

# The Risk of AKI in Patients Treated with Intravenous Solutions Containing Hydroxyethyl Starch

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## Summary

**Intravenous fluids are arguably one of the most commonly administered inpatient therapies and for the most part have been viewed as part of the nephrologist's toolkit in the management of acute kidney disease. Recently, findings have suggested that intravenous fluids may be harmful if given in excess (quantitative toxicity) and that some may be more harmful than others (qualitative toxicity), particularly for patients who already have AKI. Recent clinical trials have investigated hydroxyethyl starch solutions and found worrying results for the renal community. In this brief review, we consider the published literature on the role of hydroxyethyl starch solutions in AKI, with particular emphasis on two large recent randomized clinical trials conducted in Europe and Australia.**

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## Introduction

Intravenous (IV) fluid therapy is used extensively for both the prevention and treatment of AKI in the belief that there is often a prerenal component. Insofar as this state is believed to exist largely as a result of an intravascular volume deficit, colloid solutions, such as those containing hydroxyethyl starch (HES), might be expected to reverse the prerenal state faster and with less total volume compared with crystalloids. Their use is common around the world (Figure 1). Recent publications have highlighted the possibility that although less fluid may be required to achieve a given resuscitation endpoint using colloids, use of less fluid may actually translate into worse renal outcome.

In addition to the issue of how much fluid to give (1–3), there is the question of what type. The debate over whether colloids are better or worse than crystalloids has raged for decades and is unlikely to be resolved quickly. However, the literature is maturing and now contains several large trials that may further inform this question. In this brief review, we discuss the recently published literature regarding the use of colloid and crystalloid solutions in critically ill patients, with an emphasis on IV starch preparations and their possible nephrotoxicity.

All IV fluid therapy must (by definition) be administered into the vascular space, but it is extremely difficult to predict what will happen to a bolus of fluid, particularly when the patient is critically ill (4,5). It is believed that colloidal solutions will remain in the vascular space for longer than crystalloid solutions will (6), and this is probably true in healthy persons. In sick patients, however, the endothelial glycocalyx is often damaged, leading to a “leakier” capillary barrier for fluid (7). When colloidal solutions diffuse into the interstitium, they affect the Starling equation by reducing the oncotic pressure gradient across the capillary barrier and making further extravasation more likely (7).

Thus, the context of a fluid therapy decision is important; if the glycocalyx is damaged, then the differences between crystalloids and colloids (from a hemodynamic perspective) are far less easily observed (8).

In considering how much fluid to give, the problem is that the effects of fluid boluses (and infusions) are cumulative and persist beyond the immediate response. Colloids in particular are almost always given to correct a perceived hemodynamic deficit (especially during volume-optimization protocols [9]), but this response persists for minutes or hours at best. In contrast, their effect on total body water persists until they are excreted, which may take days (10). Even crystalloids have this property. Consider, for example that 1 L of 0.9% saline contains 9 g of NaCl. The relationship between volume overload and outcome in the critically ill population with AKI is well established (11), but the problem is one of immediate gratification with delayed cost. A busy resident may give a 500-ml colloid bolus in response to an episode of hypotension with satisfying results: The BP rises and urine flows. However, if this pattern persists for three or four shifts, then the effect on overall fluid balance is considerable (12). Patients who are sick tend to take on fluid (the best way to observe this is to assess daily weight), while those who are recovering “give it back.” The problem is that it may take days or weeks to remove the fluid given in a matter of hours during an acute deterioration. It is thus very easy to give fluids, especially when the reward is short-lived (13,14) and the cost may not be immediately apparent.

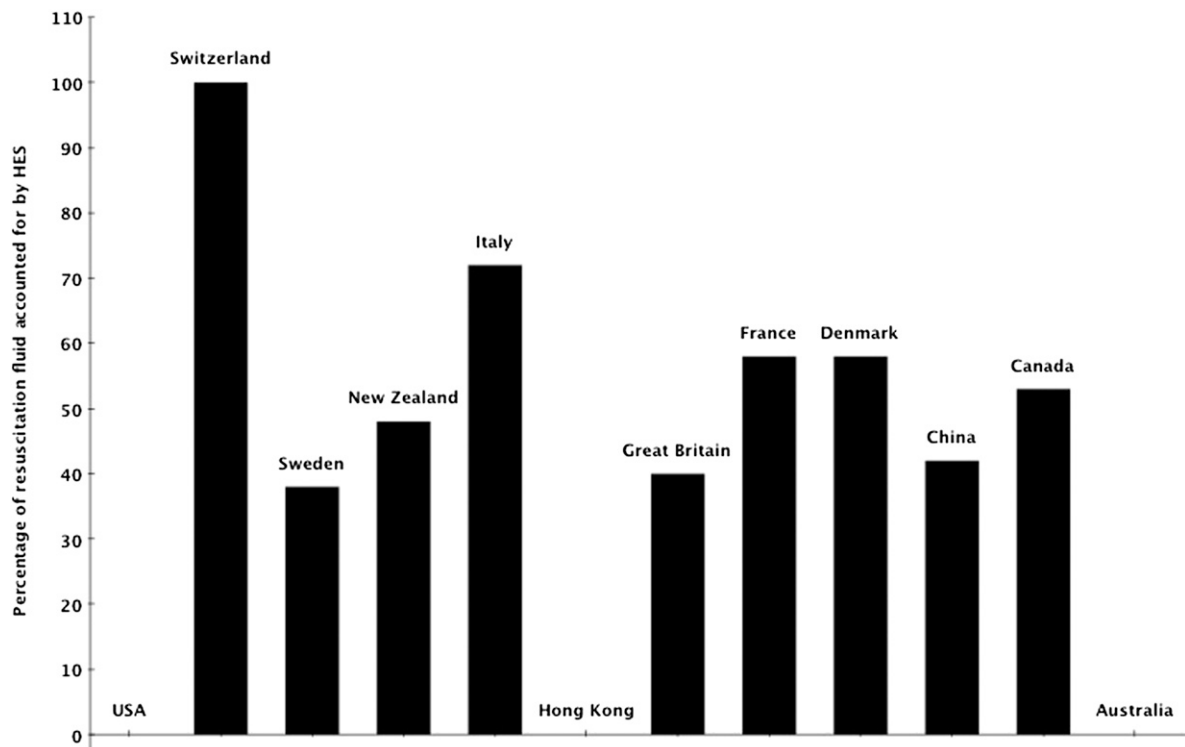
## Starch and AKI

IV starch preparations are usually described according to three characteristics: their average molecular weight; their concentration percentage; and their degree of substitution, which refers to the percentage

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**Figure 1.** | Geographical variation in starch use in the intensive care unit. HES, hydroxyethyl starch.

of hydroxyethyl residues attached to the glucose subunits. Typically, a higher molecular weight and larger substitution ratio are associated with slower metabolism and prolonged vascular retention time. The earliest evidence of renal toxicity from HES solutions came from case reports of “osmotic nephrosis” (tubular swelling due to large cytoplasmic vacuole formation) (15), a finding initially attributed only to hypertonic solutions but more recently confirmed experimentally in animals using isotonic HES (16); for a recent review, see reference 17. However, the risk to patients was less clear, and the uncertainty involves not only the concentration of the solution but also the molecular weight; degree of molar substitution (0.4–0.7) of the starch molecule; and potentially even the carrier fluid, which is typically saline or a balanced electrolyte solution. Lower-molecular-weight tetrastarch solutions (HES 130/0.4 and HES 130/0.42) have recently been introduced (18); however, reliable evidence that these newer starch solutions have less potential to induce nephrosis is limited, and this finding has been difficult to confirm.

Clinical concern for kidney injury from HES began in earnest with a study by Schortgen *et al.* (19), who compared HES 200/0.6 with gelatin and found a greater incidence of AKI, defined as a two-fold increase in serum creatinine (SCr) concentration or need for renal replacement therapy (RRT) in the HES group, but no effect on hospital survival. This study was limited by small sample size and the fact that patients randomly assigned to the HES group had a higher mean SCr level at baseline. More recently, the VISEP (Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis) study (20) randomly assigned patients with severe sepsis to receive a hypertonic (10%) solution of HES 200/0.5 or an isotonic lactate-buffered crystalloid solution (Ringer’s

lactate; osmolarity, 273 mOsm/L) for fluid resuscitation. Patients in the HES group received a median cumulative dose of 70.4 ml/kg of body weight (interquartile range, 33.4–144.2 ml/kg), and patients in the control group received 32% more total fluid than did the patients in the HES group. Although mortality was not significantly different, there was a trend toward greater overall mortality at 90 days with 10% HES. Furthermore, the 10% HES group had a significantly higher rate of AKI, defined as a doubling of the baseline SCr level or the need for renal replacement therapy (34.9% versus 22.8%) and more days of RRT. The VISEP study drew a variety of criticisms. First, the study used a factorial design with tight glucose control. Although both interventions were believed to affect kidney function, the study did not analyze possible interaction between the interventions. Second, hyperoncotic colloid solutions were already believed to affect the kidney (21), and the investigators exceeded the recommended daily dose limit for 10% HES 200/0.5 (*i.e.*, 20 ml/kg per day) by >10% in more than 38% of patients. Finally, patients in the HES group who received doses within the recommended range were not different from the crystalloid group in terms of renal function (22).

A large prospective observational study (Sepsis Occurrence in Acutely Ill Patients) found that HES infusion (median volume, 555 ml/d; interquartile range, 500–1000 ml/d) did not increase the risk for AKI (23). Added to this, Magder and colleagues compared 10% HES 250/0.45 to isotonic saline in 262 patients who underwent cardiac surgery (24) and found no evidence of nephrotoxicity—no difference in the daily creatinine, development of AKI by RIFLE (risk, injury, failure, loss, and ESRD) criteria during hospital stay (16% in both groups), or need for renal replacement therapy (1% in

each group). Of note, patients in the saline group received nearly 60% more volume for fluid resuscitation in the intensive care unit (ICU) than did the HES group (887 versus 1397 ml;  $P < 0.0001$ ). Furthermore, far fewer patients receiving HES required catecholamines the morning after surgery compared with those receiving saline (10.9% versus 28.8%;  $P = 0.001$ ).

Finally, in a study of 196 patients with severe sepsis randomly assigned to treatment with HES or saline, Guidet *et al.* (25) reported data from 174 patients who achieved hemodynamic stabilization. In patients who received HES, 1379 ml was required for hemodynamic stabilization compared with 1709 ml in the saline group. They reported no differences in renal function between the two groups but did find a trend toward increased use of dialysis in the HES group (relative risk, 1.4; 95% confidence interval [CI], 1.0–1.8;  $P = 0.08$ ) (Figure 2) (26). Of note, this dialysis signal has now been confirmed in two much larger studies of ICU patients (27,28).

### 6S and CHEST

These earlier studies set up a critical tension: Can HES reverse shock more effectively or more rapidly (or with less total volume), and will these benefits translate into less (or less severe) AKI? Or does deposition of starch molecules in the kidney (observed in animal and even some clinical studies) result in just the opposite effect—increasing risk (or worsening) of AKI? This critical tension has now been addressed by two excellent trials, the 6S (Scandinavian Starch for Severe Sepsis/Septic Shock Trial) (27) trial in 26 centers in four Scandinavian countries and CHEST (Crystalloid versus Hydroxyethyl Starch Trial) (28) in 32 centers in Australia and New Zealand. Together, both trials analyzed 7798 patients with an AKI event rate of  $>50\%$  and an RRT rate of 7.5%.

As we examine these new and important trials, it is vital to consider whether they have addressed one or both sides of the clinical question. In other words, can they assess benefit, harm, or both? As discussed earlier, the purported benefits of HES, indeed of all colloids, is the ability to more rapidly and efficiently (*i.e.*, per unit volume) reverse shock or at least correct hypovolemia. No other mechanisms have been hypothesized for a “kidney-sparing” effect of HES in patients with shock.

The 6S trial randomly assigned 798 patients with severe sepsis to receive 6% HES 130/0.42 in Ringer’s acetate

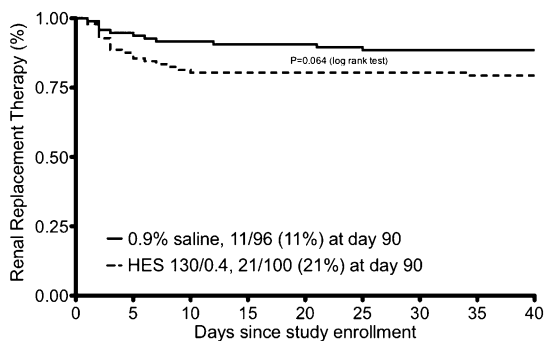
solution or Ringer’s acetate alone up to 33 ml/kg per day. The primary outcome was a composite endpoint of death or need for RRT at 90 days after randomization. At 90 days, 201 of 398 patients (51%) assigned to HES had died compared with 172 of 400 patients (43%) assigned to Ringer’s acetate (relative risk, 1.17; 95% CI, 1.01–1.36;  $P = 0.03$ ); one patient in each group was still requiring RRT. Within the 90-day period, 87 (22%) patients assigned to HES were treated with RRT compared with 65 (16%) patients assigned to Ringer’s acetate (relative risk, 1.35; 95% CI, 1.01–1.80;  $P = 0.04$ ). Furthermore, the severity of AKI was greater with HES (40% stage 2–3 by Kidney Disease Improving Global Outcomes [KDIGO] criteria [29] for creatinine) compared with 33% with Ringer’s acetate.

Thus, the 6S trial clearly demonstrated a renal toxicity signal that was manifest by both KDIGO stage 2–3 criteria and need for RRT, as well as an overall mortality difference emerging late (after about 30 days). The survival curves in 6S were strikingly similar to those seen in the earlier VISEP study (20), in which separation, although never reaching statistical significance, began at about the same time (*i.e.*, 3–4 weeks after the exposure). The late mortality (90 days and beyond) signal is especially significant because AKI would be expected to affect long-term outcome more than short-term given the ability to sustain life with RRT but would still result in increased risk of cardiovascular disease in those surviving. Indeed, in a recent observational study of patients with community-acquired pneumonia, risk of death was highest immediately after hospitalization in patients who developed AKI (30).

However, the potential to demonstrate a benefit from HES in the 6S trial was limited by a study design that ensured that most patients were already fluid resuscitated before enrollment and received nearly identical volumes of HES compared with crystalloid. Indeed, baseline values for central venous pressure, central venous oxygen saturation, and lactate were already within the target range for early goal-directed therapy as described by Rivers *et al.* (31). Having no possibility to demonstrate faster or more efficient (*i.e.*, using less volume) resuscitation with HES, the 6S trial can therefore address only safety.

By contrast, CHEST enrolled 7000 patients (including 1937 with sepsis) and randomly assigned them to receive 6% HES (130/0.4) in 0.9% saline or 0.9% saline alone for all fluid resuscitation until ICU discharge, death, or 90 days. The primary outcome was death within 90 days, and secondary outcomes included RRT and AKI. Although CHEST did not require pre-enrollment resuscitation, the study was conducted in the ICU and mean time from ICU admission to enrollment was more than 10 hours. Further, baseline values for central venous pressure and lactate (central venous oxygen saturation was not measured) were almost identical to those in 6S. Nevertheless, unlike the 6S trial, CHEST did demonstrate less use of fluid (about 30% less), faster increase in central venous pressure, and a lower incidence of new cardiovascular failure (defined as a Sequential Organ Failure Assessment score of  $\geq 3$ ) (adjusted relative risk, 0.91 [95% CI, 0.84–0.99],  $P = 0.02$ , with HES compared with saline). However, heart rate, mean arterial pressure, and lactate did not differ between the two groups during the first 4 days.

Despite this, and as was the case in both CRYSTMAS and 6S, CHEST revealed an important renal toxicity



**Figure 2.** | Time (days since enrollment in trial) to renal replacement therapy in Guidet *et al.* (25,26). HES, hydroxyethyl starch.

signal manifesting as greater use of RRT in the HES group compared with the saline group (7.0% versus 5.8%; relative risk, 1.21 [95% CI, 1.00–1.45];  $P=0.04$ ). Of note, however, unlike 6S, CHEST found a lower incidence of AKI with HES than with saline (by all RIFLE criteria: 54.0% versus 57.3; RR, 0.94 [95% CI, 0.90–0.98];  $P=0.007$ ) and no difference in the primary endpoint of death by 90 days (18% with HES versus 17% with saline; RR, 1.06 [95% CI, 0.96–1.18];  $P=0.26$ ). Furthermore, these results were consistent across all six predefined subgroups, including sepsis. When the creatinine criteria for RIFLE are considered alone, however, the toxicity signal becomes much clearer, and the benefit, in terms of renal function, is confined to increased urine flow (Figure 3). These results underscore the limitations of SCr and urine flow as measures of kidney damage. Better renal perfusion (thought by many to be protective) might have resulted in increased urine flow, whereas HES might have ultimately resulted in decreased GFR.

### Differences Across Studies

How do we reconcile these apparently inconsistent results? The main differences between CHEST and 6S are shown in Table 1 and Figure 4. Both appeared to show renal toxicity with HES by creatinine and use of RRT, but CHEST seems to show benefit in terms of total AKI (any severity) and in terms of fluid used in the first 24 hours. Finally, the renal toxicity signal in 6S also translated into an effect on survival, whereas CHEST was negative for the primary endpoint of 90-day mortality. It is compelling to speculate that overall outcomes differ because unlike 6S, CHEST found some, albeit transient, benefits for early hemodynamic endpoints. Did these benefits “trade off” with the later toxicity signal related to starch deposition into the tissues (or some other toxicity)? In this way, HES could perhaps be seen as the “gentamicin” of fluid resuscitation—useful, but associated with important toxicity. Might we then surmise that there may be a subgroup of patients for whom the benefits outweighed the risks? In addition, is there a colloid solution that allows for the hemodynamic stabilization benefits but does not present a nephrosis risk, such as human albumin solution?

An alternative interpretation is that the CHEST and 6S data are consistent. The 6S patients (Simplified Acute Physiology Score II at enrollment was 50, and predicted mortality rate

was approximately 50%) were almost “twice” as sick as the CHEST patients (Acute Physiology and Chronic Health Examination II score at enrollment was 17, and predicted mortality rate was approximately 25%) and therefore perhaps the CHEST patients were better able to deal with the hazard. If so, then in CHEST the actual effect size would be expected to be less than the 3% difference the trial was powered to find (the CHEST investigators expected a mortality of 26%). For the two trials to be inconsistent, the “real” effect would have to lie somewhere between a 4% benefit from HES and no difference. We think that this is unlikely and that the severity of illness differences between the two trial populations is a better way to reconcile the data.

However, it is also noteworthy that an important difference between 6S and CHEST is that the latter could show a benefit whereas the former could not. Furthermore, given the late start of fluids relative to the start of illness (often many hours before enrollment), one might reasonably ask whether CHEST could actually have found any overall benefit at all and whether trials are still needed to examine early resuscitation or “preoptimization” as discussed earlier. For now, we believe it is safe to conclude that HES should be avoided for patients receiving fluid resuscitation in the ICU—especially after the initial fluid is administered. The common practice of HES administration for several days seems especially inappropriate on the basis of current evidence. Finally, two other important differences have existed among trials, including 6S and CHEST: the origin of the starch and carrier solution. As shown in Table 1, 6S used a potato starch suspended in a balanced acetate-buffered solution whereas CHEST used a corn starch in saline. Both trials appropriately used the corresponding carrier as the control. Little is known about the potential differences of these products in terms of renal toxicity, but one would not expect there to be large differences because both have similar molecular weight and molar substitution.

### Does the Carrier Solution Matter?

As discussed earlier, an important difference across studies has been that HES products have varied in terms of the carrier solution used; that solution has also been, in most cases, the comparator solution. It is notable that, of the larger trials, those comparing HES with a balanced

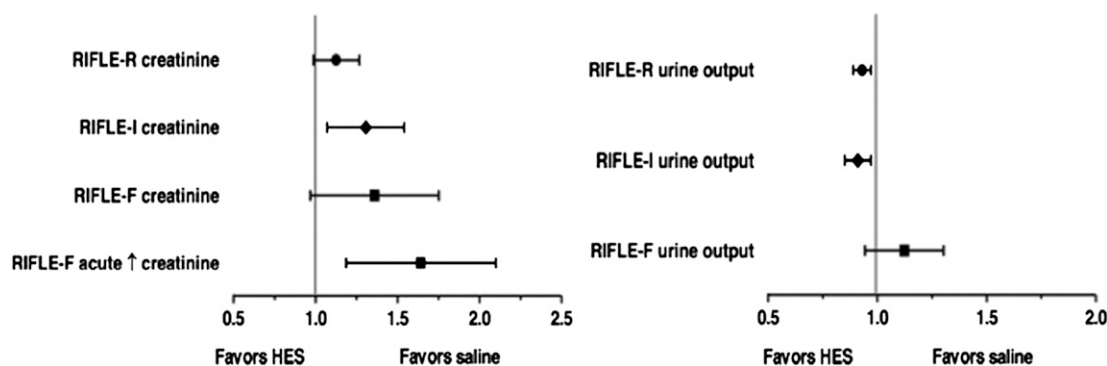
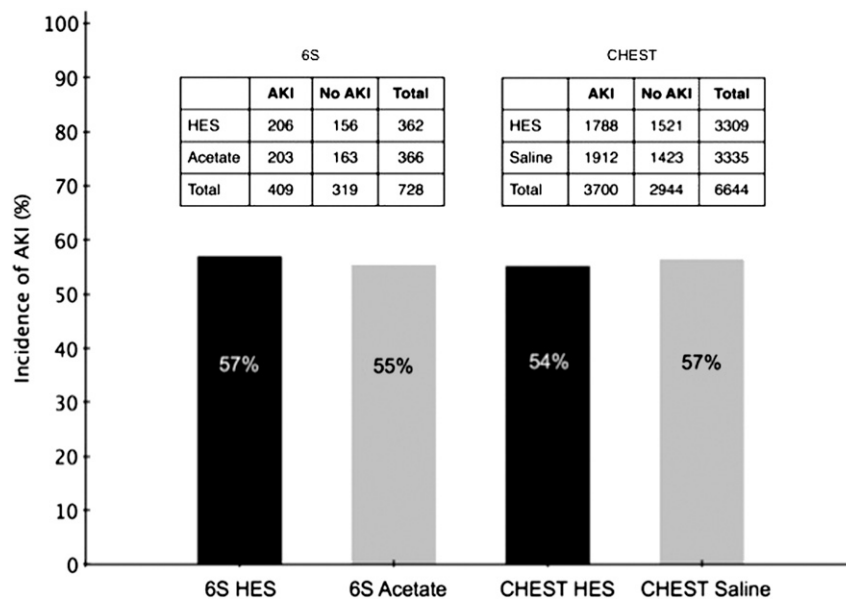


Figure 3. | Incidence of AKI by RIFLE (risk, injury, failure, loss, and ESRD) creatinine and RIFLE urine output in CHEST (Crystalloid versus Hydroxyethyl Starch Trial). HES, hydroxyethyl starch.

Characteristic	6S	CHEST
Total patients ( <i>n</i> )	798	7000
Patients with sepsis ( <i>n</i> )	798	1937
Time from ICU admission to enrollment (h)	4	11
Ratio of HES to crystalloid first 24 h	1:1	1:1.2
Differences in CVP response	No	Yes
Carrier solution	Ringer's acetate	0.9% saline
Starch origin	Potato	Corn
Results (HES versus comparator)		
RR for AKI	1.03 (0.90–1.17); <i>P</i> =0.7	0.94 (0.90–0.98); <i>P</i> =0.007
RR for use of RRT (95% CI)	1.35 (1.01–1.80); <i>P</i> =0.04	1.21 (1.00–1.45); <i>P</i> =0.04
RR for death by 90 d (95% CI)	1.17 (1.01–1.36); <i>P</i> =0.03	1.06 (0.96–1.18); <i>P</i> =0.26

ICU, intensive care unit; HES, hydroxyethyl starch; CVP, central venous pressure; RR, relative risk; RRT, renal replacement therapy; CI, confidence interval.



**Figure 4. | AKI in 6S (Scandinavian Starch for Severe Sepsis/Septic Shock Trial) and CHEST (Crystalloid versus Hydroxyethyl Starch Trial).** HES, hydroxyethyl starch.

crystalloid (VISEP, 6S) found evidence of renal toxicity, whereas those that compared HES with saline found a mixed signal (CHEST). There are reasons to believe that the carrier/comparator solution matters. It is well known that hyperchloremic solutions, such as 0.9% saline, induce metabolic acidosis (32,33). It is also known that these perturbations can induce inflammation (34) and hemodynamic instability (35) in animal experiments. Because both of these effects might produce or exacerbate AKI, we analyzed a large database containing nearly half a million patients undergoing major open abdominal surgery (36). We compared patients receiving 0.9% saline as the only IV fluid on the day of the procedure to patients receiving only Plasma-Lyte, a balanced crystalloid. We found that patients receiving saline had greater risk of adverse outcomes, including infections, rates of dialysis,

and treatments for acidosis. Recently, Bellomo and colleagues reported a reduced incidence of renal morbidity (RRT and RIFLE criteria I and F) when chloride-rich solutions were replaced with chloride-restrictive solutions in the ICU (37). The mechanisms whereby saline exacerbates AKI are not well understood. Animal studies suggest that high chloride concentrations reduce GFR *via* tubuloglomerular feedback (38). However, preliminary data in an animal model of sepsis suggest saline injures the kidney, as measured by urine neutrophil gelatinase-associated lipocalin levels and histology (unpublished data), and inflammation (plasma IL-6) was increased with saline compared with balanced crystalloid. Collectively, this evidence strongly suggests that the type of crystalloid used for comparison is at least as important as the type of HES examined.



## Risk-to-Benefit Ratio

However, is there any reason to use HES in the first place? The colloid versus crystalloid debate has raged for more than 50 years, without satisfactory resolution. The SAFE (Saline versus Albumin Fluid Evaluation) trial compared albumin with saline for fluid administration in the ICU (39) and found no overall difference between the groups for 28-day survival, ICU or hospital length of stay, days of mechanical ventilation, or days of RRT. In that study, albumin was associated with worsened outcome in patients with traumatic brain injury (40) and improved outcome in septic patients (41). A recent comprehensive Cochrane Collaboration review (42) concluded that randomized controlled trials provide no evidence that resuscitation with colloids, instead of crystalloids, reduces the risk of death in patients with trauma or burns or after surgery. Thus, if colloids offer no advantage over isotonic saline, even without significant safety issues, how can their ongoing use be justified? Although HES is a relatively inexpensive product, it still costs >45 times as much as saline.

Proponents of colloid resuscitation argue that resuscitation efficiency is superior, meaning that effective volume expansion is achieved with smaller volumes. This is not surprising given that the larger molecules in the colloid solutions tend to remain in the vascular space while crystalloids distribute readily across the extracellular fluid space. Indeed, in the SAFE trial, 29% more saline was given in the first 48 hours compared with albumin and total fluid balance during this time period was 1 L greater with saline (2.56 versus 3.5 L) (39). Although these mean differences were small in the SAFE trial, the number of patients receiving large-volume resuscitation was also small. Evidence from patients with acute lung injury suggests that more fluids result in longer duration of mechanical ventilation (43), and observational data from patients with AKI suggest that fluid overload is associated with reduced survival (44).

## Conclusions

The crystalloid-colloid controversy will not end with the 2012 contributions to the IV fluid literature, but the debate has certainly been informed by them. We believe that fluids are drugs and should be accorded the same care and attention when they are prescribed. It is probable that there is a serious—and late—hazard when starch is used as a resuscitation fluid in the ICU, and the ensuing toxicity is also serious: dialysis. This is an important endpoint for all stakeholders, patients in particular. Whether the use of starch outside the ICU has any benefit, perhaps in patients in whom the endothelial glycocalyx is better preserved (in the operating room, for example), is a question that remains to be answered. Until then, we believe that the principle of *primum non nocere* requires us to advocate for the use of crystalloid solutions in the ICU because there is no clear benefit from the use of colloids, but apparently there is plenty of evidence of harm.

## Disclosures

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