In summary, ICU bundles
- Are not perfect
- Are still evolving and always will be
- Provide the best quality for the typical patient in the ICU with the matched disorder
- Will never replace clinical decision-making
- Allow audit, feedback, and behavior change; and
- Offer education and team-building capability.

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References


Counterpoint: Are the Best Patient Outcomes Achieved When ICU Bundles Are Rigorously Adhered To? No

The Institute for Healthcare Improvement (IHI) promotes the concept of bundles to “help health care providers more reliably deliver the best possible care for patients undergoing particular treatments with inherent risks.” It defines a bundle as a “structured way of improving the processes of care and patient outcomes: a small, straightforward set of evidence-based practices—generally three to five—that, when performed collectively and reliably, have been proven to improve patient outcomes.” Furthermore, the IHI states that “bundles tie the changes together into a package of interventions that people know must be followed for every patient, every single time” and that the changes are all necessary and all sufficient, so if you’ve got four changes in the bundle and you remove any one of them,
The belief is that bundled interventions work synergistically and that the whole represents more than the sum of its parts.

Bundles have been developed and implemented for a number of clinical conditions in the ICU, including the management of patients with sepsis and the prevention of ventilator-associated pneumonia (VAP). Bundle-based checklists promote en masse implementation, and the concept of bundles has been embraced and enforced by quality and oversight organizations such as the Centers for Medicare & Medicaid Services (CMS), the Joint Commission, and the Agency for Healthcare Research and Quality. Bundle adherence has become a de facto standard to assess and compare the quality of health care delivered. The IHI takes the position that “there should be no controversy involved, no debate or discussion of bundle elements.”

We argue that there is insufficient scientific evidence to support the concept of bundling as it is currently being practiced and that the two most widely promoted bundles (the 6-h sepsis bundle and VAP prevention bundle) have elements that may be harmful as applied.

The hypothesis that bundle synergy exists has not been formally tested. Observational studies examining outcomes before and after bundle implementation are not appropriate proof-of-concept demonstrations or substitutes for prospective randomized trials. Furthermore, with multiple therapeutic interactions across heterogeneous patient populations, conclusions about the safety and efficacy of specific bundled interventions are not readily tenable. Consider, for example, the failure to recognize a lack of efficacy and possible risks of Xigris (activated protein C; Eli Lilly and Company) use in patients with sepsis. Relatively recent withdrawal of Xigris by the US Food and Drug Administration occurred despite years of its inclusion in sepsis bundles with little hint of the rather dramatic lack of efficacy during observational follow-up. Additionally, an intervention that produces a positive effect in a particular group of patients cannot be extrapolated to another group or to all patients with a similar condition. Contrary to expectation, bundles might dilute rather than enhance the benefits of specific treatment elements when combined together. Most alarming is the concept of all-or-none bundle compliance. CMS, IHI, and other quality organizations suggest that if all the elements of the bundle are not met, no credit should be given for any of the elements. In other words, credit for delivery is all or none. There is no scientific data to support this notion; indeed, the before-and-after studies that investigated the 6-h sepsis bundle strongly contradict this idea. Nolan and Berwick’s assertion that “the movement to all- or-none performance assessment is an important milestone in the journey to high quality health care” may not translate when high-quality clinical evidence is being packaged with other interventions that are unproven or harmful. Furthermore, bundles are, in essence, consensus packages that are not continually updated as evidence changes. Indeed, the 6-h sepsis bundle and the VAP prevention bundle have not been updated by the IHI since originally published in the mid 2000s. Thus, the pressure to comply with bundles may accelerate the very situation that bundles are trying to correct: outdated, potentially harmful care.

The 6-h sepsis bundle and VAP prevention bundle have been widely adopted in ICUs around the globe. What is perhaps most troubling about these particular bundles is that contrary to the claim of the IHI, none of the elements are based on level 1 evidence (ie, supported by at least two randomized controlled trials), many have no supporting evidence, and some of the elements may be associated with harm. Each element of these two bundles is listed in Table 1 with the level of support and the likelihood that the element is beneficial or harmful. Our analysis is supported by recent reviews that have systematically evaluated each bundle. Barochia et al concluded that “as administered and studied to date, only antibiotics meet the stated criteria of proof for bundle inclusion.” Furthermore, they stated that “current sepsis bundles may force physicians to provide unproven or even harmful care.” These guidelines have become regarded as the standard of care, with a major impact on the management of patients with sepsis worldwide. The Australian and New Zealand Intensive Care Society is the only professional organization to have questioned the validity of these guidelines, and because of concern that the guideline package would inappropriately be adopted by quality improvement programs and organizations (as indeed has happened), it has previously declined to endorse these guidelines. O’Grady and colleagues published a review wherein they concluded that “despite broad implementation of a bundled strategy aimed at preventing ventilator-associated adverse events in many hospitals, the ability of the bundle to prevent VAP has not been definitively established with high quality studies.” Most telling is a report from the Agency for Healthcare Research and Quality in which the authors stated that “conclusions in this area [VAP] are especially limited as we did not identify any controlled studies.”

A number of the elements included in the 6-h sepsis bundle and VAP prevention bundle may be harmful. These elements are briefly reviewed here. A central venous pressure (CVP) of 8 to 12 mm Hg is recommended as the major end point for fluid resuscitation.
in the 6-h sepsis bundle. The updated 2012 Surviving Sepsis Campaign Guidelines strongly recommend achieving a CVP of 8 mm Hg. A large sepsis study by Boyd and colleagues demonstrated that patients who met this target CVP had the highest mortality. It is important to point out that both the original and the updated meta-analysis by Marik and colleagues demonstrated no association between the CVP and intravascular volume or volume responsiveness. The only study published to date showing some relationship between CVP and volume status is in healthy standing mares. Furthermore, the concept that a low CVP generally can be relied on as supporting positive response to fluid loading is simply incorrect. A patient with a low CVP is just as likely to respond to a fluid challenge as a patient with a high CVP. Extensive data accumulated over the past decade support the concept that overzealous fluid resuscitation increases the risk of death. It is likely that fluid resuscitation guided by the 6-h bundle will result in fluid overload (Fig 1). Furthermore, placing and accurately measuring the CVP in the ED is close to an impossible task. The inclusion of a blood transfusion in the 6-h sepsis bundle is equally troubling. This recommendation is a striking deviation from currently accepted transfusion practice. In critically ill patients, blood transfusions increase the risk of infections, ARDS, multisystem organ failure, and death. Data suggest that the release of cell-free hemoglobin from banked blood may be particularly deleterious in patients with sepsis. Although the intent of blood transfusions is to increase tissue oxygenation, blood transfusions paradoxically may have the opposite effect. A number of studies failed to demonstrate an acute increase in oxygen update after blood transfusion. Furthermore, poorly deformable transfused RBCs may impede microvascular flow and compromise tissue oxygenation. The $P_{50}$ (partial pressure at which blood is 50% saturated) of stored RBCs may be as low as 6 mm Hg, with the RBCs being able to unload <6% of the carried oxygen; stored RBCs may thereby increase the central venous oxygen saturation (by binding oxygen) and compound the tissue oxygen debt by decreasing oxygen unloading. It is interesting to note that a study published by Dr Dellinger’s group concluded that “transfusion of PRBCs [packed RBCs] was associated with worsened clinical outcomes in patients with septic shock treated with EGDT [early goal-directed therapy].”

In patients with septic shock, the optimal time to initiate vasopressor and inotropic agents has not been rigorously studied. The simple algorithmic addition of inotropic and vasopressor agents without information on ventricular function and volume responsiveness is fraught with danger. A recent study by Bouferrache and colleagues compared therapeutic interventions during the initial resuscitation of septic shock guided

Table 1—Elements of the VAP Prevention Bundle and 6-h Sepsis Bundle and the Level of Evidence

<table>
<thead>
<tr>
<th>Bundle</th>
<th>Level 1 Evidence</th>
<th>Likely to be Beneficial/ Harmful</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAP bundle (preventing VAP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevation of the head of the bed to 45°</td>
<td>No</td>
<td>Uncertain, no evidence that 45° is better than 10°</td>
</tr>
<tr>
<td>Sedation vacation</td>
<td>No</td>
<td>No evidence that it reduces VAP, time on ventilator, or ICU stay</td>
</tr>
<tr>
<td>Daily oral care with chlorhexidine</td>
<td>No</td>
<td>May be beneficial; only proven in trauma/cardiac surgery</td>
</tr>
<tr>
<td>PPI or histamine-2 receptor blocker</td>
<td>No</td>
<td>Likely to be harmful; increases risk of VAP</td>
</tr>
<tr>
<td>Anticoagulants or compression devices</td>
<td>No</td>
<td>Anticoagulants likely to be beneficial; no evidence that it reduces VAP</td>
</tr>
<tr>
<td>6-h sepsis bundle (decreasing mortality)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obtain microbiology samples and lactate measure</td>
<td>No</td>
<td>Almost certain to be beneficial</td>
</tr>
<tr>
<td>Administer appropriate antibiotics</td>
<td>No</td>
<td>Almost certain to be beneficial</td>
</tr>
<tr>
<td>Administer fluid to achieve a CVP of 8-12 mm Hg</td>
<td>No</td>
<td>Likely to be harmful</td>
</tr>
<tr>
<td>Administer vasopressors to achieve an MAP &gt; 65 mm Hg</td>
<td>No</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Maintain a central venous oxygen saturation &gt; 70% With isotope therapy</td>
<td>No</td>
<td>Uncertain</td>
</tr>
<tr>
<td>With blood</td>
<td>No</td>
<td>Likely to be harmful</td>
</tr>
</tbody>
</table>

CVP = central venous pressure; MAP = mean arterial pressure; PPI = proton pump inhibitor; VAP = ventilator-associated pneumonia.

*See text for explanation.

Figure 1. Fluid balance in the first 72 h in the Rivers-EGDRx study and the ARISE fluid limited study. ARISE = Australasian Resuscitation of Sepsis Evaluation; EGDRx = Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock.
by echocardiographic assessment of hemodynamics and compared these with those of the 6-h sepsis bundle, finding poor agreement for the decision for fluid loading ($\kappa = 0.37$; 95% CI, 0.16-0.59) and inotropic support ($\kappa = 0.23$; 95% CI, $-0.04$ to 0.5).

Increasing gastric pH has been associated with an increased risk of VAP. It should, therefore, be no surprise that the use of proton pump inhibitors and histamine-2 receptor blockers have been associated with an increased risk of VAP, particularly in patients concurrently receiving enteral feeding. Furthermore, there is scant evidence that these agents reduce the risk of stress ulceration in modern critical care practice. Although patients receiving ventilation are at an increased risk of thromboembolic disease, no randomized controlled trial has been published to demonstrate that any intervention reduces this risk. Furthermore, although the VAP prevention bundle recommends compression devices to prevent DVT, little credible evidence shows that these devices have a beneficial effect.

In conclusion, a review of published scientific evidence strongly calls into question the current concept of bundling and suggests that two of the most commonly applied bundles are seriously flawed, with a number of the elements likely to cause harm. Prospective testing of bundle interventions is needed, and if this does not appear to be feasible, variation in practice may be inevitable. The interpretation of data from clinical trials and their application are best left to knowledgeable, thoughtful, and skillful physicians at the bedside. After all, it is ultimately these physicians who bear the liability for the care delivered. Conditions at each bedside need to encourage the practice of evidence-based, not eminence-based, medicine. Furthermore, any attempt by CMS or another entity to use compliance with these bundles as an indicator of quality of care or to link them to pay for performance must be vigorously challenged.

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Rebuttal From Drs Dellinger and Townsend

Dr Marik and colleagues¹ have overstated their position, attempting to convince us that ventilator-associated pneumonia bundles and sepsis bundles are potentially harmful. Despite several pages of pointing here and there, they never cite a single trial of any sort that demonstrates actual harm from bundled therapies, which is because all such trials reach the opposite conclusion.

With regard to their criticism of the all-or-none principle of bundle care, it has always been espoused by the Surviving Sepsis Campaign (SSC) that not all elements of the sepsis bundle apply to a given patient with severe sepsis; for example, some patients will not qualify for central venous pressure (CVP) and central venous oxygen saturation (ScvO₂) measurement, and severity of pathophysiology itself will prevent some goals from being achieved.

Marik et al¹ are incorrect in ascribing blood transfusion or dobutamine infusion to the sepsis bundles. These therapies have never been a part of the sepsis bundles. Although the original sepsis bundles included achieving an ScvO₂ of ≥70%, the decision about how this goal would best be achieved was left to the treating clinician.² The new sepsis bundles only require that ScvO₂ be measured (Table 1).

CVP has known limitations compared with intravascular and intracardiac volume or blood flow measurements. However, these technologies are not widely available in community hospitals, and bringing these technologies to the bedside often is not practical during the first 6 h of care.

The SSC has transitioned from use of the term “early goal-directed therapy” (one type of quantitative resuscitation) to “quantitative resuscitation.” The new sepsis bundles also deemphasize specific targets for CVP and ScvO₂, requiring only that those values are measured (Table 1).³ Practitioners may use the results accordingly and along with other variables. These modifications serve to debunk the position of Marik et al¹ that bundles are immutable once created.

How could assessing CVP be harmful? The overwhelming majority of patients with sepsis-induced tissue hypoperfusion will require a central line placed in the internal jugular or subclavian positions (or a peripherally inserted central catheter line into the superior vena cava). Transducing the CVP provides just one more variable to inform a clinician’s decision-making (likewise for ScvO₂). Like other single variables, neither

<table>
<thead>
<tr>
<th>Table 1—Surviving Sepsis Campaign Bundles 2012</th>
</tr>
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<tbody>
<tr>
<td><strong>Bundles</strong></td>
</tr>
<tr>
<td>To be completed within 3 h</td>
</tr>
<tr>
<td>Measure lactate level</td>
</tr>
<tr>
<td>Obtain blood cultures prior to administration of antibiotics</td>
</tr>
<tr>
<td>Administer broad spectrum antibiotics</td>
</tr>
<tr>
<td>Administer 30 mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L</td>
</tr>
<tr>
<td>To be completed within 6 h</td>
</tr>
<tr>
<td>Apply vaspressors (for hypotension that does not respond to initial fluid resuscitation to maintain a MAP 65 mm Hg)</td>
</tr>
<tr>
<td>In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥ 4 mmol/L (36 mg/dL):</td>
</tr>
<tr>
<td>Measure CVP⁴</td>
</tr>
<tr>
<td>Measure ScvO₂⁴</td>
</tr>
<tr>
<td>Remeasure lactate if initial lactate was elevated⁴</td>
</tr>
</tbody>
</table>

CVP = central venous pressure; MAP = mean arterial pressure; ScvO₂ = central venous oxygen saturation. Used with permission from Dellinger et al.³

¹Targets for quantitative resuscitation included in the guidelines are CVP of 8 mm Hg, ScvO₂ of 70%, and normalization of lactate.