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SPECIAL FEATURE

Re-evaluating Steroid Therapy in Septic Shock

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Dr. Nadler reports no financial relationships relevant to this field of study.

Septic shock carries a significant risk of mortality despite increasing knowledge of its pathophysiology and clinical management. Studies dating back to the 1960s suggested steroid treatment may alter the course of septic shock and led to the concept of critical illness-related corticosteroid insufficiency.[1]

In 2002, Annane et al demonstrated a mortality benefit for patients with septic shock given the combination of hydrocortisone and fludrocortisone, generating interest in this therapy and changing guidelines.[2] However, the 2008 CORTICUS trial demonstrated no mortality benefit and a re-evaluation of this guideline.[3]

Two recent trials, ADRENAL and APROCCHSS, have provided more data regarding steroid therapy for septic shock.[4,5] Comparing these seminal studies provides context for the decision about whether to treat septic shock with steroid therapy.

PAST AND CURRENT STUDIES

Annane et al published results from a placebo-controlled, randomized, double-blind trial of 299 patients with septic shock.[2] The authors enrolled adult patients with documented or strong suspicion of infection, alterations in body temperature, tachycardia, systolic blood pressure < 90 mmHg for one hour despite fluid administration, and vasopressors with organ dysfunction defined by low urine output, elevated arterial lactate, or need for mechanical ventilation. Patients were excluded if they presented with acute myocardial infarction, pulmonary embolism, advanced cancer, AIDS, or contraindications to or pre-existing indications for steroid therapy. Participants were stratified further by a 250 mcg tetracosactrin stimulation test as responders or non-responders. The intervention group received hydrocortisone 50 mg intravenously every six hours and enteral fludrocortisone 50 mcg daily for seven days. Regarding the primary endpoint, 28-day mortality in non-responders was significantly lower in the

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steroid group (53%) than in the placebo group (63%), with an odds ratio (OR) of 0.54 (95% confidence interval [CI] 0.31-0.97; $P = 0.04$).

In all patients, the OR for 28-day survival was 0.65 (95% CI, 0.39-1.01; $P = 0.09$) in the steroid vs. placebo groups. The non-responders also demonstrated both decreased ICU mortality and hospital mortality when given steroids. Time to vasopressor therapy withdrawal with steroid therapy was shorter in both the non-responder group (7 days vs. 10 days; $P = 0.001$) and the overall patient population (7 days vs. 9 days; $P = 0.01$). No adverse events were ascribed to steroid replacement therapy. Specifically, there were no increased rates of infections, bleeding, or delirium.

The authors of the CORTICUS study, published in 2008, enrolled 499 patients with sepsis and examined the response to 50 mg of hydrocortisone intravenously every six hours.[3] The inclusion criteria included evidence of infection, the systemic response to infection, and onset of shock within 72 hours. Exclusion criteria included poor prognosis and recent steroid use. All patients underwent a cosyntropin stimulation trial. The primary endpoint was 28-day mortality in non-responders. Notably, power calculation of this trial cited a sample size of 800 patients to achieve a statistical power of 80% to detect a 10% decrease in absolute mortality, assuming 50% mortality.

This trial demonstrated no difference in mortality with hydrocortisone compared with placebo in non-responders (39.2% vs. 36.1%; $P = 0.69$) or all patients (34.3% vs. 31.5%; $P = 0.51$). There was no difference in ICU mortality, death during hospitalization, death at one year, or length of stay. Oddly, time to reversal of shock with steroids was statistically lower in those patients who responded to cosyntropin (2.8 days vs. 5.8 days; $P < 0.001$) and all patients (3.3 days vs. 5.8 days; $P < 0.001$), but not in non-responders (3.9 days vs. 6.0 days; $P = 0.06$).

The authors of the HYPRESS trial, published in 2016, further evaluated the effect of hydrocortisone alone in patients with severe sepsis.[6] The inclusion criteria for this trial included evidence of infection with a systemic response, organ dysfunction not present for more than 48 hours, but excluded patients with septic shock, defined by persistent hypotension despite fluids and vasopressors. The study population received hydrocortisone 50 mg bolus followed by a continuous infusion of 200 mg per day for five days with tapering over the next six days. The primary endpoint was the occurrence of septic shock within 14 days. Power calculation in this study planned an 80% chance to detect a 15% difference, assuming a rate of septic shock in the study population of 40% with 380 total patients.

Of the 353 patients who were included in the intention-to-treat analysis, the rates of septic shock at 14 days in the placebo and study group were very similar (22.9% and 21.2%, respectively; $P = 0.70$). No significant differences were noted in many secondary endpoints, although the rates of delirium were lower in the hydrocortisone group. The rate of hyperglycemia was significantly higher with steroid administration. Another notable difference was the relatively higher proportion of patients with pneumonia and respiratory tract infections in the placebo group compared with the study group.

Most recently, the authors of two additional studies (ADRENAL and APROCCHSS) examined the response of patients with sepsis to steroids.[4,5] ADRENAL investigators randomized adult patients on mechanical ventilation with suspicion of infection, two or more systemic inflammatory response syndrome (SIRS) criteria, and the need for vasopressors or inotropes for at least four hours. Patients who received etomidate, exhibited other indications for steroids, or were expected to die within 90 days were excluded. The study compared a continuous infusion of hydrocortisone 200 mg daily for seven days vs. placebo. The primary outcome was all-cause mortality at 90 days. A population of 3,800 patients provided the trial a 90% power to detect a 5% absolute difference in the primary outcome, with an

estimated baseline mortality of 33%. However, there was no difference in 90-day mortality between the treatment and control groups (27.9% and 28.8%, respectively; $P = 0.50$). There were improvements in the secondary outcomes of median time to shock resolution, median time to discharge, and median time to cessation of mechanical ventilation. These authors also noted more adverse events in the hydrocortisone group, including hyperglycemia, hypernatremia, hypertension, and myopathy.

In contrast, APROCCHSS originally was designed to be a 2 × 2 factorial study examining activated protein C (APC) and steroids in septic shock. During the trial, APC was removed from the market, but the trial continued, focusing on the steroid effects. Inclusion criteria included indisputable or probable septic shock for < 24 hours as defined by a sequential organ failure assessment score of 3-4 in at least two organ systems and vasopressor therapy. Exclusion criteria included septic shock for > 24 hours, pregnancy or lactation, or underlying conditions that could affect short-term survival. The study group received 50 mg hydrocortisone intravenously every six hours and 50 mcg enteral fludrocortisone daily for seven days. Again, cosyntropin stimulation trials were performed. The primary outcome was 90-day all-cause mortality.

Here, the baseline mortality was assumed to be 45% and a total of 1,280 patients would be required to detect an absolute 10% difference. The primary outcome was realized in 43% of the steroid group and 49.1% of the placebo group, with a relative risk of death of 0.88 ($P = 0.03$). Mortality at ICU discharge, hospital discharge, and day 180 were all statistically less in the steroid-treated group. Furthermore, the secondary outcomes of vasopressor-free, ventilator-free, and organ failure-free days were fewer in the treatment arm. Again, more hyperglycemia was noted with steroid administration, but there was no difference in infection, bleeding, or myopathy rates between the two groups.

COMPARISONS

With these trials demonstrating conflicting outcomes with differing interventions, how can providers make decisions regarding steroid treatment for sepsis? By comparing each study design and specific patient factors within each study, some conclusions can be drawn *(See Table 1)*.

In terms of study design, the most important differences were in the intervention arms. Those studies that demonstrated mortality benefits included both hydrocortisone and fludrocortisone. It might be that both medications are required for benefit. However, the authors of the 2010 COIITS study compared hydrocortisone to hydrocortisone plus fludrocortisone, which showed no difference in mortality, although this study did not include a placebo arm without steroid therapy and was not powered specifically to detect differences in mortality.[7]

The power of each study to evaluate mortality also differed. After the 2002 study generated excitement for steroid therapy, the CORTICUS study in 2008 failed to show an improvement in mortality. However, this study was underpowered to detect changes in mortality. Both 2018 studies were

Table 1. Comparison of Major Studies of Steroids for Sepsis

Study	Number of Patients	Intervention	Length of Treatment (Days)	Study Mortality	Change in Mortality	Power to Detect Change?
Annane et al[2]	299	Hydrocortisone and fludrocortisone boluses	7	28-day mortality of 58%	6%	Yes
CORTICUS[3]	499	Hydrocortisone bolus	11	28-day mortality of 33%	Not significant	No
HYPRESS[6]	353	Hydrocortisone infusion	11	28-day mortality of 8.5%	Not significant	No
ADRENAL[4]	3,713	Hydrocortisone infusion	Up to 7	90-day mortality of 28%	Not significant	Yes
APROCCHSS[5]	1,241	Hydrocortisone and fludrocortisone boluses	7	90-day mortality of 46%	6.1%	Yes

adequately powered for their primary outcomes, although both the overall mortality and number of patients enrolled in the ADRENAL study were lower than the figures used in the power calculation. An additional difference was the length of steroid treatment. Both positive studies used steroids for seven days, then stopped. ADRENAL specified treatment up to seven days, while the other negative trials tapered steroids up to 11 days. It is possible that the adverse effects of steroid treatments increasingly outweighed the benefits with longer treatments. Patient factors also differed considerably between these studies. Studies with positive results demonstrated higher overall mortality *(See Table 1)*. This a result of differing inclusion criteria. The inclusion criteria in the two positive studies specified significant organ dysfunction with few exclusion criteria.

CORTICUS included patients with organ dysfunction, but excluded patients with poor prognosis, immunosuppression, or life expectancy of < 24 hours, not an uncommon occurrence with severe sepsis. HYPRESS specifically excluded patients with septic shock and demonstrated the lowest overall mortality of the studies. ADRENAL included SIRS criteria, but did not specify organ dysfunction, and excluded patients who were expected to die within 90 days from comorbidities. Also notable was the much higher proportion of patients with pulmonary infections in the positive studies.

While in ADRENAL, 33.8% and 36.5% of the steroid and placebo groups, respectively, had pulmonary infections; in the APROCCHSS study, 58% and 60.7%, respectively, had pulmonary infections. This is notable, as a growing body of literature suggests steroid therapy can alter the outcomes of severe pneumonia.[8]

What the outcomes of each study had in common also are informative. The 2002 Annane et al study demonstrated that steroids led to a decreased time to vasopressor therapy withdrawal in both non-responders and all patients. CORTICUS reported a decreased time to reversal of shock for all patients as well as decreased time on mechanical ventilation. ADRENAL demonstrated that hydrocortisone administration was associated with decreased median time to shock reversal, ICU length of stay, and median time on mechanical ventilation.

APROCCHSS demonstrated statistically significant improvements in vasopressor-free days and organ failure-free days, with a nonsignificant trend toward increased ventilator-free days. Except for the original Annane et al study, all reported hyperglycemia as an adverse effect of steroid treatment.

However, the COIITSS study did not demonstrate that intensive control of hyperglycemia with insulin in steroid-treated patients improved outcomes, raising the question of the clinical significance of transient hyperglycemia in this population.[7]

CONCLUSION

Much uncertainty remains regarding the benefits of steroid therapy for sepsis. Furthermore, it seems unlikely that additional, well-powered studies will be undertaken to address the questions of patient selection, treatment intervention, duration of therapy, or infusions vs. bolus therapy.[9] Current studies seem to indicate potential benefits for patients with higher levels of sepsis severity, especially in those presenting with pneumonia as the causative factor. As the only positive trials included fludrocortisone, the best evidence would be to use both intravenous hydrocortisone and enteral fludrocortisone if treating severe sepsis with steroids. There seems to be some agreement that steroid therapy in sepsis leads to shorter time to vasopressor withdrawal and the duration of need for mechanical ventilation. Predicting which patients will require longer duration of vasopressors and mechanical ventilation is difficult. Ultimately, in those patients presenting with severe sepsis with rising vasopressor needs who no longer appear to be fluid responsive, the addition of hydrocortisone and fludrocortisone may improve outcomes. ■

REFERENCES

1. Marik PE. Critical illness-related corticosteroid insufficiency. *Chest* 2009;135:181-193.
2. Annane D, Sébille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002;288:862-871.
3. Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008;358:111-124.
4. Venkatesh B, Finfer S, Cohen J, et al. Adjunctive glucocorticoid therapy in patients with septic shock. *N Engl J Med* 2018;378:797-808.
5. Annane D, Renault A, Brun-Buisson C, et al. Hydrocortisone plus fludrocortisone for adults with septic shock. *N Engl J Med* 2018;378:809-818.
6. Keh D, Trips E, Marx G, et al. Effect of hydrocortisone on development of shock among patients with severe sepsis: The HYPRESS randomized clinical trial. *JAMA* 2016;316:1775-1785.
7. COIITSS Study Investigators; Annane D, Cariou A, Maxime V, et al. Corticosteroid treatment and intensive insulin therapy for septic shock in adults: A randomized controlled trial. *JAMA* 2010;303:341-348.
8. Stern A, Skalsky K, Avni T, et al. Corticosteroids for pneumonia. *Cochrane Database Syst Rev* 2017;12:CD007720.
9. Suffredini AF. A role for hydrocortisone therapy in septic shock? *N Engl J Med* 2018;378:860-861.

ABSTRACT & COMMENTARY

Selection of Isotonic Crystalloid for Fluid Resuscitation: How Much Does It Matter?

By Elaine Chen, MD

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Dr. Chen reports no financial relationships relevant to this field of study.

SYNOPSIS: Using balanced crystalloids rather than normal saline for intravenous fluid administration in critically ill adults leads to statistically significant lower rates of major adverse kidney events, including death from any cause, new renal replacement therapy, and persistent renal dysfunction, compared to normal saline in critically ill adults. Clinical judgment should be applied when selecting fluid.

SOURCE: Semler MW, Self WH, Wanderer JP, et al. Balanced crystalloids versus saline in critically ill adults. *N Engl J Med* 2018;378: 829-839.

Intravenous crystalloid solutions are used commonly for fluid resuscitation in the ICU. Normal saline is used most often, but can be associated with hyperchloremic metabolic acidosis or acute kidney injury. In this study, Isotonic Solutions and Major Adverse Renal Events Trial (SMART), the authors hypothesized that use of "balanced" crystalloids would result in lower overall incidence of death, new renal replacement therapy, and persistent renal dysfunction compared to saline.

The study was a single-center, pragmatic, unblinded, cluster-randomized, multiple-crossover trial that took place from June 2015 through April 2017. All adults admitted to a participating ICU during the study time frame were included. Each ICU was randomized, by month, to use either saline or balanced crystalloid (lactated Ringer's or PlasmaLyte, at the clinician's preference) whenever intravenous fluids were administered. Fluid therapy administered in the ED and operating room were coordinated with the admitting ICU when possible.

Over the course of 23 months, 15,802 patients from five ICUs were enrolled in the trial. Baseline characteristics were similar between the groups. Approximately 5% of patients in each group received any volume of unassigned crystalloid due to crossing over of months. In the saline group, there was a higher incidence of measured plasma chloride > 110 mmol/L (23.5% vs. 35.6%; $P < 0.001$) and plasma bicarbonate < 20 mmol/L (35.2% vs. 42.1%; $P < 0.001$), with greater differences among those patients receiving larger fluid volumes.

The primary outcome, the presence of a major adverse kidney event within 30 days, was the composite of death, new renal replacement therapy, and persistent renal dysfunction (defined as final inpatient creatinine value ≥ 200% of baseline value). This outcome was noted in 1,139 patients in the balanced crystalloids group and 1,211 patients in the saline group, with a marginal odds ratio (OR) of 0.91 (95% confidence interval [CI], 0.84-0.99; $P = 0.04$). The difference in rate of primary outcome between groups was greater among patients who received larger fluid volumes.

Among patients with sepsis, 30-day in-hospital mortality was 25.2% in the balanced crystalloid group and 29.4% in the saline group (adjusted OR, 0.80; 95% CI, 0.67-0.97; $P = 0.02$). Regarding secondary outcomes, overall 30-day mortality was observed in 818 patients in the balanced crystalloid group compared with 875 patients in the saline group ($P = 0.06$). New renal replacement therapy occurred in 189 patients in the balanced crystalloid group and 220 patients in the saline group ($P = 0.08$). Renal dysfunction during hospitalization did not differ between groups.

The authors proposed that while the absolute differences are modest, if the findings were extrapolated to the 5 million patients admitted to ICUs each year, the reduction in death, new renal replacement therapy, or persistent renal dysfunction could be substantial. Strengths of this trial included large sample size, trial design that allowed early delivery of assigned fluid, and minimal selection bias. Limitations included the single-center setting and the unblinded nature of the study. PlasmaLyte and lactated Ringer's were studied together, so differences between the two types of balanced crystalloids cannot be evaluated in this study.

■ COMMENTARY

The authors of SMART reported that the use of balanced crystalloids for intravenous fluid

administration resulted in a lower rate of major adverse kidney events, the composite outcome of death from any cause, new renal replacement therapy, or persistent renal dysfunction than the use of saline. While this was statistically significant, none of the three individual outcomes reached statistical significance. Additionally, the differences were modest, with an absolute difference of 1.1% in the composite measure.

Interestingly, the authors of the SALT-ED trial[1] (the results of which were published in the same issue of *The New England Journal of Medicine* as SMART) studied the same fluids in a non-critically ill population. Those authors reported no significant difference in the primary outcome of hospital-free days to day 28, but, statistically, observed a similar outcome regarding major adverse kidney events within 30 days (a secondary outcome), with balanced crystalloids resulting in a lower incidence of major adverse kidney events within 30 days than saline (4.7% vs. 5.6%, adjusted OR, 0.82; 95% CI, 0.70-0.95, $P = 0.01$).

Caution is recommended in interpreting the results of this study. After albumin and hydroxyethyl starch were shown to produce adverse patient-centered outcomes, saline has been the crystalloid of choice for resuscitation despite a lack of evidence for its safety and efficacy. Large-volume saline administration is associated with hyperchloremic metabolic acidosis and acute kidney injury. Prior observational trials suggested lower rates of acute kidney injury and lower mortality when balanced solutions were used. However, none of the current commercially available balanced crystalloid solutions, which substitute anions such as lactate, acetate, gluconate, or bicarbonate in place of chloride to partially buffer or balance the solution, are truly "balanced"; they are all relatively hypotonic and are associated with generation of a metabolic alkalosis.[2]

Should this study inform a change in practice? In my own practice, I had already selected balanced crystalloids frequently prior to these trial results. Several years ago, our hospital pharmacy encouraged us to avoid PlasmaLyte in favor of normal saline or lactated Ringer's because of cost, but now the cost differential is less substantial. When teaching my trainees, I will encourage them to consider a balanced crystalloid in the ICU rather than saline, which seems to be the default. We should be thoughtful about our choice of fluid rather than automatically reaching for what is most comfortable and familiar. Each patient in whom fluid administration is considered warrants this thought: Is fluid administration necessary? If so, which fluid will provide the most benefit and the least harm? ■

REFERENCES

1. Self WH, Semler MW, Wanderer JP, et al. Balanced crystalloids versus saline in noncritically ill adults. *N Engl J Med* 2018; 378:819-828.
2. Myburgh J. Patient-centered outcomes and resuscitation fluids. *N Engl J Med* 2018;378:862-863.

ABSTRACT & COMMENTARY

Sepsis-related Neurologic Dysfunction Strongly Associated With Long-term Mortality

By Betty Tran, MD, MSc, Editor

SYNOPSIS: In this multicenter, retrospective study, acute neurologic dysfunction was the organ dysfunction most strongly associated with short- and long-term mortality in patients surviving a sepsis hospitalization.

SOURCE: Schuler A, Wulf DA, Lu Y, et al. The impact of acute organ dysfunction on long-term survival in sepsis. *Crit Care Med* 2018;46:843-849.

Based on the most recent Sepsis-3 definitions, sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] Organ dysfunction is measured by an increase in the Sequential Organ Failure Assessment (SOFA) score; even a modest increase in SOFA score is associated with in-hospital mortality in excess of 10%.[1] However, given the heterogeneity in sepsis presentations, it is not clear if different organ dysfunction is associated with different outcomes. In this retrospective study of randomly selected patients admitted for sepsis through the ED at 21 Kaiser Permanente Northern California hospitals, Schuler et al aimed to study the effect of each of six different types of acute, sepsis-related organ failure (hepatic, renal, coagulation, neurologic, cardiac, respiratory)

on long-term mortality. Acute organ dysfunction was quantified using the SOFA score, with modification for selected organ systems to include other clinically relevant data and recorded as a maximum at 48 hours and over the course of hospitalization. Outcomes included hospital mortality and post-sepsis mortality only in patients who were discharged alive. Care was taken to adjust for concomitant organ dysfunction in patients who could be experiencing multiple organ dysfunction. Several sensitivity analyses were performed, including a propensity score model to adjust for presepsis/hospital risk factors that could predispose patients to specific organ dysfunctions.

Overall, 30,163 septic patients were evaluated, with a median follow-up time for survivors of 797 days (interquartile range, 384-1,219 days). Overall hospital mortality was 9.4%, one-year mortality was 31.7%, two-year mortality was 44.0%, and three-year mortality was 59.7%. The most prevalent organ dysfunction was cardiac (62.4%), with the least common liver (16.5%). The organ dysfunctions most strongly associated with hospital mortality were neurologic (odds ratio [OR], 1.86; $P < 0.001$), respiratory (OR, 1.43; $P < 0.001$), and cardiac (OR, 1.31; $P < 0.001$).

Acute neurologic dysfunction was the organ dysfunction most strongly associated with increased long-term mortality (for each 1-point increase in SOFA subscore, OR, 1.18; 95% CI, 1.15-1.20; $P < 0.001$). This finding remained consistent in all sensitivity analyses, including adjustment for other concomitant organ dysfunction, as well as propensity score models accounting for presepsis conditions that influenced acute organ dysfunction more than any other condition.

■ COMMENTARY

This study adds to the growing body of research focused on long-term patient outcomes and sequelae after a hospitalization for sepsis. We know that acute neurologic dysfunction occurs commonly in septic patients,[2] and that it is associated with adverse outcomes;[3] hence its incorporation into the quick SOFA score aimed to identify patients at increased risk for poor outcomes due to infection. Although these findings will need to be validated in other studies, Schuler et al suggested that acute sepsis-related neurologic dysfunction is the organ dysfunction that most strongly correlates to short- and long-term mortality.

Strengths of this study included long-term follow-up for a large cohort, detailed adjustment for confounding factors (such as illness severity and concomitant other organ dysfunction), and a sensitivity analyses. The sensitivity analysis included a robust propensity score model that accounted for more than 3,000 diagnosis codes. These codes identified presepsis clinical conditions with clinical face validity that carried the highest likelihood of development of acute organ dysfunction, which allows for one to isolate the effect of sepsis hospitalization rather than chronic organ dysfunction.

Whether this is a true causative relationship is unclear based on the retrospective nature of this study. However, this finding may carry implications for sepsis-related in-hospital and discharge prognoses to inform patients' families/surrogates, as well as provide insight for future investigations into the mechanisms by which sepsis affects long-term survival. ■

REFERENCES

1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;315:801-810.
2. Shankar-Hari M, Rubenfeld GD. Understanding long-term outcomes following sepsis: Implications and challenges. *Curr Infect Dis Rep* 2016;18:37.
3. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of clinical criteria for sepsis. For the Third International Consensus Definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;315:762-774.

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CME/CE QUESTIONS

1. **Regarding steroid treatment for sepsis:**
   a. all studies showed a significant decrease in mortality.
   b. all studies showed a significant increase in mortality.
   c. no studies showed an improvement in mortality.
   d. None of the above

2. **Trials of steroid therapy for sepsis have demonstrated:**
   a. hydrocortisone therapy alone failed to improve mortality.
   b. hydrocortisone plus fludrocortisone improved mortality.
   c. steroid therapy leads to hyperglycemia.
   d. All the above

3. **The best evidence of benefit from steroid treatment for sepsis would be for patients presenting with:**
   a. severe sepsis admitted with pneumonia treated with hydrocortisone and fludrocortisone.
   b. diabetic ketoacidosis admitted with urinary tract infection.
   c. transient hypotension after elective knee surgery.
   d. severe sepsis already present for four days treated with hydrocortisone infusion.

4. **Based on the SMART trial, the use of balanced crystalloid solutions, compared with saline, is associated with:**
   a. decreased incidence of chloride > 110 mmol/L.
   b. increased incidence of normal anion gap acidosis.
   c. lower 30-day in-hospital mortality.
   d. decreased incidence of acute kidney injury.

5. **The authors of the SMART trial reported lower rates of major adverse kidney events among critically ill adult patients who received balanced crystalloids compared with saline. Which of the following was *not* included in the definition of "major adverse kidney event?"**
   a. Death from any cause
   b. Acute oliguria with urine output < 400 mL in 24 hours
   c. New renal replacement therapy
   d. Persistent renal dysfunction

6. **In the study by Schuler et al, which organ dysfunction was most strongly associated with hospital mortality in patients hospitalized for sepsis?**
   a. Renal
   b. Cardiac
   c. Respiratory
   d. Neurologic

CME/CE OBJECTIVES

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- identify relevant topics in the practice of critical care medicine;
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