

Fluid resuscitation in severe sepsis and septic shock: An evidence-based review

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Objective: In 2003, critical care and infectious disease experts representing 11 international organizations developed management guidelines for fluid resuscitation in severe sepsis and septic shock that would be of practical use for the bedside clinician, under the auspices of the Surviving Sepsis Campaign, an international effort to increase awareness and improve outcome in severe sepsis.

Design: The process included a modified Delphi method, a consensus conference, several subsequent smaller meetings of subgroups and key individuals, teleconferences, and electronic-based discussion among subgroups and among the entire committee.

Methods: The modified Delphi methodology used for grading

recommendations built on a 2001 publication sponsored by the International Sepsis Forum. We undertook a systematic review of the literature graded along five levels to create recommendation grades from A to E, with A being the highest grade. Pediatric considerations to contrast adult and pediatric management are in the article by Parker et al. on p. S591.

Conclusion: Fluid resuscitation of severe sepsis may consist of natural or artificial colloids or crystalloids. Fluid challenge should be administered and repeated based on response (increase in blood pressure and urine output) and tolerance (evidence of intravascular volume overload). (Crit Care Med 2004; 32[Suppl.]:S451–S454)

Septic shock can be associated with both absolute and relative hypovolemia. Large fluid deficits can exist as a consequence of external (e.g., diarrhea, sweating) or internal (e.g., edema, peritonitis) losses. Relative hypovolemia in sepsis is related to the maldistributive defect with vasodilation and peripheral blood pooling. Hypovolemia can lead to reduced circulating blood volume, diminished venous return, and in severe cases, arterial hypotension. Hypovolemia may also contribute to microcirculatory compromise, leading to organ dysfunction and, ultimately, multiple organ failure. Adequate fluid resuscitation is, therefore, one of the keystones in the management of shock, the aims being to preserve intravascular fluid volume, restore effective tissue perfusion, and reestablish and maintain a balance between tissue oxygen demand and supply. Volume repletion in patients with septic shock produces significant increases in cardiac output and systemic oxygen delivery (1, 2), and although vasopressor agents are common adjuncts to fluid resuscitation, fluids

alone are sometimes sufficient to reverse hypotension and restore hemodynamic stability (3).

At initial glance, fluid resuscitation in shock may seem rather straightforward. After all, what can be so difficult about giving fluids? However, in medicine, things are never as simple as they first appear. Optimal fluid resuscitation remains a matter of hot debate, particularly in recent years with controversy and debate surrounding the use of albumin and red blood cell transfusions. The end points of fluid resuscitation also remain unclear. Nevertheless, review of the literature enables some recommendations to be established, and these are graded below according to the strength of the available evidence.

Question: Should colloid solutions be used in preference to crystalloids in the initial resuscitation from septic shock?

Uncertain; Grade C

Recommendation: Fluid resuscitation may consist of natural or artificial colloids or crystalloids. There is no evidence-based support for one type of fluid over another.

Grade C

Rationale: Patients with septic shock can be successfully resuscitated with crystalloids and colloids: the choice of fluid is

probably less important than the quantity given, with cardiac output and systemic oxygen delivery increasing in proportion to the degree of intravascular volume expansion achieved.

There has been long-standing debate regarding the negative and positive effects of crystalloid vs. colloid fluids in the resuscitation from septic shock. The two groups of fluids are largely indistinguishable in terms of their effects on preload recruitable stroke volume and oxygen delivery, and patients with septic shock can be successfully resuscitated with crystalloid or colloid, although the choice of fluid remains controversial. Colloids are usually preferred in Europe, and crystalloids are more widely used in North America. When crystalloids and colloids are titrated to the same level of filling pressure, they restore tissue perfusion to the same degree (4), but because of their propensity for leakage into the extravascular space, to achieve the same effect, approximately three times more volume of crystalloid is required than colloid, and slightly longer infusion periods may be necessary to achieve comparable hemodynamic end points. Of note, colloid solutions are much more expensive than crystalloid solutions, even when taking into account the reduced volumes required.

Crystalloids are generally regarded as first-line fluids for the hemodynamically

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stable patient, and in the typical scenario, colloids are administered in addition to rather than in lieu of crystalloids. However, when the patient is hemodynamically compromised, many clinicians prefer colloids. There are few data supporting these choices. A systematic review by Choi et al. (5) of studies comparing crystalloids and colloids in adult patients requiring fluid administration found just 17 relevant studies, and only three of these included critically ill patients. Overall, no differences were found in length of stay, pulmonary edema, or mortality among patients treated with crystalloids or colloids. In a Cochrane review, Alderson et al. (6) focused their end points on mortality and reported no differences in survival between crystalloid and colloid resuscitation. However, in a systematic review including 19 randomized controlled trials, Schierhout and Roberts (7) reported an increased mortality in patients given colloids vs. those given crystalloids. None of the studies included in these meta-analyses specifically focused on patients with septic shock.

The choice of crystalloid or colloid may be influenced by their effects on various variables, including coagulation and renal function, although further study is needed to clarify the importance of these on outcome. Crystalloid solutions have been associated with hypercoagulability, whereas colloids like hydroxyethyl starches were described to exert rather inhibitory effects on plasmatic coagulation and platelet aggregation (8–10). Third-generation hydroxyethyl starches, however, probably cause fewer effects on coagulation (11), of particular importance in the surgical/trauma patient. Effects on renal function may also be important. In a randomized, controlled study of 129 patients with severe sepsis or septic shock (12), 6% hydroxyethyl starch (200 kDa, 0.60–0.66 substitution) administration was associated with higher frequencies of acute renal failure and oliguria and higher serum creatinine concentrations than gelatin administration. Another area of keen interest is the regional effect of fluids on tissue oxygenation. In septic hypovolemic patients, Asfar et al. (13) reported that gelatin increased intramucosal pH, whereas intramucosal pH decreased slightly in patients treated with hydroxyethyl starches. In patients undergoing major abdominal surgery, Lang et al. (14) noted that a third-generation hydroxyethyl starch improved tissue oxygenation compared to saline solution. Clearly, the decision is

not only between colloid and crystalloid, but within groups, which colloid and which crystalloid. Further studies comparing specific fluids in precisely defined groups or patients are needed before evidence-based guidelines can be issued recommending one fluid over another.

Question: Is fluid challenge recommended for suspected hypovolemia?

Yes; Grade E

Recommendation: Fluid challenge in patients with suspected hypovolemia (suspected inadequate arterial circulation) may be given at a rate of 500–1000 mL of crystalloids or 300–500 mL of colloids over 30 mins and repeated based on response (increase in blood pressure and urine output) and tolerance (evidence of intravascular volume overload).

Grade E

Rationale: Fluid challenge must be clearly separated from an increase in maintenance fluid administration. Fluid challenge is a term used to describe the initial volume expansion period in which the response of the patient to fluid administration is carefully evaluated. During this process, large amounts of fluids may be administered over a short period of time under close monitoring to evaluate the patient's response and avoid the development of pulmonary edema. The degree of intravascular volume deficit in patients with severe sepsis varies. With vasodilation and ongoing capillary leak, most patients require continuous aggressive fluid resuscitation during the first 24 hrs of management. Input is typically much greater than output, and input/output ratio is of no utility to judge fluid resuscitation needs during this time period.

Question: Should we use human albumin in resuscitation from septic shock?

Uncertain; Grade C

Recommendation: Until further study results are available, human albumin may be used when considered appropriate, notably in hypoalbuminemic patients.

Grade C

Rationale: Hypoalbuminemia is a relatively common finding in critically ill patients for various reasons, including malnutrition, liver dysfunction, gastrointestinal losses, and leaky capillaries. Hypoalbuminemia is associated with increased mortality rates

and prolonged intensive care unit and hospital stays (15, 16). Albumin has been used as a resuscitation fluid since the early 1940s, and it is only in recent years that its place has been questioned, notably following a meta-analysis published in 1998 that included 30 trials and 1,419 critically ill patients (17). The authors noted an overall increase in mortality in patients treated with albumin and concluded, dramatically, that for every 17 critically ill patients treated with albumin, there is one additional death. This meta-analysis has been criticized largely for its selection criteria and its assessment of trial methodologic quality, and a second, larger meta-analysis including 42 trials could not confirm the findings, even suggesting a reduced mortality when assessing only trials of higher methodologic quality (18). Meta-analyses, by their nature, include heterogeneous patient groups, and it is difficult to apply their results to everyday clinical practice and individual patients. A meta-analysis has suggested that albumin is beneficial in critically ill patients with hypoalbuminemia (16), and in patients with acute lung injury and hypoproteinemia, albumin plus furosemide improved fluid balance, oxygenation, and hemodynamic variables (19).

Randomized clinical trials are urgently needed in specific patient groups to define whether albumin has a place as a resuscitation fluid and, if so, in which patients it should be employed. A prospective, controlled, randomized, double-blind study comparing 4% human albumin solution with 0.9% sodium chloride (saline) in critically ill patients requiring fluid resuscitation (the Saline vs. Albumin Fluid Evaluation (SAFE) study) has recently been completed, having enrolled 7,000 patients. The results of this study showed identical mortality rate in patients receiving albumin or 0.9% sodium chloride. Subgroup analysis revealed that albumin may have some (albeit not statistically significant) benefit in patients with severe sepsis (20).

Question: Can one offer a general recommendation for a minimum hemoglobin concentration regardless of resuscitation status in septic shock?

Uncertain; Grade C

Recommendation: Critically ill patients can tolerate lower hemoglobin levels than previously appreciated, but anemia is associated with increased mortality. The transfusion needs for each individual patient must be assessed according to

their clinical status and to underlying and concomitant disease processes. During initial resuscitation, early goal-directed resuscitation may guide the hemoglobin target.

Grade C

Rationale: The optimal hemoglobin and hematocrit for patients with septic shock is unclear, and recent years have seen several changes in attitudes toward blood transfusions in critically ill patients. First, optimal transfusion triggers have been rethought, with studies suggesting that with the possible exception of patients with acute myocardial disease (21), patients can tolerate and may even benefit from hemoglobin levels lower than the traditional 10 g/dL (22). Anemia in critically ill patients is associated with a worse outcome, but blood transfusions have also been associated with increased mortality (23), and the challenge is to decide who should receive a transfusion and when. Interestingly, recent epidemiologic evidence suggests that red blood cell transfusions may no longer be associated with increased mortality. This apparent change may be related to the widespread introduction of leuko-reduction in recent years. The use of leuko-reduced blood has been associated with fewer infectious complications, and in a retrospective, before/after cohort study, Hebert et al. (24) showed that leuko-reduction was associated with reduced mortality rates. In light of these findings, a randomized, controlled trial reassessing transfusion triggers in septic patients is perhaps warranted.

General Recommendations to Assess End Points of Fluid Resuscitation

Precise end points for fluid resuscitation have not been defined, largely because of problems in monitoring the regional microcirculation and oxygenation, and changes may persist at a local level while systemic hemodynamic and oxygenation variables seem to have stabilized. Various end-point variables have been suggested and include blood lactate levels and mixed venous oxygen saturation ($\text{S}\bar{\text{V}}\text{O}_2$), but each end point must be considered in its context, and the combination of clinical variables (mean arterial pressure, urine flow, skin perfusion, level of consciousness) with blood lactate levels is most useful.

$\text{S}\bar{\text{V}}\text{O}_2$ can be measured in patients with a Swan-Ganz catheter in place. $\text{S}\bar{\text{V}}\text{O}_2$ is dependent on cardiac output, oxygen demand, hemoglobin, and arterial oxygen saturation. The normal $\text{S}\bar{\text{V}}\text{O}_2$ is 70% to 75% in critically ill patients, but it can be elevated in septic patients due to maldistribution of blood flow. Nevertheless, it is useful to measure $\text{S}\bar{\text{V}}\text{O}_2$ because if cardiac output becomes inadequate, $\text{S}\bar{\text{V}}\text{O}_2$ will decrease. Importantly, a normal or high $\text{S}\bar{\text{V}}\text{O}_2$ does not necessarily indicate adequate tissue oxygenation, and a low $\text{S}\bar{\text{V}}\text{O}_2$ should prompt rapid intervention to increase oxygen delivery to the tissues.

Hyperlactatemia (>2 mEq/L) is typically present in patients with septic shock and may be secondary to anaerobic metabolism due to hypoperfusion. However, the interpretation of blood lactate levels in septic patients is not always straightforward. A number of studies have suggested that elevated lactate levels may result from cellular metabolic failure in sepsis rather than from global hypoperfusion. Elevated lactate levels can also result from decreased clearance by the liver. Nevertheless, the prognostic value of raised blood lactate levels has been well established in septic shock patients (25), particularly if the high levels persist (26, 27). In addition, blood lactate levels have been shown to have greater prognostic value than oxygen-derived variables (28).

The usefulness of goal-directed therapy in heterogeneous groups of critically ill patients has not been demonstrated (29, 30). However, Rivers et al. (31) evaluated the effects of early goal-directed therapy in patients with severe sepsis and septic shock vs. standard therapy. In-hospital mortality was 30.5% in the group assigned to early goal-directed therapy, compared with 46.5% in the standard therapy group ($p = .009$). This study used restoration of a central venous oxygen saturation of $>70\%$ as one of its goals, and this was met in 95% of the early goal-directed group, compared with just 60% of the standard treatment group ($p < .001$). Patients in the early goal-directed treatment groups received more fluids (5 vs. 3.5 L, $p < .001$) and more were given red cell transfusions (64 vs. 18.5%, $p < .001$) in the first 6 hrs than in the standard treatment group (31), emphasizing the importance of early and adequate fluid resuscitation in patients with severe sepsis.

Fluid resuscitation should be commenced as early as possible in the course of septic shock (even before intensive

care unit admission). Requirements for fluid infusion are not easily determined so that repeated fluid challenges should be performed. Fluid challenges require the definition of four components: 1) the type of fluid to be administered (e.g., natural or artificial colloids, crystalloids), 2) the rate of fluid infusion (e.g., 500–1000 mL over 30 mins), 3) the end points (e.g., mean arterial pressure of >70 mm Hg, heart rate of <110 beats/min), and 4) the safety limits (e.g., central venous pressure of ~ 15 mm Hg).

Patients should be carefully observed for evidence of pulmonary and systemic edema during fluid resuscitation. Central venous pressure (central venous pressure) is initially required to evaluate the complex relation between intravascular blood volume and cardiac function. When central venous pressure increases, a pulmonary artery catheter is probably required, although the role of the pulmonary artery catheter has been debated (32). Central venous oxygen saturation measurements may provide useful information when a pulmonary artery catheter has not or cannot be inserted.

In conclusion, fluid resuscitation in septic shock is beset with controversy. Which fluid, which end points, and when to transfuse, all are questions for which there are no adequate answers and few available data. What is certain is that early and adequate fluid resuscitation improves outcomes. Further randomized, clinical trials are urgently needed to better clarify the optimal fluid resuscitation of the patient with septic shock.

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