Recent trials have failed to demonstrate a survival benefit from the use of hydroxyethyl starches (HES) as a colloid in fluid resuscitation and have raised concerns of renal harm. In severe sepsis, there is a concerning signal of increased mortality. New high-quality systematic reviews consistently demonstrate a statistically non-significant relative risk of death of 1.08 - 1.10 and a significant 25% increased chance of requiring renal replacement therapy. The HES literature contains many industry-affiliated reviews of indifferent quality. Traditional efficacy confidence limits may warrant re-evaluation when considering these harms. Newer formulations of HES and more focused indications for use show benefit on surrogate endpoints, but these trials are currently underpowered to ensure safety.

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In such patients the baseline mortality rate can be as high as 40%. Even assuming half that (20%), a relative risk of 1.09 gives an absolute mortality increase of 1.8%, or one extra death for every 56 deaths. The HES literature contains many industry-affiliated reviews of indifferent quality. Traditional efficacy confidence limits may warrant re-evaluation when considering these harms. Newer formulations of HES and more focused indications for use show benefit on surrogate endpoints, but these trials are currently underpowered to ensure safety.

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clinical endpoints, such as length of ICU stay, use of mechanical ventilation or presence of major bleeding, showed a statistically significant advantage of HES over crystalloids.

Renal harm
Both the Gattas[11] and Zarychanski[11] reviews found convincing evidence of renal harm. In Gattas et al’s review, there was a 27% relative increase in the need for renal replacement therapy in patients given HES compared with crystalloid (RR 1.27, 95% CI 1.10 - 1.46). The equivalent RR in the Zarychanski review was 1.32 (95% CI 1.15 - 1.50) where the control intervention was not always crystalloid.

Assessing the potential for harm
Formal assessment of harm is complex, and may be unfamiliar to clinicians without expertise in pharmaco-epidemiology. Convincing safety signals usually require large numbers in the numerator, and registration trials are underpowered for this. Patient numbers several times higher than those used in efficacy trials are required. Accrual of harms may not proceed at the same rate as benefits, so acute resuscitation trials with short-term endpoints will not detect harms taking weeks to accrue. An appropriate comparator is important – pooling trials where some control groups were given other colloids rather than crystalloids dilutes harm signals.

The 0.05 type I error rate used to measure the certainty of an effect is purported to have originated with Fischer[16] and was adopted by the Food and Drug Administration (FDA)[15] and other medicines regulators. It makes sense to minimise the probability of a false-positive statement when determining efficacy. However, do we need to be 95% sure of danger before avoiding a course of action?[20] Table 2 illustrates the effect of changing type I error rates on statements of certainty.

Unlike the albumin controversy, where an earlier Cochrane review[17] raised concerns about harm that were not confirmed in a subsequent large trial (SAFE[18]), the current HES harm signal comes from information on more than 10 000 patients and is robust.

Scoring reviews versus keeping score of the number of reviews
Manufacturers react appropriately to safety concerns by commissioning reviews. Guidelines on assessing the quality of a systematic review exist.[19] High-quality reviews are reliable if the underlying trials are unbiased, and if adequate patient numbers have accrued. A ‘review of reviews’ on HES raises some concerns.[22]

The authors identified 165 reviews published between 1976 and 2010, of which 7% contained a meta-analysis. Of the higher-quality reviews, 83% were not supportive of HES versus 20% of the lower-quality reviews. Of 124 positive reviews, 70 were written by only 14 experts, and 10 of these authors had identifiable potential conflicts of interest. An unsuspecting reader is more likely to encounter multiple low-quality positive reviews than the few high-quality ones. Simple repetition does not imply truth.

Identifying industry influence
It is helpful to identify reviews at risk of bias. Clues include finding authors with clear affiliations to HES manufacturers, reviews listing

Table 1. Hydroxyethyl starch reviews

<table>
<thead>
<tr>
<th>Author</th>
<th>Date</th>
<th>Indication</th>
<th>HES type</th>
<th>Bias risk</th>
<th>Mortality RR (95% CI)</th>
<th>Renal harm RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hartog et al[20]</td>
<td>2011</td>
<td>80% elective surgery</td>
<td>130/0.4</td>
<td>Insufficient data</td>
<td>1.11 (1.00 - 1.23)</td>
<td>1.36 (1.08 - 1.72)</td>
</tr>
<tr>
<td>Perel et al. (Cochrane)[21]</td>
<td>2013</td>
<td>'Critically ill patients'</td>
<td>All</td>
<td>Low</td>
<td>1.10 (1.02 - 1.19)</td>
<td>1.27 (1.10 - 1.46)</td>
</tr>
<tr>
<td>Gattas et al.[22]</td>
<td>2013</td>
<td>'Acutely ill patients'</td>
<td>130/0.4 or 0.42</td>
<td>Low</td>
<td>1.08 (0.97 - 1.21)</td>
<td>1.32 (1.15 - 1.50)</td>
</tr>
<tr>
<td>Zarychanski et al.[23]</td>
<td>2013</td>
<td>'Critically ill patients'</td>
<td>All</td>
<td>Moderate</td>
<td>1.09 (1.02 - 1.17)</td>
<td>1.32 (1.15 - 1.50)</td>
</tr>
<tr>
<td>Haase et al.[24]</td>
<td>2013</td>
<td>Sepsis</td>
<td>130/0.38 - 0.45</td>
<td>Low to moderate</td>
<td>1.11 (1.00 - 1.23)</td>
<td>1.36 (1.08 - 1.72)</td>
</tr>
</tbody>
</table>

RR = relative risk; CI = confidence interval.
*Renal harm measured as need for renal replacement therapy.

Table 2. Sensitivity analysis* of differences in type I error rate for a pooled effect size (mortality) from the three major trials (VISEP,[25] CHEST,[6] SAFE[18])

<table>
<thead>
<tr>
<th>Confidence interval</th>
<th>Relative risk 1.10</th>
<th>Risk difference 0.021</th>
<th>Statistically significant</th>
</tr>
</thead>
<tbody>
<tr>
<td>99%</td>
<td>0.990 - 1.225</td>
<td>-0.002 - 0.044</td>
<td>No</td>
</tr>
<tr>
<td>95%</td>
<td>1.015 - 1.194</td>
<td>0.003 - 0.038</td>
<td>Yes</td>
</tr>
<tr>
<td>90%</td>
<td>1.029 - 1.178</td>
<td>0.006 - 0.036</td>
<td>Yes</td>
</tr>
<tr>
<td>50%</td>
<td>1.071 - 1.132</td>
<td>0.015 - 0.027</td>
<td>Yes</td>
</tr>
<tr>
<td>33%</td>
<td>1.082 - 1.121</td>
<td>0.017 - 0.025</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*If VISEP, which contributes only 6.7% of the weight of the combined three trials, is omitted, for the remaining two trials the relative risk of death changes to 1.088, with a 95% CI from 0.997 to 1.187, and a 95% CI from 1.511 to 1.776. *Mantel-Haenszel, fixed-effect meta-analysis.
a manufacturer as sponsor or originator of a review, and reviews looking at endpoints where the focus is on physiological variables or other short-term surrogate markers rather than patient-relevant clinical measures. Missing features often include a clearly defined trial search strategy, and a table listing inclusions and exclusions, and the reasons for these. Lack of power to detect harm even after study pooling may be underemphasised. Measure of internal validity (trial quality scores) may be absent, and control groups inappropriate. Pooling methods may be unusual or use methods that do not take account of differences in baseline prevalence and trial size.[21] The introduction and discussion sections may contain non-scientific ‘emotive’ words and product trade names.

For example, a 2013 industry-associated review[22] of 17 studies of HES in surgical patients found ‘no evidence of renal dysfunction’. Only 6 of these studies (a total of 437 patients) had a crystalloid comparator, trial quality was not formally reported, and there was a manufacturer as sponsor or originator of a review, and reviews looking at endpoints where the focus is on physiological variables or other short-term surrogate markers rather than patient-relevant clinical measures. Missing features often include a clearly defined trial search strategy, and a table listing inclusions and exclusions, and the reasons for these. Lack of power to detect harm even after study pooling may be underemphasised. Measure of internal validity (trial quality scores) may be absent, and control groups inappropriate. Pooling methods may be unusual or use methods that do not take account of differences in baseline prevalence and trial size.[21] The introduction and discussion sections may contain non-scientific ‘emotive’ words and product trade names.

**Conclusion**

Imagine another decade of HES use following current practice. If industry-associated opinion leaders are right, our patients would be unscathed. However, if the systematic reviews are correct, we would have ignored powerful signals of harm, and continued to expose our patients to a product that may increase mortality in sepsis, and may increase the need for dialysis in resuscitation. With these caveats, and in the absence of adequately powered studies to confirm safety in other situations, it is difficult to justify ongoing use of these products.

**Conflict of interest.** The authors have no financial or intellectual conflict of interest.

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