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Making a pragmatic choice for fluid resuscitation in the critically ill

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One of the oldest debates in medicine is whether patients with hypovolemic shock should be resuscitated with colloids (e.g., albumin or hydroxy ethyl starches (HES)) or crystalloids (e.g., normal saline or Ringer's lactate). Despite thousands of patients enrolled in trials of alternative fluid strategies, consensus remains elusive and practice is widely variable.¹ The argument for colloids is that, because they rely on oncotic pressure gradients created by their suspensions of large molecular weight protein or starch, they selectively expand the intravascular space.² In contrast, crystalloids, which rely on the osmotic gradients of their solutes, equilibrate more rapidly across intra and extravascular spaces. Thus, to achieve similar restoration of blood volume, more volume of crystalloid may be necessary, with unwanted excess edema.³ However, shock states, such as sepsis, induce endothelial leak with extravasation of protein and other large molecules,⁴ which undermines the theoretical advantage of colloids. Furthermore, colloids are considerably more expensive; human-derived colloids, such as albumin, carry theoretical risks of infection; and the large molecule proteins and starches may have unwanted immunogenic effects.³ Some starches also appear to cause renal injury.⁵

The debate increased considerably in 1998 when the Cochrane collaboration published a meta-analysis suggesting albumin not only offered no benefit, but appeared to increase mortality.⁶ The study was accompanied by a provocative editorial and stimulated passionate responses in both the lay and medical press.^{7, 8} One key concern was that the literature upon which the meta-analysis was based consisted predominantly of studies that were not relevant, too old, very small, or of poor quality.^{8, 9} This finding prompted the launch of several much larger and higher quality trials, including the SAFE, VISEP, 6S, CHEST and CRYSTAL trials. SAFE randomized nearly 7,000 general ICU patients in Australian and New Zealand to albumin or normal saline and found no differences in mortality or any secondary outcomes.¹⁰ VISEP randomized 537 patients with severe sepsis to 10%

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pentastarch or Ringer's lactate, and found the starch worsened renal outcomes and possibly increased mortality.¹¹ The 6S trial randomized 804 patients with severe sepsis in 26 Scandinavian ICUs to 6% HES versus Ringer's acetate and reported that HES increased 90-day mortality and increased the incidence of renal injury.¹² The CHEST trial, also from Australia and New Zealand, randomized 7000 general ICU patients to HES or normal saline and found a higher incidence of renal replacement therapy with HES but no difference in mortality.¹³

The fifth trial, the CRYSTAL study, is reported by Annane et al. in this issue of *JAMA*.^(ref) CRYSTAL was a pragmatic trial, comparing crystalloids to colloids for adults in acute hypovolemic shock in 57 ICUs across three continents. Randomization was stratified by site and by diagnosis (i.e., hypovolemic shock due to trauma, sepsis, or other causes). The study was designed to detect a 5% absolute difference in mortality at 28 days but was terminated based on a predefined stopping rule after 2,857 of the planned 3,010 patients had been enrolled. Patients managed with colloids received significantly less fluid than those treated with crystalloids. Nevertheless, mortality did not differ at 28 days, (359/1414 (25.4%) deaths among the colloid-treated patients and 390/1443 (27.0%) deaths among the crystalloid-treated patients) although the colloid group had more days free of vasopressors and mechanical ventilation at 7 and 28 days and had a significantly lower mortality at 90 days (30.7% vs 34.2%). Other secondary outcomes, including measures of renal function, did not differ and there were no significant treatment-by-strata effects.

There are some notable features to the design and execution of this trial. The authors targeted patients freshly admitted to the ICU as soon as resuscitation was required. They also then continued treatment assignment throughout the ICU. For these reasons, the authors considered that use of blinded study fluids would be impractical. Instead, clinicians could use available crystalloids or colloids, depending on the randomization. Compliance was monitored by hospital pharmacists and appeared to have been generally excellent, although there were some allowable crossover indications, such as use of albumin for documented hypoalbuminemia. The consequence of these decisions was that the entire period of ICU fluid management was nicely separated into crystalloids or colloids. However, the study only compared the two classes of fluids, and not any specific agent. Also, lack of blinding leaves the study open to potential bias.

The apparent benefit of colloids at 90 days should be interpreted with caution. Other large trials of ICU interventions have similarly shown no difference at 28 days but significant differences at 90 days.^{11, 14} A possible explanation is that patients who do poorly are sustained on life support for several weeks before the clinical team decides further care is futile, leading to delayed separation in survival curves. However, in this instance, 90-day mortality was a secondary outcome, and the confidence intervals approach 1.0. Thus, the findings support the notion that colloids do not worsen outcome, but any conclusion that these fluids improve mortality would require validation.

So where do things stand? The five large contemporary trials all have differences in design and results. Although all were based in the ICU, they differed with regard to whether patients were general ICU patients, specifically in shock at the time of enrollment, or

specifically having severe sepsis. All but CRYSTAL were blinded and tested a specific colloid versus a specific crystalloid, but no two trials tested the same combination. The trials testing HES failed to find benefit and raised concern about renal injury and possible increased mortality.^{5, 11-13} It is less obvious from these studies that albumin is harmful, except perhaps in specific groups such as those with traumatic brain injury.¹⁵ Two other not yet reported studies of albumin in septic shock may help clarify this issue (NCT0070712; NCT00327704).¹⁶ In the meantime, until further studies confirm the possible benefits of colloids reported in CRYSTAL, it seems reasonable to choose the less expensive crystalloids as first line treatment for shock, as advocated in recent guidelines.¹⁷

Nevertheless, the debate does not appear to be over. Despite several large well-designed trials, the issue is still left with some divergent results in clinically important outcomes. These studies do, however, inform the next steps for future research. First, the CRYSTAL investigators demonstrated it was possible to randomize at the onset of resuscitation in the ICU. However, it would be desirable in future studies to move randomization up to the point where the first fluids, perhaps in the emergency department or even in the ambulance, are administered, assuming appropriate human subjects protection. Second, if mortality is the primary outcome, it probably should be determined later than 28 days, ideally at 60 or 90 days. Third, depending on the results of the two other albumin trials, there may still be a need to determine in one more study whether colloids offer an advantage in hypovolemic shock. Fourth, none of the published trials addressed whether the chloride content of the fluid interventions could have influenced results. Given recent concern of potential harm from chloride overload during resuscitation,¹⁸ it would be reasonable to either study chloride-poor solutions or otherwise adjust for potential confounding by chloride load.

Finally, the choice of fluids is not, in fact, a binary choice easily tested by a two-group comparative trial, and there may be no definitive answer to the question of whether patients with hypovolemic shock should preferentially receive colloids or crystalloids. Rather, there are a number of complexities, including the type of shock requiring resuscitation, the resuscitation targets, and the use of adjunctive vasoactive therapies. In addition, any given fluid choice could have both beneficial and harmful effects, with trade-offs that vary depending on the other complexities listed above. Thus, perhaps the most important message from the latest round of trials is that simply performing larger 2-group trials with greater rigor will not bring the field to consensus. Instead, more complex study designs should be considered, perhaps with multiple study interventions and use of adaptive trial design methods such as response-adaptive-randomization,¹⁹ to better capture the complexity of modern resuscitation options.

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