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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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."[1] 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."[1] 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,

you wouldn't get the same results—meaning: the patient won't have as high a chance of getting better. It's a cohesive unit of steps that must all be completed to succeed.[1]

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).[2,3] 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."[1] 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[4] 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[7] 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."[7] 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.[8] O'Grady and colleagues[5] 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."[9]

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

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

Bundle	Level 1 Evidence	Likely to be Beneficial/ Harmful
VAP bundle (preventing VAP)		
Elevation of the head of the bed to 45°	No	Uncertain, no evidence that 45° is better than 10°[5]
Sedation vacation	No	No evidence that it reduces VAP, time on ventilator, or ICU stay[6]
Daily oral care with chlorhexidine	No	May be beneficial; only proven in trauma/cardiac surgery
PPI or histamine-2 receptor blocker	No	Likely to be harmful; increases risk of VAP[a]
Anticoagulants or compression devices	No	Anticoagulants likely to be beneficial[a]; no evidence that it reduces VAP
6-h sepsis bundle (decreasing mortally)		
Obtain microbiology samples and lactate measure	No	Almost certain to be beneficial
Administer appropriate antibiotics	No	Almost certain to be beneficial
Administer fluid to achieve a CVP of 8-12 mm Hg	No	Likely to be harmful[a]
Administer vasopressors to achieve an MAP > 65 mm Hg	No	Uncertain[a]
Maintain a central venous oxygen saturation > 70%		
With inotrope therapy	No	Uncertain[a]
With blood	No	Likely to be harmful[a]

CVP = central venous pressure; MAP = mean arterial pressure; PPI = proton pump inhibitor; VAP = ventilator-associated pneumonia.
[a]See text for explanation.

in the 6-h sepsis bundle.[3,10] The updated 2012 Surviving Sepsis Campaign Guidelines strongly recommend achieving a CVP of 8 mm Hg.[11] A large sepsis study by Boyd and colleagues[12] 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[13,14] 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.[13] Furthermore, the concept that a low CVP generally can be relied on as supporting positive response to fluid loading[11] 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.[13,14] 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).[12,15,16] Furthermore, placing and accurately measuring the CVP in the ED is close to an impossible task.[17] 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.[18] Data suggest that the release of cell-free hemoglobin from banked blood may be particularly deleterious in patients with sepsis.[19,20] 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.[21,22] Furthermore, poorly deformable transfused RBCs may impede microvascular flow and compromise tissue oxygenation.[21,22] 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]."[23]

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[24] compared therapeutic interventions during the initial resuscitation of septic shock guided

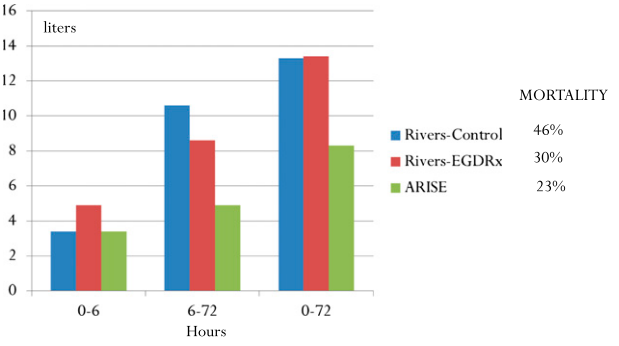

FIGURE 1. Fluid balance in the first 72 h in the Rivers-EGDRx study[15] and the ARISE fluid limited study.[16] ARISE = Australasian Resuscitation of Sepsis Evaluation; EGDRx = Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock.

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.[5] 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.[25] 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 colleagues[1] 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 ($Scvo_2$) measurement, and severity of pathophysiology itself will prevent some goals from being achieved.

Marik et al[1] 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 $Scvo_2$ of $\geq 70\%$, the decision about how this goal would best be achieved was left to the treating clinician.[2] The new sepsis bundles only require that $Scvo_2$ be measured (Table 1[3]).

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 $Scvo_2$, 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 al[1] 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 $Scvo_2$). Like other single variables, neither

Table 1—*Surviving Sepsis Campaign Bundles 2012*

Bundles
To be completed within 3 h
Measure lactate level
Obtain blood cultures prior to administration of antibiotics
Administer broad spectrum antibiotics
Administer 30 mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L
To be completed within 6 h
Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation to maintain a MAP 65 mm Hg)
In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥ 4 mmol/L (36 mg/dL):
Measure CVP[a]
Measure $Scvo_2$[a]
Remeasure lactate if initial lactate was elevated[a]

CVP = central venous pressure; MAP = mean arterial pressure; $Scvo_2$ = central venous oxygen saturation. Used with permission from Dellinger et al.[3]

[a]Targets for quantitative resuscitation included in the guidelines are CVP of 8 mm Hg, $Scvo_2$ of 70%, and normalization of lactate.

Point: Are the Best Patient Outcomes Achieved When ICU Bundles Are Rigorously Adhered To? Yes

Abbreviations: CMS = Centers for Medicare & Medicaid Services; CVP = central venous pressure; IHI = Institute for Healthcare Improvement; LOS = length of stay; $Scvo_2$ = central venous oxygen saturation; SSC = Surviving Sepsis Campaign; VAP = ventilator-associated pneumonia

> Care bundles can be a powerful driver for improving the reliability of delivery of evidence-based care and patient outcomes. It remains to be seen whether the success that has been achieved in acute admissions and ICUs can be reproduced in general wards.[1]

> Standardization of most aspects of intensive care medicine has an enormous potential to improve patient care and outcomes, reduce ICU/hospital length of stay as well as healthcare expenditures. Despite promising results from large studies, standards known to improve patient outcomes have not been widely implemented.[2]

ICU bundles have emerged as important tools in addressing clinical health-care conditions with evidence-based medicine. An ICU bundle is a set of treatment goals (usually three to seven) that when grouped and achieved together over a finite time span are believed to promote optimum outcomes. The Institute for Healthcare Improvement (IHI) has been one of the main proponents of the bundle concept. Bundle-based care is based on evidence-based medicine. Bundles exist for the prevention of surgical site- and catheter-associated central line infections as well as for the prevention of urinary tract infections, weaning from ventilation, promotion of palliative care, treatment of sepsis, and prevention of pressure ulcers. ICU protocols standardize the implementation of bundle care components. A primary advantage of bundle care is the structuring of care processes to promote consistency in the management of clinical conditions.[3] Large collaborative groups, such as the Michigan Health & Hospital Association Keystone ICU, VHA Inc (Voluntary Hospital Association), and the Institute for Healthcare Improvement 5 Million Lives Campaign, have shown improved care and better patient outcomes with the use of bundles.[4]

As patient management in the ICU has improved over the years, morbidity and mortality have decreased. To optimize patient outcomes in the ICU, a health system that is efficient, safe, and patient centered is needed. It is important to minimize potentially harmful variations in care. One approach has been to use ICU bundles as goals of therapy, typically in combination with ICU protocols. Evidence-based guidelines, although important reference documents, do not have an appreciably high impact on changing bedside behavior.[5] When changes come, they tend to be slow. However, guidelines are important for creating quality indicators. Quality indicators are those goals of therapy that, when achieved, are believed to favorably influence patient outcome. Because ICU bundles are derived from evidence-based medicine guidelines, they are predicted to improve outcome. Despite many randomized trials showing the benefit of protocolized care,[6-12] there are few randomized trials that compare care with vs care without ICU bundles. The majority of data supporting ICU bundles is based on historical controls and has included mechanical ventilation, central line blood steam infection prevention, sepsis, and other bundles.[13] ICU bundles, however, are not without critics who are weary of cookbook medicine. There may be concern about clinical judgment being supplanted or about complacency. Additionally, the effect on learning has been raised in the context of medical education.[14]

Protocols are a logical extension of guidelines centered on patient care flow, and when followed, they facilitate achievement of the quality indicators contained within ICU bundles. Protocols have been shown to improve outcomes in the ICU. For example, evidence from the literature indicates that protocol-directed extubation is a beneficial approach to facilitate liberating patients from mechanical ventilation.[15,16]

Protocols ideally are developed by hospital champions across the multidisciplinary team to facilitate buy-in. An important advantage of ICU bundles is that they allow for data collection, leading to the most important and powerful changers of bedside behavior: audit and feedback. Properly designed ICU protocols

should not constrain decision-making but instead focus the provider's attention on the commonalities of patients with a specific illness.[17] Protocol-driven care with measurement and audit and feedback of target ICU bundle quality indicators should not eliminate the need for clinical judgment. To the contrary, constant attention is needed to detect the subtleties inherent in each patient. The presence of protocols in ICU bundles should never negate deviations when a particular patient scenario warrants. Likewise, they are not a substitute for the lifelong learning process. In fact, as new evidence becomes available, new guidelines become available, new quality indicators evolve, new protocols are developed, and up-to-date and more successful ICU bundles arise.

Although some practitioners have been skeptical of the effect of protocols on teaching appropriate clinical management of select diseases, protocols are excellent tools to use for discussion and education, especially because they embody a multidisciplinary approach to critical care that can enhance teaching teamwork.[18] A retrospective cohort equivalent study demonstrated that fellows trained in a highly protocolized environment performed as well on the American Board of Internal Medicine Critical Care Certification Examination as it relates to mechanical ventilation as those who trained in critical care units that were not highly protocolized.[19] Equally important is the ability of protocols to improve patient safety by decreasing errors of both omission and commission.

To reduce the cost of critical care, it is crucial to reduce unnecessary variations in practice patterns that exist across providers and ICU environments. Garland et al[20] demonstrated that variation in ICU physician practices and resource utilization accounts for a large proportion of variability in ICU costs. The association between physician identity and variability in cost was found to be independent of severity of illness, and the variation was not associated with length of stay (LOS). Although LOS is known to be tightly associated with cost, LOS did not explain much of the variation in cost in this study. Rather, the variation was largely attributable to variation in discretionary resources (eg, laboratory, radiology, pharmacy, blood bank services). Importantly, the variation in resource use was not associated with mortality. Taken together, these data suggest that increased use of discretionary resources does not necessarily translate to improved patient outcomes.

Novel solutions are required to solve the variation problem. The first of these solutions will involve better standardization of practice through protocols, care pathways, and ICU bundles. In general, the goal of protocols is to eliminate the unnecessary variation and complexity of care that do not add value. In an era of accountable care, physicians are increasingly asked to provide care that is not only evidence based but also value based, and standardization is a requisite step in ensuring value. Protocol-directed care in the ICU (eg, sedation, analgesia, glycemic control, ventilator management, liberation from mechanical ventilation) has already been shown to reduce practice variation and improve outcomes. Thus, using standardization of critical care practices to also reduce costs should be acceptable from the patient and family perspective.

Although it is already well accepted that protocols and care pathways should be used in aspects of critical care practice where the evidence of clinical effectiveness is clear, in many aspects of critical care practice, the available evidence is less clear or incomplete. It is important to recognize that standardization of care pathways are also needed in these areas that are not yet governed by hard evidence of efficacy or clinical effectiveness on the grounds that reducing practice variation lowers costs.

Historically, physicians have been paid for services, not results. In 1772 BC, Hammurabi's code allowed a surgeon to be paid 10 shekels of silver every time he performed a procedure, such as opening an abscess or treating a cataract with a bronze lancet. Interestingly, it also instructed that if the patient should die or lose an eye, the surgeon's hands were to be cut off. This is somewhat overboard, but it does make a point. Over time, we have evolved to the place where physicians are paid for what we do independent of what happens in the process. It is likely that health-care reimbursement of the future will reward quality. ICU bundles and the associated quality indicators are a potentially good fit with these changes that are occurring in health-care delivery.

Protocols can minimize inconsistencies in the care of similar patients in the ICU by different intensivists. Variability is inherent in our practice because our behavior is a product of varied educational backgrounds and experience. An individual physician might even respond differently to similar patient situations. Given this knowledge, we know that protocols can prove useful when applied judiciously and thoughtfully because their intent is to reduce unnecessary variation in physician response to patients with defined disease conditions. Protocols can also affect knowledge translation because they are one method to more quickly adapt new information to bedside care. For example, knowledge translation of the value of low tidal ventilation, as demonstrated by the ARDS Network ARMA (Prospective, Randomized, Multi-Center Trial of 12 mL/kg Tidal Volume Positive Pressure Ventilation for Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome) trial, was delayed for a long period before adoption at the bedside.[21]

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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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."[1] 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."[1] 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,

CVP nor $ScvO_2$ is a know all, be all. We also disagree with the comment that measurement of the CVP in the ED is "a close to an impossible task" because hospitals that have joined the SSC have achieved this goal repeatedly.

It is curious that Marik et al[1] selected the Australian and New Zealand Intensive Care Society as an example of the difficulties with the international adoption of the SSC guidelines because this organization is a sponsor of the 2012 guidelines.[3] It is even more curious that even critics, cited and referenced by Marik et al,[1] have conceded in their own meta-analysis that "sepsis care bundles were associated with consistent and significant increases in survival across eight studies."[4]

In conclusion, it is self-evident that care cannot be improved without understanding the deviation from known standards. Resisting standardization will simply perpetuate inefficient variation in care that has contributed to our unsustainable health-care economy. Partly for this reason and others, the United States ranks 37th among the world's health-care systems for quality of care, including individual longevity, according to World Health Organization rankings.[5] Recently, Congress recognized the need for consistency and set a different course to correct economic and quality forces in American health care. There appears to be little strength left in the argument to preserve do-whatever-you-want care. We believe strongly that the time has come for reporting performance measures in severe sepsis and other serious critical illnesses.

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Rebuttal From Dr Marik et al

Drs Dellinger and Townsend's[1] suggestion that bundles are always evolving is a key reason why bundles should not be universally mandated. Mechanisms invoked by bundles to produce benefits may also produce harm. Until the US Food and Drug Administration's suspension, several years of organized advocacy accelerated diffusion of Xigris (Eli Lilly and Company) therapy in nonselected populations. Systematic promotion of evidence illustrates the power of bundles to magnify ineffective therapies. Strategies like the catheter-related bloodstream infection prevention bundle may work because of unique contextual factors at play at institutional, national, or specialty-specific levels.[2] It is not clear that such checklist bundles can be transplanted without insight into the host culture.[3]

Drs Dellinger and Townsend stress that bundles should be evidence based, yet we have shown that with few exceptions, the elements of the 6-h sepsis bundle and ventilator-associated pneumonia bundle are not based on credible scientific evidence. There is surprisingly few data to support the contention that outcomes are improved when ICU bundles are rigorously followed. Before-and-after trials investigating effects of bundle implementation have reported reductions in mortality, apparently justifying bundle validity and calling for widespread adoption.[4] However, before-and-after trials should be viewed with skepticism because they are plagued by publication bias, patient selection bias, temporal bias, and the Hawthorne effect. Furthermore, such studies provide compelling data for the concept that bundling is seriously flawed and that several individual elements of bundles do not improve patient outcome (except for the timely use of antibiotics). For example, in the Edusepsis study conducted in Spain, only early, broad-spectrum antibiotic treatment was associated with improved outcomes.[5] It is noteworthy that in this study, mortality fell from 44% to 39% ($P = .04$) despite the fact that compliance with the 6-h sepsis bundle was only 10%, suggesting that factors other than bundle compliance were responsible for improved outcome. In the prospective, two-phase cohort study by Westphal et al,[6] patients with severe sepsis/septic shock were resuscitated in

accordance with the 6-h sepsis bundle. In the first phase of the study, patients were identified through usual clinical practice, whereas in the second phase, active surveillance for signs of sepsis risk was used. There were significant differences between phases I and II in the time required for the identification of severe/sepsis septic shock and in hospital mortality (61.7% vs 38.2%, $P < .001$); however, compliance with the 6-h sepsis bundle did not differ (32% vs 25%). Similarly, Shiramizo et al[7] noted a fall in mortality in patients with severe sepsis/septic shock from 41.4% to 16.2% between 2008 and 2009, despite a decline in compliance with the 6-h sepsis bundle. It is likely that earlier identification of sepsis and earlier administration of antibiotics are responsible for the mortality difference in all the before-and-after studies, with the other elements either having no beneficial effect or possibly being harmful. Many basic questions regarding the resuscitation of patients with sepsis remain unanswered: What type of fluid should be used (is saline the right fluid)? What BP should be targeted? How best to titrate fluids?

Dissemination of what does not work ought to match the marketing of treatments that work. In summary, we reiterate that the concept of bundling is scientifically unproven with no credible evidence that all-or-none bundle compliance improves patient outcomes. Physicians should not be mandated to provide care that may be potentially harmful.

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Rebuttal From Drs Dellinger and Townsend

Dr Marik and colleagues[1] 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 ($Scvo_2$) measurement, and severity of pathophysiology itself will prevent some goals from being achieved.

Marik et al[1] 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 $Scvo_2$ of $\geq 70\%$, the decision about how this goal would best be achieved was left to the treating clinician.[2] The new sepsis bundles only require that $Scvo_2$ be measured (Table 1[3]).

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 $Scvo_2$, 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 al[1] 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 $Scvo_2$). Like other single variables, neither

Table 1—*Surviving Sepsis Campaign Bundles 2012*

Bundles
To be completed within 3 h
Measure lactate level
Obtain blood cultures prior to administration of antibiotics
Administer broad spectrum antibiotics
Administer 30 mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L
To be completed within 6 h
Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation to maintain a MAP 65 mm Hg)
In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥ 4 mmol/L (36 mg/dL):
Measure CVP[a]
Measure $Scvo_2$[a]
Remeasure lactate if initial lactate was elevated[a]

CVP = central venous pressure; MAP = mean arterial pressure; $Scvo_2$ = central venous oxygen saturation. Used with permission from Dellinger et al.[3]

[a]Targets for quantitative resuscitation included in the guidelines are CVP of 8 mm Hg, $Scvo_2$ of 70%, and normalization of lactate.

CVP nor $ScvO_2$ is a know all, be all. We also disagree with the comment that measurement of the CVP in the ED is "a close to an impossible task" because hospitals that have joined the SSC have achieved this goal repeatedly.

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