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Surviving Sepsis: Updates to the Management Bundle

Author

Sean R. Townsend, *MD*
Intensivist, Pulmonary and Critical Care Unit
Brown University & Rhode
Island Hospital,Institute for Healthcare Improvement
Providence, Rhode Island,USA

There is considerable controversy and debate surrounding much of what we do at the bedside in critical care, and the management of sepsis is no exception. Developing a global standard of care for sepsis management, based on consensus amongst international experts is a real challenge. Much has been written and discussed about the value of protocols and bundles in general, and the individual elements of the sepsis bundles from theSurviving Sepsis Campaign (SSC) in particular. These bundles are officially being used and compliance data being collected in 250 hospitals in 30 countries. Several manuscripts have been already been published that demonstrate a significant reduction in mortality through the use of the sepsis bundles. Nonetheless, debate about the use of bundles, or protocols and the choice of specific strategies in the sepsis bundles, continues. Many feel that protocols or bundles are not necessary to improve care, while others argue that recent published studies mandate a change in some bundle elements.

The largest controversy surrounding the use of bundle strategies is whether bundles, once established, can keep up pace with the literature to remain up to date. In the interest of clarification, and since the publication of the 2008 Surviving Sepsis Campaign International Guidelines for the Management of Severe Sepsis and Septic Shock, it is now reasonable to discuss whether updates to the Surviving Sepsis Campaign's Management Bundle are now necessary (SSC 2008). The Management Bundle aimed to standardise, to the extent possible, care practices within individual hospitals for the first 24 hours of care that patients with severe sepsis and septic shock received. The three most common areas of debate at the time the bundles were built have remained even now the use of steroids, tight glucose control, and activated Protein C.

Glucose Control

The two studies that have continued to raise the question of whether tight glucose control is safe and effective for patients with severe sepsis and septic shock were published in 2006 and 2008 respectively (Van den Berghe et al. 2006; Brunkhorst et al. 2008). Both articles have raised questions about the safety and efficacy of glucose control in medical ICU patients. The question for improvement minded physicians is does tight glucose control without hypoglycemia improve outcomes for patients with severe sepsis and septic shock?

Unfortunately, this is a case where the literature has confused physicians. The first reports from Van den Berge in cardiac surgery patients demonstrated a benefit from tight glucose control. In the second study in a medical ICU and in the VISEP trial there was a significant hypoglycemia rate. In the second Van den Berge trial, there was a benefit for patients who survived in the ICU longer than 3 days. One of the problems with these trials however, is that the experiment of tight glucose control without hypoglycemia was not tested since the glucose control was not tight but caused unacceptable hypoglycemia. The purpose of the VISEP trial was to determine if the benefit of strict glucose control, as seen in Dr. Van den Berghe's initial study, applies to patients with severe sepsis and septic shock. Using the same targets and protocol as Dr. Van den Berghe, investigators randomised patients to conventional insulin therapy (goal, 180 to 200 mg/dL) or intensive insulin therapy (goal, 80 to 110 mg/dL).

The trial was stopped early, after enrollment of 480 patients, due to the increased incidence of hypoglycaemia in the intensive arm (17.6%) versus the conventional therapy arm (4.5%). The reporting of hypoglycemia as a life-threatening incident was also significantly higher in the treatment arm than in the control arm (5.3% vs 2.1%, respectively). There were no significant differences in the 28- or 90-day mortality rates between the two arms. A trend toward longer ICU stay by approximately two days was seen in patients in the intensive arm. Multivariate analyses showed intensive insulin therapy and the patients' age to be risk factors for hypoglycemia.

Both trials used the same insulin titration protocol, but all that we really know is that a protocol that worked in a surgical ICU did not work well in a medical ICU and that the protocol, when unrefined and handed-off for implementation to nurses unfamiliar with the protocol, caused hypoglycemia. We do not know if a protocol that actually resulted in tight control in a medical ICU would result in benefit.

The other issue is does controlling in a wider range of 80 to 150 mg/dl give similar benefit? A few observational trials have suggested that

protocols aimed at this level have lower incidence of hypoglycaemia and most likely benefit patients compared to the no protocol to control glucose. All told, the Surviving Sepsis Campaign has evaluated the evidence in the new guidelines and chosen not to change the bundle element. The rationale and evidence grade and strength of recommendation are detailed in the guidelines themselves.

Corticosteroids in Sepsis

The CORTICUS trial was recently completed and showed no effect of steroids except earlier reversal of shock in those patients who had shock reversed and a non-statistically significant trend toward more patients with shock reversal (Sprung et al. 2008). Do we really need a policy on the use of steroids in the ICU with this new information? It is important to recognise that the CORTICUS trial enrolled a different patient population than the trial conducted by Ananne, which showed a beneficial effect of steroids on patient survival (Ananne et al. 2002). The CORTICUS patients were less ill by severity score and it is postulated that many vasopressor refractory patients were not allowed entry into the trial by the treating physician since centers participating in the CORTICUS trial had steroids available to be given as an alternative to trial enrollment. This likely created selection bias. In the CORTICUS trial, patients could be enrolled up to 72 hrs after onset of septic shock (as opposed to 8 hours for the Annane trial). To get into the Annane trial, patients had to exhibit hypotension after fluid resuscitation and vasopressor administration which was not the case for the CORTICUS study where patients only needed to be on vasopressors after fluid resuscitation, thus the two patient populations were arguable very different.

The CORTICUS trial was considered in our new SSC recommendations for steroid administration. Our new recommendation suggests that steroids should be given to patients with blood pressure poorly responsive to fluid resuscitation and vasopressor therapy. This is a level 2 (weak) recommendation, which is prefaced by "suggest" with the implication being that the clinician probably should give them in the scenario listed in the recommendation. We no longer recommend a cortisol stimulation test to make decision for administering for the reasons alluded to in the CORTICUS paper, including variability in the cortisol stimulation test assays currently available.

Given the potentially different patient populations, as well as other factors, it is probably more imperative than ever that hospitals develop a policy in their ICU's for the rational administration of steroids. In using the steroid bundle element, it is important for hospitals participating in the SSC to remember that the steroid indicator is scored based on compliance with the hospitals' own policy (based on the practical considerations and controversies that appear as of yet unresolved). In the extreme, if a hospital makes a policy not to use steroids in septic shock, then technically that hospital would get credit for all patients just the same as a hospital that used steroids for all patients with septic shock. Likewise, if the policy is made to only use corticosteroids for patients within certain parameters for central venous pressure and moderate to high doses of vasopressors with ongoing hypotension and hypoperfusion, then again that is what the hospital is scored against.

Activated Protein C

The Surviving Sepsis Campaign downgraded their recommendation on the administration of recombinant human activated protein C (rhAPC) in the newest guidelines based on evidence published since the PROWESS trial. This determination again has raised the question, do we need a policy on the rational administration of rhAPC or should we even be considering using the drug? As with steroids, any controversy around the effect of the drug in the literature is probably best resolved by standardising your ICU's policy with respect to administering the drug.

We have updated our previous recommendation for use by recommending rhAPC with a level 2 (weak), which is prefaced by “suggest” with the implication being that the clinician probably should give them in the scenario listed in the recommendation. The recommendation for use is reprinted here:

“We suggest that adult patients with sepsis induced organ dysfunction associated with a clinical assessment of high risk of death such as APACHE II ≥25 or multiple organ failure receive APC (Grade 2B).”

Likewise, the new recommendations include a level 1 (strong) recommendation against use with APACHE II < 20 or with one organ failure (Grade 1A). Also included is a level 2 (weak) recommendation that patients within 30 days of surgery, otherwise qualifying for rhAPC, receive rhAPC (Grade 2C).

Conclusion

As hospitals were allowed to review the literature with regards to the management bundles and make high level policies for their own institutions with regard to steroid and rhAPC administration, the SSC has, at this time deferred making changes to these bundle elements. It still seems prudent to us that hospitals work to standardise their care patterns so that they can measure their results and evaluate what works best for their patients. With respect to glucose control, the SSC standard has always been more liberal than the Leuven protocol consistent with a beneficial effect seen in subgroup analyses of these trials as well as some observational data. It will be essential to continue to monitor upcoming trial results and incorporate new information into future recommendations. Finally, the SSC itself will soon be able to comment directly on the experience of hospitals that have used the SSC bundles to treat patients with severe sepsis and septic shock with data when the greater than 16,000 patient database is fully analysed.

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