Chapter 14
Bundled Therapies in Sepsis

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Introduction

In recent years, there has been an increased focus on delivering appropriate, efficient, and effective medical care. As a result of this, a number of tools and techniques have been developed and increasingly used to assist in this process. One such entity is that of care bundles or, more simply, bundles. These are a set of evidence-based interventions that, when implemented together, tend to result in significantly better outcomes than when implemented individually [1]. Bundles usually consistent of three to five elements and are targeted for a defined patient population or care setting. Their effectiveness is centered on bringing together independent practices and tying them into a package that needs to be completed for each encounter with these patients or care settings [2].

A variety of key factors are associated with the development of bundles. Each individual element within the bundle, when possible, should be based upon well-established evidence. If lower grade evidence including expert opinion is utilized, ongoing re-evaluation and periodic updating of the bundles and their associated elements should occur. As a general recommendation, the included elements should be between three and five in number and descriptive in manner rather than proscriptive, so as to aid in appropriate local customization [1]. In addition, a multidisciplinary approach should be used in their development and implementation. This not only ensures broad acceptance of the reasoning behind them but also allows for a consistent focus on how they should be utilized to deliver the most effective care possible. This broad, team-based approach to bundles also prevents them from devolving into simple checklists.

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Checklists, while helpful, tend to contain a series of tasks and processes that often fall under either the "nice to do" or "have to do" categories [2]. They also have the potential to get overloaded with an increased number of elements while lacking a well-delineated owner. Their utilization also tends to be extremely broad and not targeted toward specific patients or care settings. As a result of all of this, omission of various elements within a checklist, or the entire list altogether, may not necessarily impact a patient to a large degree. This is in stark contrast to a bundle, however, given their focused usage and more scientifically robust construction. An omission of an element within a bundle, or a bundle altogether, is much more likely to result in a negative outcome for a patient.

This leads to arguably the most important factor associated with the development of care bundles: compliance with them is measured in an "all or none" approach. If all elements have been completed, or if an element was not completed but documented as contradicted for a specific reason, then the bundle is counted as complete for that specific patient or setting. If any element is absent in the documentation, then the bundle is incomplete. The "all or none" method limits variability and assures that evidenced-based care is being delivered consistently. In addition, it also promotes improvement methods to focus on processes of care so as to facilitate improved bundle usage, and ultimately patient outcomes [1].

History

Care bundles were initially developed around 20 years ago. They have been used within a number of different medical and surgical specialties and perhaps most prominently within cardiology [3]. In recent years, their use has been increasingly explored and utilized within the field of critical care. [4, 5]. Berenholtz et al. further advanced this idea with an article published in 2002. The authors reviewed 35 years' worth of critical care literature for interventions that could prevent avoidable morbidity and mortality in intensive care [6]. Six evidence-based interventions were ultimately identified that were felt to be able to improve intensive care outcomes: effective assessment of pain, appropriate use of blood transfusions, prevention of ventilator-associated pneumonia, appropriate sedation, appropriate peptic ulcer disease prophylaxis, and appropriate deep vein thrombosis prophylaxis [7]. The latter four of these interventions were subsequently clustered together to form a ventilator care bundle.

The Institute of Healthcare Improvement (IHI) then used these works to help develop two care bundles that ultimately were a key part of the "100,000 Lives Campaign" and the "5 Million Lives Campaign" [8]. The IHI Ventilator Bundle was the first of these and consisted of four elements: elevation of the head of the bed to between 30° and 45°, daily "sedation" vacations and assessment of readiness to extubate, peptic ulcer disease prophylaxis, and deep venous thrombosis prophylaxis. A fifth element, "daily oral care with chlorhexidine," was added a few years later [9]. The overall goal with this tool was to reliably provide care that prevented certain

adverse events associated with patients receiving mechanical ventilation. The second bundle that was developed was the IHI Central Line Bundle. The five elements with this tool consisted of hand hygiene, maximal harrier precautions, chlorhexidine skin antisepsis, optimal catheter site selection, and daily review of line necessity with prompt removal of unnecessary lines [10]. Both these bundles were noted to have a positive effect with increasing rates of compliance resulting in decreased rates of ventilator adverse events and central line associated infections [11–13]. These successes subsequently allowed the bundle concept to be more easily applied to other areas within the field of critical care including severe sepsis and septic shock.

The Surviving Sepsis Campaign and Initial Care Bundles

The Surviving Sepsis Campaign was created in 2002 to increase awareness and improve care for patients with severe sepsis and septic shock. This movement represented a combined effort from multiple professional societies including the European Society of Intensive Care Medicine, and the Society of Critical Care Medicine with the overall goal of reducing mortality from sepsis by 25% by 2009, which represented the 5-year anniversary of its initial release of guidelines in 2004 [14]. The campaign has consisted of four phases. The first was undertaken in early 2002 and 2003 and consisted of an introduction to the campaign and along with a push to define the scope of the problem posed by sepsis and to also increase awareness [15]. The second phase consisted of the creation of evidence-based guidelines for the management of severe sepsis and septic shock via an international consensus committee and the initial set, as previously noted, was published in 2004. The third phase of the Surviving Sepsis Campaign was then undertaken with collaboration with the Institute of Healthcare Improvement. The goal of this step was to disseminate the guidelines into everyday clinical care while also gathering data on their implementation and effect [15].

This was accomplished using a variety of instruments including educational programs to continue to increase awareness and adherence with the guidelines as well as performance measures and quality improvement indicators deigned to provide feedback regarding how often patients were receiving guideline-based care [15, 16]. In addition, and arguably most importantly, two sepsis care bundles were created from elements within the Surviving Sepsis Guidelines. In keeping with the one of core mantras associated with care bundles, “the aim of the sepsis bundle is twofold: first, to eliminate the piecemeal application of guidelines that characterizes the majority of clinical environments today, and second, to make it easier for clinicians to bring the guidelines into practice” [16].

The initial bundles that were created from the Campaign’s evidence-based guidelines were the Sepsis Resuscitation Bundle and the Sepsis Management Bundle. The Resuscitation Bundle consisted of six elements to be completed within the first 6 h of a patient’s presentation. The elements included checking a serum lactate, obtaining blood cultures prior to the administration of antibiotics, administering

broad spectrum antibiotics within 3 h of emergency department admission or within 1 h for non-emergency department intensive care unit admissions, delivering an initial fluid bolus of 20 mL/kg of crystalloid (or colloid equivalent) in the event of hypotension and/or a lactate level greater than 4 mmol/L followed by the administration of vasopressors for hypotension not responding to initial fluid resuscitation to maintain a mean arterial pressure (MAP) greater than or equal to 65, and lastly, in the event of persistent hypotension despite fluid resuscitation and/or a lactate level greater than 4 mmol/L achieving a central venous pressure (CVP) greater than 8 mmHg and/or a central venous oxygen saturation ($S_{cv}O_2$) of greater than 70% [17]. The Management Bundle consisted of four elements that recommended to be accomplished within the first 24 h of presentation. These included the administration of low-dose steroids for septic shock in accordance with standardized hospital policy, drotrecogin alfa (activated) administered in accordance with standardized hospital policy, glucose control maintained greater than the lower limit of normal but less than 150 mg/dL and inspiratory plateau pressures maintained less than 30 cmH_2O for mechanically ventilated patients (see Fig. 14.1) [17].

These two bundles were subsequently disseminated with the rest of the Campaign's educational materials and quality indicators. To fully facilitate the improvement of the delivery of care for sepsis, an international registry was also created as part of the Surviving Sepsis Campaign and a number of regional networks were established to facilitate data collection and assistance with performance improvement [15]. The first large-scale analysis of the Campaign and its participating sites was published in 2010. A total of 165 participating sites with 15,022 subjects between January 2005 and March 2008 were examined. Initial compliance at all sites in the first quarter with both bundles was noted to be low, at only 10.9% for the resuscitation bundle and 18.4% for the management bundle. These rates were noted to increase linearly with time, however, up to 31.3% ($p < 0.001$) by the end of 2 years for the resuscitation bundle and 36.1% ($p = 0.008$) for the management bundle (see Fig. 14.2). In addition, compliance with each indi-

Severe Sepsis Bundles:
Sepsis Resuscitation Bundle
(To be accomplished as soon as possible and scored over first 6 hours):
1. Serum lactate measured.
2. Blood cultures obtained prior to antibiotic administration.
3. From the time of presentation, broad-spectrum antibiotics administered within 3 hours for ED admissions and 1 hour for non-ED ICU admissions.
4. In the event of hypotension and/or lactate > 4 mmol/L (36 mg/dl): a) Deliver an initial minimum of 20 ml/kg of crystalloid (or colloid equivalent). b) Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) > 65mm Hg.
5. In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate > 4 mmol/L (36 mg/dl):
a) Achieve central venous pressure (CVP) of > 8mm Hg.
b) Achieve central venous oxygen saturation (ScvO2) of > 70%.*
Sepsis Management Bundle
(To be accomplished as soon as possible and scored over first 24 hours):
1 Low-dose steroids administered for septic shock in accordance with a standardized hospital policy.
2 Drotrecogin alfa (activated) administered in accordance with a standardized hospital policy.
3 Glucose control maintained > lower limit of normal. but < 150 mg/dl (8.3 mmol/L).
4 Inspiratory plateau pressures maintained < 30 cm H2O for mechanically ventilated patients.
*Achieving a mixed venous oxygen saturation (SvO2) of 65% is an acceptable alternative.

Fig. 14.1 Initial resuscitation and management bundles produced by the Surviving Sepsis Campaign in 2004. Reproduced from Levy MM, Dellinger RP, Townsend SR et al. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. Crit Care Med. 2010; 38:367–374

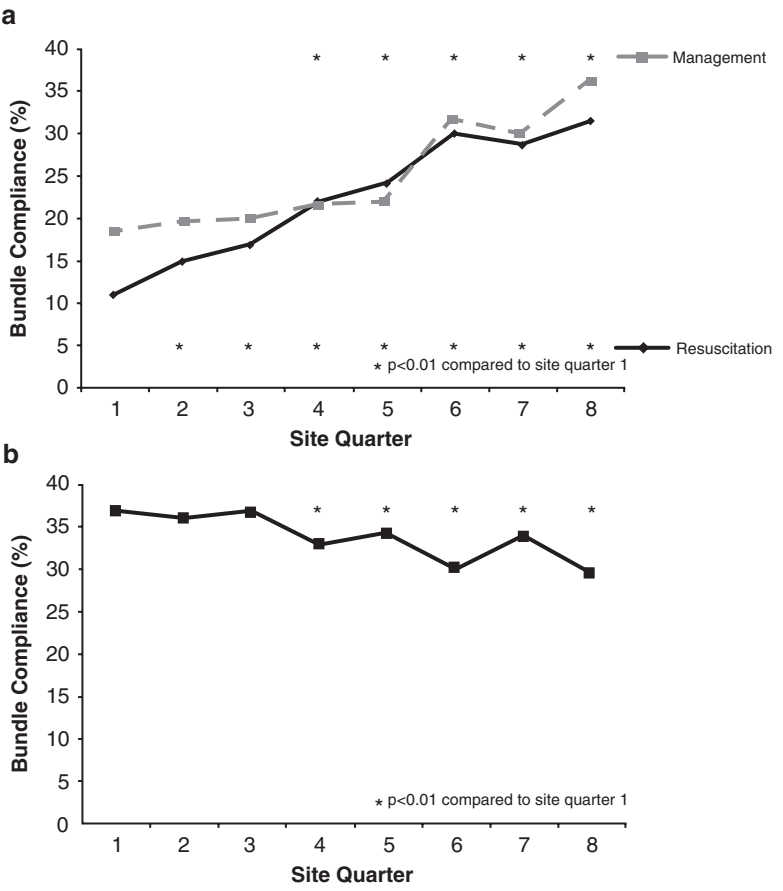

Fig. 14.2 Compliance and mortality change over time. (**a**) Change in the percentage of patients compliant with all elements of the resuscitation bundle (*dotted line*) and the management bundle (*solid line*) over 2 years of data collection (*$p < 0.01$ compared with the first quarter). Note that both *Y* axes are truncated at 40% to emphasize relative change over time as opposed to absolute change. (**b**) Change in hospital mortality over time (*$p < 0.01$ compared with first quarter). Reproduced from Levy MM, Dellinger RP, Townsend SR et al. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. Crit Care Med. 2010; 38:367–374

vidual bundle element was noted to increase significantly as well, with the exception of inspiratory plateau pressure, which was high at baseline [17]. Unadjusted hospital mortality was noted to decrease during this 2 year period from 37 to 30.8% ($p = 0.001$) and the adjusted odds ratio for mortality was noted to improve for each successive quarter that a site participated in the Campaign. This resulted in an adjusted absolute drop of 0.8% per quarter with an overall drop of 5.4% (95% confidence interval 2.5–8.4) over 2 years [17]. These results were interpreted as encouraging but a definitive relationship between increased compliance and mor-

tality reduction could not be directly established given the overall study design. There was clear association, however, with participation in the Surviving Sepsis Campaign and continuous quality improvement in sepsis care as well as decreased hospital mortality [3, 17]. This relationship continued to be demonstrated in the most recent analysis of the Campaign as well. Over a period of now seven and a half years, increased compliance was noted to be associated with a 25% relative risk reduction in mortality [18].

A similar trend was also noted in studies performed outside the Surviving Sepsis Campaign but still utilizing both care bundles. In a prospective observational study published by Gao et al. in 2005, which was one of the first studies examining bundle compliance and hospital mortality, the impact of compliance with both the resuscitation and management bundles was examined in 101 consecutive critically ill patients with severe sepsis and septic shock at two teaching hospitals in England [19]. The rate of compliance with the resuscitation bundle was noted to be 52% and the management bundle was 30%. Noncompliance with the resuscitation bundle was associated with a relative risk of in-hospital mortality of 2.12 (95% confidence interval 1.20–3.76) while noncompliance with the management bundle was associated with a relative risk of in-hospital mortality of 1.76, although this did not achieve statistical significance [19].

A prospective observational study performed at a teaching hospital in Belgium examined not only bundle compliance and mortality but also the time to compliance [20]. Among 69 consecutive patients admitted to the intensive care unit with severe sepsis or septic shock, compliance with the resuscitation bundle was obtained in 72%. This cohort had a significant lower mortality rate of 16% as compared to a mortality rate of 44% among those patients whose care was not compliant with the resuscitation bundle [20]. No significant difference in mortality was noted in the patients whose care was compliant with the management bundle, but among patients whose care was compliant with the management bundle after only 12 h, a statistically significant lower mortality rate of 10% was noted as compared to 39% among whose who were compliant after 24 h [20].

A subsequent meta-analysis, which consisted of a total of 21 studies including the two highlighted above, examined the use of both the resuscitation and management bundles and their association with survival among patients with severe sepsis and septic shock. A total of 23,438 patients were pooled for analysis and the overall compliance rate with the bundles was noted to be around 50% [21]. Compliance with the resuscitation bundle was noted to be two times more likely to be associated with survival (odds ratio of 2.124, 95% confidence interval 1.701–2.651), while compliance with both bundles together demonstrated a slightly lower but still significant impact (odds ratio 1.744, 95% 1.421–2.141) [21].

More recently, significant improvements were noted in mortality in conjunction with an increase in bundle compliance among 4329 adults admitted with severe sepsis or septic shock among a group of 18 ICUs in both Utah and Idaho from 2004 through 2010 [22]. In this particular cohort, mortality was observed to decrease from 21.2% in 2004 to 8.7% in 2010 while all-or-none total bundle compliance simultaneously increased from 4.9 to 73.4%. Interestingly, and not overly surprising,

increased compliance with the initial resuscitation bundle was noted to be associated with a lower probability of being eligible for further resuscitation and the need for management bundle elements [22].

Current Sepsis Bundle Practices

As the Surviving Sepsis Campaign moved through its third phase and into its fourth, which is focused on reinvigorating the campaign and recommitting to improving mortality from sepsis, two revised sets of guidelines were released, first in 2008 and then again most recently in 2012 [15]. With both updates, changes were made reflective of the most recent evidence available for the evaluation and treatment of sepsis [23]. As a result of the most recent guideline changes in 2012, along with continued evaluation of data from the international registry, two major changes were made to the care bundles.

The first of these was that the management bundle, which consisted of several elements targeted for completion within the first 24 h, was removed in its entirety [22]. After analyzing the series of well-designed randomized controlled trials examining the use of steroids in adult septic shock, no benefit was noted on outcome [23, 24]. A lack of definitive conclusiveness was also noted for the management of blood sugars [23, 25, 26]. At the same time, given the results of the PROWESS-SHOCK trial, which showed no benefit for droctrecogin alfa (recombinant human activated protein C) in patients with severe septic shock as well as its subsequent removal from the market by the FDA, its role in the guidelines and subsequent care bundles was negated [23, 27]. In the SSC dataset, compliance with the inspiratory plateau pressure target of less than 30 cmH_2O was consistently over 80% and thus it was dropped as a target for performance improvement.

The second major change was to the resuscitation bundle. The major impetus for this change was tied to one of the important premises associated with care bundles, that there should be constant reevaluation of the bundle elements with periodic updating so as to encourage continuous improvement of both care process and outcomes [1, 5]. A recent review of seven and a half year's worth of data consisting of nearly 30,000 patients in the Surviving Sepsis Campaign database revealed a 25% relative risk reduction in mortality associated with a statistically significant increase in bundle compliance and for every hour delay seen with antibiotic administration, a 5–7% increase in mortality was noted [18, 28, 29]. In addition, lactate, blood culture obtainment, antibiotic administration, intravenous fluid administration, central venous pressure, and central venous oxygen saturation ($ScvO_2$) were all noted to be statistically significant independently and significantly associated with a decreased odds ratio of mortality (see Table 14.1) [18, 29].

As a result of these findings, the resuscitation bundle was divided into two parts, with the goal of emphasizing early detection and early intervention. The first component, the initial resuscitation bundle, currently consists of four elements to be completed within the first 3 h of a patient's presentation: measure a lactate level,

Table 14.1 Hospital mortality adjusted odds ratio modeled individually for each element in bundle compliance using a generalized estimating equation population-averaged logistic regression

	Participation in SSC, year	Hospital mortality OR[a]	95% Cl	*p*
Initial care bundle (first 6 h of presentation)				
Measured lactate	<2	0.80	0.73–0.89	<0.001
	2 to <3	0.67	0.59–0.76	<0.001
	≥3	069	0.63–0.75	<0.001
Blood cultures before antibiotics	Not applicable[b]	0.82	0.77–0.87	<0.001
Broad-spectrum antibiotics	Not applicable[b]	0.85	0.81–0.90	<0.0001
Fluids and vasopressors	<2	0.86	0.73–1.01	0.074
	2 to <3	0.63	0.48–0.81	<0.001
	≥3	0.74	0.62–0.88	0.001
CVP > 8mmHg	Not applicable[b]	0.84	0.78–0.91	<0.0001
$Scvo_2 > 70\%$	Not applicable[b]	0.83	0.76–0.90	<0.001
All resuscitation measures	Not applicable[b]	0.79	0.73–0.85	<OJO01
Management bundle (First 24 h after presentation)				
Steroid policy	<2	0.96	0.84–1.09	0.527
	2 to <3	0.76	0.64–0.89	0.001
	≥3	0.88	0.79–0.99	0.031
rhAPC policy	Not applicable	0.93	0.87–1.00	0.061
Glucose policy	Not applicable	0.71	0.68–0.75	< 0.001
Plateau pressure control	Not applicable	0.81	0.74–0.89	< 0.001
All management measures	Not applicable	0.74	0,69–0.79	< 0.001

Reproduced from Levy MM, Rhodes A, Phillips GS et al. Surviving Sepsis Campaign: Association between performance metrics and outcomes in a 7.5-year study. Crit Care Med. 2014; October 1. Epub ahead of print

SSC surviving sepsis campaign, *OR* odds ratio, *CVP* central venous pressure, *$Scvo_2$* central venous oxygen saturation, *rhA PC* recombinant human activated protein C

[a]Hospital mortality odds ratio for those patients where the bundle- element was achieved compared to when the bundle was not achieved, and the results are adjusted by sight quarter of participation and the Sepsis Severity Score

[b]No significant interaction ($p < 0.05$) between the bundle element and years of participation in the Surviving Sepsis Campaign. If the interaction was significant, then the odds-ratio is given for each level of participation

obtain blood cultures prior to administration of antibiotics, administer broad spectrum antibiotics, and administer 30 mL/kg of crystalloid fluid for hypotension or a lactate level greater than 4 mmol/L [23]. The second part, the septic shock bundle, currently consists of three elements to be completed within 6 h of a patient's presentation; apply vasopressors for hypotension that does not respond to initial fluid resuscitation to maintain a mean arterial pressure (MAP) greater than or equal to 65, in the event of persistent arterial hypotension despite volume resuscitation or an initial lactate greater than or equal to 4 mmol/L a central venous pressure (CVP) and/or central venous oxygen saturation ($ScvO_2$) should be measured, and lastly, to re-measure a lactate level if the initial lactate was elevated (see Fig. 14.3) [23].

SURVIVING SEPSIS CAMPAIGN BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:
1) Measure lactate level
2) Obtain blood cultures prior to administration of antibiotics
3) Administer broad spectrum antibiotics
4) Administer 30 mL/kg cry stalloid for hypotension or lactate ≥4mmol/L

TO BE COMPLETED WITHIN 6 HOURS:
5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥ 4 mmol/L (36 mg/dL):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation ($Scvo_2$)*
7) Remeasure lactate if initial lactate was elevated*

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

Fig. 14.3 Current surviving sepsis campaign bundles. Reproduced from Dellinger RP, Levy MM, Rhodes A et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012. Crit Care Med. 2013; 41:580–637

Controversies with Sepsis Bundle Practices

Despite the increased uptake of care bundles within the field of critical care, a number of criticisms of them exist along with criticisms regarding their usage in the evaluation and treatment of patients with severe sepsis and septic shock. These critiques are varied in their approach and reasoning and they often cite a number of reasons for opposition to the idea of using care bundles. These range from arguing that the bundles are used by industries as a marketing tool or that they are inefficient due to the inclusion of too many individual elements [30, 31].

One of the major and often repeated criticisms is that there is a lack of formal evidence supporting the process of bundling. Opponents note that the idea of bundle synergy has not been clearly examined. In addition, it is argued that results from before and after the implementation of bundles are not definitive "proof-of-concept" demonstrations or are appropriate substitutes for prospective randomized trials [32]. This point regarding a lack of robust scientific evaluation of the impact of bundles on clinical outcomes has been acknowledged by bundle proponents, including the Surviving Sepsis Campaign, and thus studies demonstrating their effectiveness should be interpreted with some degree of caution [17, 19]. At the same time, however, there has been no data demonstrating any degree of harm posited by the use of care bundles and their established trend of effectiveness has continued with their continued use [28, 33]. In addition, bundles are reflective of a method focused on overall performance improvement for the entire process of care associated with a particular patient or care setting [2, 11]. Thus, standardized controlled trials and

their associated outcomes may be insensitive in their ability to capture all of the relevant results from this method.

A second major criticism of the use of care bundles in sepsis is that in adopting an "all or none" approach to bundle compliance, a lack of clinical autonomy and a failure to tailor therapy to each individual patient develops [32, 34]. An element that seems to get missed in this argument, however, is that all the elements within the sepsis care bundles have always been acknowledged to potentially not apply to every patient with severe sepsis or septic shock [33]. If a particular element is felt to not apply to a particular patient or care setting, as long as that reasoning is documented and acknowledged then the bundle may still be counted as complete [1, 33]. In recent years, this issue has centered on the use of central venous pressure for assistance with guiding volume resuscitation [32, 34, 35]. Given the presence of new data from both inside and outside the Campaign, the Surviving Sepsis Campaign's bundles have subsequently reflected this change and as previously noted, it is now part of the septic shock bundle to simply be checked within the first 6 h in the presence of persistent hypotension or hyperlactatemia [23, 33]. The simple act of transducing a central venous pressure in a patient with septic shock is unlikely to be harmful and the subsequent result can be added to the clinical data available to the clinician at the bedside to then make an informed decision regarding further therapy. At the same time, the majority of the critiques of this "all or none" approach are centered in tertiary or quaternary centers where more often than not, multiple advanced therapies and providers are available at the bedside in a moment's notice [30, 34, 35]. A large number of smaller institutions exist, however, and may not have these same resources and advanced capabilities. Thus, relying on an "all or none" approach with these care bundles in these settings limits potentially harmful variability and allows the delivery of consistent, performance improvement driven care [33, 36].

Conclusion

In closing, it is clear that care bundles seem to be effective instruments in delivering consistent care and improving patient outcomes across the field of medicine. Over the past few years, they seem to have been particularly effective in improving the processes of care and outcomes associated with sepsis, largely through the work of the Surviving Sepsis Campaign [18, 28]. One of key tenets of care bundles, however, is that they are reflective of an ongoing improvement process that is embraced by the entire environment around them [1, 6]. As the field of critical care continues to embrace this concept in increasing numbers, bundled care for sepsis as well as sepsis care overall, will undoubtedly continue to improve and the elements included in care bundles will change and evolve over time as the evidence base changes and the field moves forward [37].

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