al,\textsuperscript{56} 
1996 & NCT & 24 & Renal transplantation & Donor care involved infusion of HES vs no HES & Urinary output lower (P < .05) in patients receiving HES (1001 ± 1028 mL) vs no HES (2097 ± 1490 mL) and dopamine requirement higher (16 ± 12 vs 4 ± 4 µg/kg/min; P < .05); 25\% frequency of osmotic nephrosis-like lesions in both groups; no difference in serum creatinine level at 1, 3, and 6 mo after transplantation \\
\hline
Cittanova et al,\textsuperscript{55} 1996 & RCT & 69 & Kidney transplants from brain-dead donors & 6\% HES of medium molecular weight (200/0.60-0.66) as much as 33 mL/kg followed by gelatin if needed vs gelatin only for plasma volume expansion in kidney donors & During first 8 d after transplantation, 33\% of kidney recipients required hemodialysis or hemodiafiltration in HES-gelatin group, as compared with 5\% of gelatin-only patients (P = .029); serum creatinine concentrations lower in gelatin-only group (P = .009) \\
\hline
\end{tabular}
\caption{Noncardiac Surgery}
\end{table}
Table 3. Noncardiac Surgery (cont)

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Design</th>
<th>No. of Patients</th>
<th>Setting</th>
<th>Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehne et al, 1997</td>
<td>RCT</td>
<td>25</td>
<td>Hypovolemia in surgical patients</td>
<td>12 mL/kg 10% HES vs no HES postoperatively</td>
<td>In HES group, postoperative increases in α1-microglobulin, Tamm-Horsfall protein, and brush border N-acetyl-β-D-glucosaminidase; no glomerular function differences</td>
</tr>
<tr>
<td>Bothner et al, 1998</td>
<td>RCT</td>
<td>750</td>
<td>Minor elective surgery</td>
<td>6% HES (200/0.5) vs RL for intraoperative and postoperative volume expansion</td>
<td>621 ± 351 mL† total HES volume infused; no differences in incidence of anaphylactoid reactions or pruritus</td>
</tr>
<tr>
<td>Deman et al, 1999</td>
<td>NCT</td>
<td>109</td>
<td>Renal transplantation</td>
<td>6% HES of medium molecular weight (200/0.5) vs HES of high molecular weight (450/0.7) vs gelatin-albumin administered to donor 12-24 h before organ retrieval</td>
<td>No differences in incidence of delayed graft function; higher postoperative creatinine levels in HES of high vs medium molecular weight groups</td>
</tr>
<tr>
<td>Karoutsos et al, 1999</td>
<td>RCT</td>
<td>42</td>
<td>ASA grade I patients undergoing total hip or knee replacement</td>
<td>3.5% modified gelatin solution (35 kDa) vs 6% HES of low molecular weight (200/0.5) vs 5% albumin</td>
<td>Hypercoagulability demonstrated at thromboelastography in gelatin but not other groups (P&lt;.001)</td>
</tr>
<tr>
<td>Kurnle et al, 1999</td>
<td>RCT</td>
<td>60</td>
<td>Major abdominal surgery</td>
<td>6% HES of low (70/0.5) vs medium (200/0.5) molecular weight vs modified gelatin (35 kDa) for volume replacement</td>
<td>α1-microglobulin increased 3.3-fold and 2.0-fold in patients &lt;65 y and ≥65 y, respectively, receiving HES of low molecular weight (P&lt;.05 for both age categories) but not other groups</td>
</tr>
<tr>
<td>Omar et al, 1999</td>
<td>NCT</td>
<td>50</td>
<td>Prostatectomy for benign prostatic hyperplasia</td>
<td>15 mL/kg 6% HES (200/0.5) vs equal volume of 5% albumin during operation</td>
<td>Factor VIII:C levels and platelet aggregation declined, respectively, by 25% and 31% in HES but not albumin group (P&lt;.05 for both comparisons)</td>
</tr>
<tr>
<td>Torchio and Danzinger, 2000</td>
<td>NCT</td>
<td>154</td>
<td>Colorectal surgery</td>
<td>Albumin vs no albumin perioperatively; &lt;50 mL of albumin administered in 42% of albumin recipients</td>
<td>Albumin administration an independent risk factor for infection</td>
</tr>
<tr>
<td>Huraux et al, 2001</td>
<td>NCT</td>
<td>40</td>
<td>Abdominal surgery</td>
<td>Intraoperative infusion of 20 vs 30 mL/kg 6% HES of medium molecular weight (200/0.6)</td>
<td>Both HES doses induced thrombocytopenia, prolonged aPTT, and reduced levels of factor VIII:C and von Willebrand factor (P&lt;.05 for all comparisons)</td>
</tr>
<tr>
<td>Trull et al, 2002</td>
<td>RCT</td>
<td>60</td>
<td>Liver transplantation</td>
<td>In patients receiving tacrolimus or cyclosporine, fluid replacement with albumin vs gelatin during first 2 postoperative weeks; all groups received gelatin in cases of bleeding &gt;1000 mL/h</td>
<td>Serum creatinine level elevated in recipients of gelatin and albumin, compared with that in other groups (P&lt;.001); acute rejection risk higher in tacrolimus plus albumin group (P=.03), indicating tacrolimus binding by albumin</td>
</tr>
</tbody>
</table>

Abbreviations: aPTT, activated partial thromboplastin time; ASA, American Society of Anesthesiology; CS, cohort study; CVP, central venous pressure; HES, hydroxyethyl starch; RCT, randomized controlled trial; RBC, red blood cell; RL, Ringer lactate.

†Mean ± SD.

CIRCULATORY DYSFUNCTION

The occurrence of circulatory dysfunction marked by increased plasma renin activity and aldosterone has been investigated in patients who have ascites and are undergoing large-volume paracentesis. The incidence of circulatory dysfunction was significantly higher after infusion of dextran than of albumin in 2 RCTs, but not in a third. Circulatory dysfunction was also more frequent in patients receiving gelatin than in those receiving albumin.

HEPATIC DYSFUNCTION

Repeated infusion of HES in conjunction with dialysis resulted in the development of ascites that necessitated Denver shunt implantation in 1 case. In 1 recent study, HES deposition in hepatic Kupffer cells was associated with worsening of hepatic dysfunction after HES infusion. Pump priming with HES, as compared with albumin, during cardiac surgery has been found to increase levels of liver enzymes during and after cardiopulmonary bypass surgery.
TISSUE DEPOSITION

Hydroxyethyl starch is deposited in a variety of tissues, including skin, liver, muscle, spleen, intestine, trophoblast, and placental stroma.\(^5,60,55,96,101\) Such deposition often has been described in association with pruritus.\(^5,56\) Tissue deposits persist as long as 54 months after HES administration.\(^96\) Organ deposition of dextran has been reported in 1 NCT of patients undergoing long-term hemodialysis.\(^35\) Tissue deposition of administered albumin has not been detected at necropsy examination.\(^5\)

**COMMENT**

The major conclusion emerging from this systematic review is that there are clinically important differences in safety among colloids. Many of the differences have been demonstrated between albumin and HES, possibly because these 2 colloids have been more extensively investigated than have dextran and gelatin.

The incidence of adverse events in albumin recipients was low. Albumin administration was not consistently associated with any characteristic types of adverse events. This observation is perhaps unsurprising, because albumin infusion serves to replenish the normal endogenous colloid. Although albumin is isolated from human plasma, we could identify no evidence of viral disease transmission attributable to albumin.

Bleeding associated with artificial colloid administration has been widely reported.\(^8\) Such complications have been particularly frequent in the cardiac surgery setting, necessitating increased blood product use and increased costs of care.\(^87,98\) Bleeding complications can be particularly troublesome because of the long half-life of HES and because discontinuation of HES infusion cannot immediately resolve coagulopathy.

Although potentially life threatening, anaphylactoid reactions were relatively infrequent for all colloids. Hydroxyethyl starch, as compared with albumin, more than quadrupled the incidence of anaphylactoid reactions, whereas dextran more than doubled them. The incidence of these reactions in recipients of gelatin was greater by more than an order of magnitude than that after albumin infusion. Because artificial colloids are derived from nonhuman source materials, they may be recognized as foreign and hence are more likely to provoke an immune-mediated response. The foreign nature of artificial colloids may also hinder metabolic clearance and promote tissue deposition.

Although HES has been widely used for several decades, HES-related pruritus has been widely described only since the early 1990s.\(^93\) Its late recognition as a clinical entity appears to be at least partly because of the lengthy delay in onset of symptoms, in many cases occurring after discharge. This adverse effect was initially characterized in otologic patients receiving relatively high HES doses to improve microcirculation. Besides otologic indications, we identified evidence of HES-associated pruritus in studies of general\(^90\) and cardiac\(^99\) surgery, patients receiving intensive care,\(^95,106\) and subarachnoid hemorrhage.\(^105\) In our MA, the pooled odds of pruritus were significantly increased by HES exposure. Although the effect was dose related, many patients receiving less than the recommended 20 ml/kg HES maximum were affected.\(^95,96\) In a cardiac surgery study, more than half of the patients developing pruritus had received less than the recommended HES maximum.\(^99\)

We compiled substantial evidence linking HES exposure to increased risk of renal failure. This effect has been characterized in the settings of surgery,\(^74,93\) sepsis,\(^108\) and kidney transplantation.\(^94,96\) Adverse effects of HES in kidney transplantation have, however, been controversial.\(^89\)

Outside the United States, HES products of varying molecular weight and/or molar substitution have been introduced. It has often been argued that adverse effects of HES are primarily attributable to preparations of higher molecular weight and greater molar substitution.\(^61,70\) The basis for such putative differences is the more rapid clearance of HES of lower molecular weight and less highly substituted forms. In our MA, neither HES molecular weight nor molar substitution significantly affected the odds of pruritus. More broadly, our systematic review failed to reveal consistent differences among HES preparations with respect to safety.

On the basis of extensive evidence, albumin appears to be in general the safest colloid of the 4 we reviewed. In some settings, other factors such as the desirability of anticoagulant activity might mitigate in favor of artificial colloids. In any case, results of our review suggest the need to consider the contrasting safety profiles of colloids in clinical decision making.

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*References 3, 21, 27, 40, 49, 50, 56, 60, 62, 73, 87, 92, 98, 104, 109.*

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**Table 4. Pooled Incidence Rate Ratios for Anaphylactoid Reactions**

<table>
<thead>
<tr>
<th>Colloid</th>
<th>Pooled Incidence Rate Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyethyl starch</td>
<td>4.51</td>
<td>2.06-9.89</td>
</tr>
<tr>
<td>Dextran†</td>
<td>2.32</td>
<td>1.21-4.45</td>
</tr>
<tr>
<td>Gelatin</td>
<td>12.4</td>
<td>6.40-24.0</td>
</tr>
</tbody>
</table>

*Relative to albumin: 1 study\(^59\) was excluded from pooled incidence rate ratio calculation because reported data were restricted to severe anaphylactoid reactions only.
†Includes data from 2 dextran studies\(^57,75\) in which some patients received hapten inhibition and others did not; use of hapten inhibition in the remaining 2 dextran studies\(^59,60\) was unspecified.

**Table 5. Pooled Odds Ratios for Pruritus Associated With HES**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pooled Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>HES exposure (HES vs no HES)</td>
<td>1.78</td>
<td>1.23-2.58</td>
</tr>
<tr>
<td>HES dose (100-g increment)</td>
<td>1.46</td>
<td>1.38-1.55</td>
</tr>
<tr>
<td>HES molecular weight (450 kDa vs 200 kDa)</td>
<td>1.32</td>
<td>0.55-3.16</td>
</tr>
<tr>
<td>HES molar substitution ratio (≤0.5 vs &gt;0.5)</td>
<td>1.19</td>
<td>0.54-2.60</td>
</tr>
</tbody>
</table>

Abbreviation: HES, hydroxyethyl starch.
CA 95949, (e-mail: mwilkes@hygeiaassociates.com).


56. Laxenare MC, Charpentier C, Feldman L. Réaction anaphylactoides aux sub-


