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Clinical controversies in the management of critically ill patients with severe sepsis

Resuscitation fluids and glucose control

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Abbreviations: ANZICS CTG, Australian and New Zealand Intensive Care Society Clinical Trials Group; CHEST, Crystalloid versus Hydroxyethyl Starch trial; COIITSS, corticosteroid treatment and intensive insulin therapy for septic shock; DIGAMI, diabetes mellitus insulin glucose infusion in acute myocardial infarction; EGDT, early goal directed therapy; HES, hydroxyethyl starch; ICU, intensive care unit; NICE SUGAR, Normoglycemia in Intensive CarE and Survival Using Glucose AlgoRithm Trial; OR, odds ratio; RR, relative risk; SAFE, Saline versus Albumin Fluid Evaluation (study); SAFE TRIPS, Saline versus Albumin Fluid Evaluation Translation of Research into Practice study; SSC, Surviving Sepsis Campaign; VISEP, Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis study; 6S, Scandinavian Starch for Severe Sepsis/Septic Shock trial; 95% CI, 95% confidence interval

Severe sepsis with multiple organ dysfunction remains the most common cause of death for patients treated in intensive care units. As there is no specific treatment for severe sepsis, current management consists of antibiotics, source control and the use of supportive therapies to sustain life while waiting for the adverse effects of sepsis-induced organ dysfunction to subside. Despite the central role of supportive therapies, few have been subjected to rigorous evaluation; two exceptions are the choice of resuscitation fluid and intensity of glucose control. Current data support the use of a crystalloid fluid with the addition of albumin when needed for fluid resuscitation. Administration of hydroxyethyl starch is harmful and should be avoided. Stress hyperglycemia should be treated when blood glucose concentration exceeds 180 mg/dL (10.0 mmol/L) and when insulin therapy is needed it should be targeted to a blood glucose concentration of 144–180 mg/dL (8–10 mmol/L).

Introduction

Severe sepsis with multiple organ dysfunction remains a major killer and, outside units treating patients with traumatic brain injury, the most common cause of death for patients treated in intensive care units (ICUs). The case fatality rate for patients with severe sepsis has decreased in recent years but an increasing incidence and an aging population means that the burden of disease from severe sepsis will continue to increase in both developed and developing countries. Despite decades of investigation and the expenditure of billions of dollars, there is no specific treatment that is effective in the management of patients with severe sepsis. As a result treatment consists of antibiotics, source control and the use of supportive treatments to sustain life while waiting for antibiotics to work and the effects of sepsis-induced organ dysfunction to subside. Despite the central role of supportive therapies, few have been subjected to rigorous evaluation. In recent years the advent of national and international clinical trials groups working individually and together has resulted in the conduct of large scale investigator-initiated clinical trials that are now producing more robust data to guide the management of critical ill patients including those with severe sepsis. This article will address two areas that have been the subject of intense investigation, namely choice of resuscitation fluid and intensity of glucose control in the Intensive Care Unit.

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Fluid Resuscitation

Fluid resuscitation has long been and remains first line treatment in the management of patients with severe sepsis and septic shock. In 2004 the Surviving Sepsis Campaign (SSC), a collaboration of a broad section of sponsoring organizations involved in the investigation and treatment of patients with severe sepsis and septic shock, published guidelines for the management of such patients.[1] The first recommendation was that resuscitation of a patient with severe sepsis or sepsis induced hypoperfusion should begin as soon as the syndrome was recognized with recommendations to maintain central venous pressure, mean arterial pressure, urine output, and central venous oxygen saturation. The acute resuscitation algorithm was based on a trial of Early Goal Directed Therapy (EGDT) and the first step in the algorithm was the administration of intravenous fluid to support intravascular volume.[2] However, neither the SSC guideline nor the EGDT trial offered any advice on the choice of fluid merely stating that the resuscitation fluid should be natural or artificial

colloids or crystalloid solutions and that there was no evidence-based support for one type of fluid over another.[1]

Albumin for resuscitation of patients with severe sepsis

At the time the Surviving Sepsis Campaign was publishing its guidelines the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG) was publishing the Saline vs. Albumin Fluid Evaluation (SAFE) study.[3] The SAFE study was the first "mega-trial" conducted in critical care;[4] it randomized 6997 patients to fluid resuscitation with either 4% albumin or 0.9% saline. The primary outcome measure for the study was all-cause mortality 28 d after randomization. Although the SAFE study included a broad range of patients who required fluid resuscitation in the Intensive Care Unit, one of the three pre-defined subgroups was patients with severe sepsis. The SAFE study enrolled 1218 patients who had severe sepsis at baseline; 603 of these were randomly assigned to receive albumin and 615 to receive saline.

In patients with severe sepsis the mortality rate in those who received albumin was 30.7%, compared with a mortality rate of 35.3% of those who received saline. The relative risk (RR) for those assigned to receive albumin compared with saline of 0.87 (95% confidence interval [CI] 0.74–1.02), $P = 0.09$.[3]

The subgroup analysis comparing the relative risk of death for patients assigned albumin as opposed to saline for patients with or without severe sepsis yielded a P value for the test of common relative risk of 0.06. This analysis provided support for the hypothesis that while albumin and saline were equivalent in the overall ICU population, patients with severe sepsis might respond differently and benefit from being resuscitated with albumin. This suggestion was supported by the later publication of a more detailed analysis of the SAFE study data.[5] However, as with all sub group analysis within large clinical trials, even if significant these results would best be viewed as hypothesis generating. Interestingly, in the patients with severe sepsis the estimate of the treatment effect was similar in patients whose baseline serum albumin concentration was 25 g/L or less and in those whose baseline serum albumin concentration was more than 25 g/L (OR for albumin vs. saline 0.74, 95% CI 0.0.50–1.10 vs. OR 0.79, 95% CI 0.57–1.11 respectively; P value for heterogeneity = 0.80). Thus resuscitation with albumin may be preferred to resuscitation with saline in patients with severe sepsis but the effect does not appear to be dependent on the serum albumin concentration.[5]

Whether albumin offers a benefit over crystalloid remains to be clarified. A recent metaanalysis examined the effect of albumin-containing solutions compared with other solutions for fluid resuscitation of patients with sepsis and concluded that use of albumin-containing solutions was associated with lower mortality.[6] However, the result of the metaanalysis was quite dependent on pilot studies conducted in children with severe malaria in Africa.[7,8] Subsequently a large phase III trial randomly assigned 2141 African children with severe febrile illness and impaired perfusion to resuscitation with albumin boluses or saline boluses or no boluses at all.[9] Despite operating in challenging and resource-poor environments the trial was conducted to the highest standards and produced surprising results. There was no difference in the main outcomes between children assigned to receive albumin or those assigned to saline, but children assigned to receive no fluid boluses had decreased mortality at both 48 h and 4 weeks compared with both the albumin and saline groups. At four weeks mortality was 12.2%, 12.0%, and 8.7% for the albumin-bolus, saline-bolus, and control groups, respectively; $P = 0.004$ for a comparison between the bolus and no bolus groups. Also interesting and as yet unexplained is a subsequent analysis reporting that the increased mortality in children who received boluses was as a result of cardiovascular collapse despite evidence that boluses produced earlier signs of shock reversal.[10] The external validity of these results remains hotly debated as the children in the trial could not be supported with mechanical ventilation, inotropic agents, or vasopressors as would occur in developed world ICUs.

Consequently, the whether resuscitation with albumin is beneficial in patient with severe sepsis remains to be clarified and further data are awaited. Two studies conducted in Europe remains to be reported in full, they are the Early Albumin Resuscitation During Septic Shock study conducted in France,[11] and Volume Replacement with Albumin in Severe Sepsis conducted in Italy.[12] The full results of these trials will shed further light on this controversy.

Hydroxyethylstarch (HES) for resuscitation of patients with severe sepsis

In 2008 the Surviving Sepsis Campaign published a second iteration of the International Guidelines for the Management of Severe Sepsis and Septic Shock.[13] They again highlighted the importance of early fluid resuscitation and recommended the administration of either crystalloid or colloid fluid for resuscitation. Once again the publication of the guidelines coincided with a high-profile publication that would question the assumption that all fluids could be considered equal in the resuscitation of patients with severe sepsis. The trial in question was the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) Study by the German Competence Network for Sepsis (SepNet).[14] The trial was a 2 × 2 factorial trial, one arm of which compared outcomes of patients with severe sepsis resuscitated with 10% Pentastarch (HES) vs. those resuscitated with a crystalloid; in the VISEP study the crystalloid was modified ringers lactate. HES is a widely used resuscitation fluid, particularly in Europe.[15] HES is manufactured from amylopectin, a highly branched starch, obtained from maize or potatoes. Different formulations of HES are characterized by their molecular weight and degree of molar substitution of hydroxyl groups with hydroxyethyl groups. A higher molecular weight and higher molar substitution decrease hydrolysis by serum amylases and so lead to increased intravascular persistence and therefore more prolonged plasma volume expansion. However, these properties have been linked to increased toxicity although this claim, which has been framed mainly to suggest that more recent formulations with lower molecular weight and lower molar substitution are safer, has been disputed.[16]

The VISEP study used HES 200/0.5 (a third generation HES with an average molecular weight of 200 kDa and degree of hydroxy ethyl substitution of 0.5). Although patients assigned

Table 1. Relative risk of death for patients with severe sepsis randomly assigned to receive colloid versus crystalloid in blinded randomized controlled trials

Study name	*N*	Colloid	Crystalloid	Relative risk (RR) of death	95% CI for RR
		Albumin	*Normal saline*		
SAFE	1218	185/603 (30.7%)	217/615 (35.3%)	0.87	0.74–1.02
		HES 200/0.5	*Modified ringers*		
VISEP	535	107/261	93/274	1.21	0.97–1.50
		HES 130/0.42	*Ringers acetate*		
6S	798	201/398	172/400	1.17	1.01–1.36
		HES 130/0.4	*Normal saline*		
CRYSTMAS[23]	196	40/100 (40.0%)	32/96 (33.3%)	1.20	0.83–1.74
CHEST	1921	248/976	224/945	1.07	0.92–1.25

to HES had more rapid normalization of central venous pressure, a planned interim analysis after the enrolment of 600 patients found significantly higher incidence of renal failure among patients assigned to receive HES; 31.0% (95% CI 25.4–36.7) vs. 18.8% (14.1–23.4%) $P = 0.001$. Mortality was also increased in those assigned to HES but not significantly so ($P = 0.09$). As a result the trial was suspended by the Data and Safety Monitoring Board and no further patients were enrolled.

Despite these findings and other data suggesting that HES might be harmful in critical ill patients, an international cross sectional study of fluid resuscitation practices in 391 intensive care units (the SAFE TRIPS study) found that colloid solutions were administrated more frequently than were crystalloid solutions and that HES was the most commonly administered colloid solution.[15]

The formulation of HES used in the VISEP study has largely been replaced in clinical practice by HES with a lower average molecular weight and a lower degree of molar substitution, these changes were designed and claimed to reduce the toxic effects of HES. At the time of the SAFE TRIPS study the most commonly used HES was HES 130/0.4, a HES with an average MW of 130 kDa and molar substitution of around 0.4. In order to test whether the newer formulations of HES were safe and efficacious in patients with severe sepsis the Scandinavian Critical Care Trials Group conducted the Scandinavian Starch for Severe Sepsis/Septic Shock (6S) trial.[17] The trial compared HES 130/0.42 in Ringers Acetate with Ringers Acetate for fluid resuscitation of patients with severe sepsis. In the trial 804 patients underwent randomization and 798 were included in a modified intent to treat analysis. At 90 d after randomization 51% of patients assigned to receive HES 130/0.42 had died as compared with 43% assigned to ringers lactate, a relative risk for those assigned hydroxyethylstarch compared with ringers lactate of 1.17 (95% CI 1.01–1.36, $P = 0.03$). Additionally, in the 90 d study period 87 patients assigned to receive HES 130/0.42 were treated with renal replacement therapy compared with 65 patients assigned to receive ringers lactate; RR 1.35, 95% CI 1.01–1.80, ($P = 0.04$). These results supported the results of the VISEP study suggesting that resuscitating patients with severe sepsis with HES compared crystalloid produced harm in the form of acute kidney injury and an increased risk of death.

Further support for the suggestion that resuscitation with HES confers harm has come from the **C**rystalloid vs. **H**ydroxy**E**thyl**S**tarch **T**rial (CHEST) conducted by the ANZICS CTG.[18] This trial randomized 7000 patients being treated in intensive care units in Australia or New Zealand to receive HES 130/0.4 in normal saline or normal saline for fluid resuscitation. Patients were followed to the first of 90 d or death and the study also demonstrated an increase in the use renal replacement therapy in patients assigned to receive HES; 235/3352 patients (7.0%) in those assigned HES and 196/3375 (5.8%) in those assigned saline (RR 1.21; 95% CI, 1.00 to 1.45; $P = 0.04$).[18] Subsequent to the publication of CHEST several metaanalyses have also cautioned against the use of HES in critically ill patients overall,[19,20] and specifically in patients with severe sepsis,[21,22] because of concerns it may increase mortality and strong evidence that it increases the risk of significant kidney injury.

The CRYSTMAS study was a further study that compared administration of HES 130/0.4 and normal saline in patients with severe sepsis.[23] The study recruited 196 patients with severe sepsis from 24 ICUs in France and Germany. The primary outcome reported was the surrogate endpoint of amount of fluid needed to achieve hemodynamic stability, and although the trial had insufficient power to detect important differences in mortality, the crude mortality rate was increased in the patients assigned to receive HES, 40/100 (40.0%) vs. 32/96 (33.3%); RR 1.20, 95% CI 0.83–1.74 (**Table 1**).

As a result of these studies the latest iteration of the Surviving Sepsis Campaign guidelines recommend fluid resuscitation with a crystalloid solution as the initial choice of fluid with consideration of the addition of albumin in patients who continue to require substantial amounts of crystalloid to maintain adequate mean arterial pressure.[24] They further recommend avoiding HES in patients with severe sepsis.

Which crystalloid for patients with severe sepsis?

The most commonly used crystalloid solution in the SAFE TRIPS study was normal saline.[15] Normal saline is 0.9% sodium chloride. It contains 154 mmol/L of sodium and chloride and

while it is close to isotonic with interstitial fluid, it is an acid with a pH of around 5. Rapid administration of large volume of normal saline will produce a dilutional hyperchloremic metabolic acidosis,[25] although whether this is harmful to patients or not is unclear. Concerns about the high chloride content of normal saline has led some clinicians to prefer and recommend so called "balanced salt solutions" as crystalloid alternatives to normal saline. Balance salt solutions contain other anions to reduce the concentration of chloride; they are relatively hypotonic as they have a lower sodium concentration than extracellular fluid. The main anions in extracellular fluid are chloride and bicarbonate but as bicarbonate-containing solutions are unstable in plastic containers balanced salt solutions contain other anions such as acetate, lactate, gluconate, and malate instead of bicarbonate; however, none are truly balanced or physiological.[26] Recent registry studies,[27] and studies using historical controls,[28] have suggested that crystalloid solutions with lower chloride content may be preferable to normal saline. However, there have been no head-to-head trials comparing normal saline to any balanced salt solution in critically ill patients with sufficient statistical power to examine effects on important patient centered endpoints. Given that normal saline remains a widely used fluid, and crystalloid solutions are administered to tens, if not hundreds, of thousands of acutely ill patients each day, this is a major omission from current medical knowledge.

Pending correction of that knowledge gap, the recommendations of the latest surviving sepsis campaign guidelines to use crystalloid fluids as the first line treatment to resuscitate patients with severe sepsis and septic shock, and to add albumin in patients who continue to require large amounts of fluid to maintain mean arterial pressure are eminently reasonable and evidence-based.[24]

Intensity of Glucose Control in Severe Sepsis

Stress hyperglycemia

Hyperglycemia is a common response to any form of acute illness and is highly prevalent in patients with the severe sepsis and indeed in all patients treated in intensive care units.[29-33] In trials of intensive glucose control over 98% of patients in ICUs will have a blood glucose recorded above the upper limit for normal for fasting.[34-36] Stress hyperglycemia results from increased hepatic glucose production, from peripheral insulin resistance, and from the use of treatments common in the ICU such as corticosteroids, sympathomimetic agents, and glucose-containing infusions. Until quite recently stress hyperglycemia was seen as a normal and possibly beneficial physiological response to promote cellular glucose uptake; as a result hyperglycemia was often tolerated and only treated when severe enough to exceed the renal threshold for glucose excretion and produce an osmotic diuresis and hypovolemia.

Evidence in favor of stricter blood glucose control

Evidence that stricter control of blood glucose might improve patients' outcome began to accumulate following the publication of the Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) Trial in 1995.[37] By today's standards the degree of glycemic control targeted in DIGAMI was modest. The goal was to maintain a blood glucose concentration of less than 215 mg/dL (11.9 mmol/L) in the intervention group and allow a higher blood glucose concentration in the control group. Despite these modest goals DIGAMI demonstrated improvements in long-term outcomes in patients with the lower blood glucose target.[37]

Intensive glucose control in critical care

A far more aggressive approach was taken by Van den Berghe et al. who, in 2001, published in a landmark paper reporting a single center study from a surgical intensive care unit in Leuven, Belgium.[35] In that study patients were randomly assigned to blood glucose target of normoglycemia (80–110 mg/dL; 4.4–6.1 mmol/L) or to conventional control. In the conventional control group blood glucose was treated when it exceeded 216 mg/dL (12.0 mmol/L) with a subsequent target of 180–200 mg/dL (10.0–11.1 mmol/L) once insulin therapy had been commenced. The trial reported a 34% relative reduction in the risk of in-hospital deaths in patients assigned to intense glucose control. Although the trial reported remarkable results, a number of commentators voiced methodological concerns,[38] in particular there appeared to be high mortality in both arms of the trial, and as it was a single centered study the external validity was unclear, it was unblinded, and the feeding regimen included administration of 200–300 g per day of intravenous glucose early in the ICU course.[38] Despite these concerns intensive glucose control was recommended in guidelines and adopted by many intensive care units around the world.

Glucose control in patients with severe sepsis

Van den Berghe's trial was conducted in a surgical intensive care unit and the number of patients with severe sepsis the baseline was not reported. However, the authors reported that intensive glucose control reduced episodes of septicemia by 46% and markers of inflammation were less commonly abnormal in the intensive glucose control group ($P \leq 0.02$). Patients who were assigned to intensive glucose control were also less likely to be treated with prolonged courses of antibiotics, an affect attributed to a lower rate of bacteremia in intensive treatment group.[35] This was also linked to a lower mortality rate in patients who did have bacteremia within the intensive glucose control group. Furthermore, excess deaths in the conventionally treated group were almost exclusively due to multiple organ failure with a proven septic focus providing support for the biological rationale that intensive glucose control was able to prevent severe sepsis or to improve recovery from severe sepsis when it did occur.

In 2006 Van den Berghe and colleagues published a near identical trial conducted in the medical ICU in their hospital.[36] The trial used the same targets for blood glucose and the same feeding regimen. In the medical ICU mortality was not significantly reduced by intensive glucose control although intensive glucose control was associated with reduced time to weaning from mechanical ventilation and reduced time to discharge from both the ICU and the hospital; additionally patients treated with intensive glucose control had a reduced incidence of acute kidney injury.

The first trial to specifically examine the effect of intensive glucose control in patients with severe sepsis was the VISEP study conducted in 18 academic tertiary centers in Germany (see

Table 2. Relative risk of death for patients with severe sepsis randomly assigned to intensive or conventional glucose control

Study name	*N*	Intensive glucose control (IGC)	Conventional glucose control (CGC)	Relative risk of death (IGC vs.CGC)	95% CI for RR
Annane (COIITSS)	509	117/255	109/254	1.07	0.88–1.30
Arabi	122	18/55	15/67	1.46	0.81–2.62
Brunkhorst[a]	535	98/247	102/288	1.12	0.90–1.39
NICE-SUGAR	1299	202/673	172/626	1.09	0.92–1.30
Savioli	90	14/45	13/45	1.08	0.57–2.03
Van den Berghe[b]	950	160/479	172/471	0.91	0.77–1.09
Yu	55	4/28	4/27	0.96	0.27–3.47
ALL	3560	613/1782	587/1778	1.04	0.95–1.14

[a]Brunkhorst (VISEP), IIT arm was stopped early so not all patients randomized to IIT vs. CIT. [b]Van den Berghe, patients classified post-hoc to severe sepsis or not.

above).[14] In common with the fluid resuscitation arm of the trial, the glucose control arm of this 2 × 2 factorial study was stopped early for safety reasons. Patients assigned to intensive glucose control suffered a significantly increased risk of severe hypoglycemia, which was considered potentially harmful, and there was no evidence of any beneficial effect and in particular no reduction in mortality at either 28 or 90 d.[14]

As the SSC guidelines recommend that patients with fluid and vasopressor resistant septic shock be treated with corticosteroids, and corticosteroids exacerbate stress hyperglycemia, Annane and colleagues conducted the Corticosteroid Treatment and Intensive Insulin Therapy for Septic Shock (COIITSS) Study to determine whether intensive glucose control would be beneficial in patients who were being treated with hydrocortisone for septic shock.[39] In the study 509 patients with septic shock were randomly assigned in 11 intensive care units in France. Patients treated with intensive glucose control experienced more episodes of severe hypoglycemia and had a marginally but statistically insignificant increase in risk of death.

The disappointing findings of the VISEP and COIITSS studies are consistent with the results of other studies where intensive glucose control has been linked with an increased risk of moderate and severe hypoglycemia,[34,39-42] both of which are positively associated with an increased risk of death,[43,44] without providing any evidence of benefit. Currently the totality of trial evidence suggests that intensive glucose control does not decrease mortality either in critically ill patients overall,[34-36,40-42,45] or in those with severe sepsis,[14,39,45,46] (**Table 2**) or that it reduces infection rates or length of stay.[47]

The largest trial to examine the effects of intensive glucose control in critically ill patients to date is the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE SUGAR) study.[34] This study randomly assigned 6104 critically ill patients from 42 hospitals in Australia, New Zealand, Canada, and the United States to a blood glucose target of either 81–108 mg/dL (4.5–6.0 mmol/L) or less than 180 mg/dL (<10 mmol/L) with insulin being used in the higher range group to maintain blood glucose between 144 and 180 mg/dL (8–10 mmol/L) when needed. The NICE SUGAR study found that patients assigned to intensive glucose control had an increased risk of death at 90 d; (27.5% vs. 24.9%, P = 0.02) Patients with severe sepsis at baseline were identified as a predefined subgroup in the NICE SUGAR study but there was no evidence that patients with severe sepsis responded any differently to intensive glucose control then did other critically ill patients in the trial.[34] Thus current recommendations are that for critically ill patients overall, and for patients with severe sepsis, insulin therapy should be started when blood glucose exceeds 180 mg/dL (10 mmol/L) with the goal of maintaining blood glucose between 144 and 180 mg/dL (8–10 mmol/L) with insulin when necessary.[24,48]

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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