The severe sepsis bundles as processes of care: A meta-analysis

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\textbf{Summary}

\textbf{Objective:} The use of the sepsis bundles in patients with severe sepsis and septic shock has been controversial in the last decade. Clinical studies have reported beneficial, as well as negative results. We conducted a meta-analysis to assess the clinical evidence and to evaluate survival effects.

\textbf{Data source:} Database searches (2004–current) of Medline, CINAHL, Pubmed, Cochrane, Scopus and Google scholar databases which covered full publications, abstracts from conferences and digital thesis were performed using the search terms sepsis, septic shock and/or bundles, processes of care, guidelines, early goal directed therapy, resuscitation.

\textbf{Results:} From 253 identified studies, 21 sepsis bundle original studies were selected and included 23,438 patients. The Resuscitation 6 hour Bundle pooled analysis (1819 patients) achieved the greatest survival benefit (odds ratio (OR) 2.124, 95% CI 1.701–2.651, \(p<0.000\)) with the Management 24 hour Bundle pooled analysis the lowest survival benefit (16,521 patients) (OR 1.646, 95% CI 1.036–2.614, \(p<0.035\)). Both bundles together (Complete Bundle) achieved a combined survival benefit (OR 1.744, 95% CI 1.421–2.141, \(p<0.000\)). ScvO2 and blood glucose components were analysed individually to assess their contribution to survival.
In this last decade "care bundles" have transformed clinical practice resulting in greater synergy and teamwork within the "best practice" endeavour. A bundle is a selected set of interventions or processes of care distilled from evidence-based practice components that when implemented as a group presents a more robust picture of the quality of care provided, benchmarks performance and improves patient outcomes. Reports that several practices instituted together could reduce the prevalence of catheter-related infection or mortality in mechanically ventilated patients support this approach.

Interestingly, care bundles have also been observed to work more effectively together as a one process rather than simply a sum of its components. In addition, this phenomenon remains to be fully investigated but one hypothesis suggests that care bundle application and compliance result in changes to the clinical team behaviour and performance rather than just the survival attributes of each bundle component. There is gathering evidence that this concept of care bundles is gaining endorsement. In Australia, the Australian Commission on Safety and Quality in Health Care has endorsed the use of 'bundles' and surveillance for the prevention of health care acquired infections. In the United States, recent comprehensive prevention programs that 'bundle' a group of three to five evidence-based Health Care Associated Infection (HAI) strategies have significantly reduced ICU-acquired infections. Likewise, critical care nurses are familiar with the "FAST HUG" acronym (Feeding, Analgesia, Sedation, Thromboembolic prophylaxis, Head-of-bed elevation, stress Ulcer prevention, and Glucose control), which has become part of critical care unit culture and performance indicators. FAST HUG is a concept, not a bundle, but illustrates how evidential protocols combined together can assist with quality care delivery.

In the last decade the Surviving Sepsis Campaign (SSC) has produced the well endorsed guidelines for the care of patients meeting the criteria for severe sepsis first in 2004 and then updated in 2008. From these guidelines the "Severe Sepsis Bundles" have been formulated consisting of Resuscitation 6 hour Bundle and a Management 24 hour Bundle as described in Table 1. Initially the SSC was promoted with pharmaceutical companies’ funding and promotion, although generally welcomed led to strong criticism by various groups, which was equally robustly rebutted. Additionally, the reliance on predominantly single studies with remarkable survival outcomes such as Rivers et al. for early goal directed therapy (EGDT) the main component of the Resuscitation Bundle, has led to a decade of debate leaving the clinician at the beside unsure of the effectiveness of the evidence.

In Australia where the mortality rate for severe sepsis is one of the lowest in the world, scepticism and doubt regarding the utility of the sepsis bundles are ubiquitous. On the other hand, low Australian mortality rates may be associated with processes of care such as shorter waiting times in emergency departments and ease of access to affordable medical care including critical care services compared to other countries. Irrespective of these issues, the Australian and New Zealand Intensive Care Society (ANZICS) could not support the 2008 sepsis guidelines and is reported in an editorial by Hicks and colleagues:

"ANZICS has therefore reluctantly concluded that it would not be appropriate to sponsor the entire package of the 2008 Guidelines, because some components did not reflect current practice in Australia and New Zealand and some have not been proven superior to current practice bi-nationally."
Table 1 Components in two sepsis bundles formulated by the Surviving Sepsis Campaign.8,9

<table>
<thead>
<tr>
<th>Bundle title</th>
<th>Components</th>
</tr>
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<tbody>
<tr>
<td>Sepsis Resuscitation 6 hour Bundle (to be</td>
<td>Obtain microbiology samples and lactate measure Administer appropriate antibiotics Administer early resuscitation therapy including: - Fluids to achieve a central venous pressure of 8—12 mm Hg - Vasopressors to achieve a mean arterial blood pressure &gt; 65 mm Hg - Maintain central venous oxygen saturation ≥70% with packed red blood cells or inotrope therapy Administer low-dose corticosteroids based on hospital policy Administer recombinant human activated protein C based on hospital policy Maintain glycaemic control (120—150 mg/dL) or (6.8—8.4 mmol/L) Maintain plateau airway pressures ≤30 cm H2O in mechanically ventilated patients</td>
</tr>
<tr>
<td>completed within 6 h of admission)</td>
<td></td>
</tr>
<tr>
<td>Sepsis Management 24 hour Bundle (to be</td>
<td>Administer low-dose corticosteroids based on hospital policy Administer recombinant human activated protein C based on hospital policy Maintain glycaemic control (120—150 mg/dL) or (6.8—8.4 mmol/L) Maintain plateau airway pressures ≤30 cm H2O in mechanically ventilated patients</td>
</tr>
<tr>
<td>completed within 24 h of admission)</td>
<td></td>
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</tbody>
</table>

Instituted early in the patient’s hospital course, specifically upon recognition of sepsis in the ED. The study found that patients who received the protocol had a 16% absolute reduction in in-hospital mortality as compared with those patients who received standard care (30.5% vs 46.5%). In fact, a survey indicated that EGDT is used in a minority of academic EDs, largely due to the complexity and invasiveness of the protocol.21 Furthermore, the ARISE investigators20 in their observational study of EGDT demonstrated that maintaining continuous central venous oxygen saturation greater than or equal to 70% (ScvO2 ≥70%) was not part of routine Australian resuscitation practice and needs clarification in terms of its survival benefit. Therefore, to establish if EGDT is applicable to other settings than Rivers et al., a randomized control trial is being conducted internationally.22

In relation to the Sepsis Management 24 hour Bundle, recent revised recommendations23 related to the blood glucose component levels suggest that until additional information is available, teams seeking to implement glucose control should consider initiating insulin therapy when blood glucose levels exceed 180 mg/dL with a goal blood glucose approximating 150 mg/dL as was observed in the beneficial arm of the NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation) study.24 NICE-SUGAR demonstrated that the primary outcome variable, 90-day mortality, was actually increased in patients randomly assigned to intensive insulin therapy, against intravenous insulin therapy titrated to keep blood glucose in the normal range (80—110 mg/dL or 4.5—6.0 mmol per litre (mmol/L)), compared to conventional glucose control, with a target of 180 mg or less per decilitre (10.0 mmol or less per litre) in patients with severe sepsis. The NICE-SUGAR trial reflecting data collected in a set of more than 6000 patients is the largest most compelling study to date on glucose control in ICU patients given its inclusion of multiple ICUs and hospitals, and a more general patient population. Aside from these updated recommendations, blood glucose level targets have always been conservative in the Management 24 hour Bundle (120—150 mg/dL or 6.8—8.3 mmol/L). Therefore the survival benefit of the blood glucose recommendation in the Sepsis Management 24 hour Bundle needs to be established in sepsis patients.

Since the publishing of the 2004 guidelines many small observational cohort studies25—46 have been published suggesting a survival benefit and were included in the meta-analysis. However, sepsis is a complex and heterogeneous disease and alongside the methodological limitations of observational studies including selection bias, unpowered studies with small sample sizes and different designs of each of the studies involved the question remains, is there a survival benefit with compliance of the sepsis bundles?

The aim of this paper was to perform a meta-analysis on studies examining sepsis bundles and their association with patient survival in order to inform current clinical practice. In addition, the ScvO2 component of the Resuscitation 6 hour Bundle and the blood glucose component of the Sepsis Management 24 hour Bundle were analysed in terms of a sepsis population to determine their associations with survival.
Methods

Literature search

The meta-analysis design followed the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) to maintain quality and reduce selection bias.47 A search of Medline, CINAHL, Pubmed, Cochrane, Scopus and Google scholar databases which covered full publications, abstracts from conferences and digital thesis were performed using the search terms sepsis, septic shock and/or bundles, processes of care, guidelines, early goal directed therapy and resuscitation. There were no randomized control trials reporting the use of sepsis bundles as the variable of interest. Unpowered observational cohort studies, both retrospective and prospective were the only studies available with cases and controls. The study conducted by Gao et al. in 200525 was the first study of its kind with the sepsis bundles as the variable of interest. Unpowered observational cohort studies, both retrospective and prospective were the only studies available with cases and controls. The study conducted by Gao et al. in 200525 was the first study of its kind with the sepsis bundles as the variables of interest and hospital mortality as the first outcome of interest (compliance as the second) given that the first of the sepsis guidelines and bundles were published in 2004.8 This is an important study to note as it was the first to set the trend in reporting a survival benefit from the implementation of the sepsis bundles and hence has been cited consistently by later studies.

Citation maps were created with Scopus citation database using Gao et al. and cross referenced to the sepsis guidelines publications in both 20048 and 20089. The sepsis guidelines and updates were published in both Critical Care Medicine and the Intensive Care Medicine journals. All the studies following the Gao et al. publication25 cited this study except for one. Two hundred and fifty three studies were identified with the sepsis bundles as the variable of interest and hospital mortality as the outcome of interest. Scopus email alerts were used to report new studies as they were published. This search was first conducted in 2008, then again two monthly using the same format until the end of 2010. This repetition of searches allowed the author to watch the development within the literature with regards to sepsis bundles as a process of care. The literature search strategy is described in Fig. 1.

Two independent research assistants followed the same search strategy previously described using the PRISMA guide. Consensus was achieved by comparing compiled abstracts from printouts of the database search summaries using the specific selection criteria. All of the studies matched except for the 2 abstracts which were from conferences that the author attended.

Of these studies 21 (Table 2) were selected as they included the use of the sepsis bundles albeit

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Figure 1  Meta-analysis literature search strategy.
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<tr>
<th>Author</th>
<th>Patient recruitment location</th>
<th>Study design</th>
<th>Patient types mean Apache II and age</th>
<th>Intervention and time period/time comment/bundle compliance</th>
<th>Hospital mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gao et al. (N = 101)</td>
<td>England: 2 acute NHS teaching hospitals Critical Care Unit</td>
<td>Prospective, observational; intra cohort comparison of SSC bundle compliant vs non-compliant groups</td>
<td>Medical, surgical Median Age 69 (51—78) IQR Mean Apache II = 20 (7.7)</td>
<td>Modified SSC resuscitation and management Bundles Compliance: Resuscitation: 52% Management: 30% SSC bundles compliance resuscitation: 15% Management: 23% Both bundles: 8.6%</td>
<td>Resuscitation: full compliance: 23%, partial compliance: 49% Management: full compliance: 29%, partial compliance: 50%</td>
</tr>
<tr>
<td>Douglas et al. (abstract) (N = 509)</td>
<td>Colorado, USA: 10 community hospitals Emergency and critical care units</td>
<td>Prospective, observational; intracohort comparison of SSC bundle compliant vs non-compliant groups</td>
<td>Medical, surgical Apache II not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kortgen et al. (N = 60)</td>
<td>Germany: 1 hospital academic university Critical Care unit admissions</td>
<td>Retrospective, cohort study</td>
<td>Medical, surgical Median Apache Control = 31 (26—35) IQR SOP = 35 (30—37) IQR Median age 59 vs 68</td>
<td>Non-SSC sepsis bundle Compliance with use of the modified bundle not reported; individual process measures cited reporting significant improvements EGDT similar to 6 h bundle Compliance not reported</td>
<td>Hospital mortality Before: 53% After: 27%</td>
</tr>
<tr>
<td>Trzeciak et al. (N = 38)</td>
<td>New Jersey, USA: 1 hospital; academic university Emergency department</td>
<td>Retrospective cohort with historical controls</td>
<td>Medical, surgical Mean Apache II = 23.85 (10) SD Mean Age 66.8 (14.3) vs 62.5 (16.5)</td>
<td></td>
<td>Hospital mortality No EGDT 43.8% EGDT 18.2%</td>
</tr>
<tr>
<td>Micek et al. (N = 120)</td>
<td>Missouri, USA: 1 hospital; academic medical centre Emergency department</td>
<td>Before/after design</td>
<td>Medical, surgical trauma Mean Apache II = 22.5 (8.3) SD Mean age 68.0 (16.1) vs 61.4 (20.0)</td>
<td>Three admission order sets based on the SSC guidelines Compliance not reported</td>
<td>28-day mortality Before: 48% After: 30% Hospital mortality Before: 48.3% After: 35% Historical controls: 29.4% Protocol: 20.3% N/S</td>
</tr>
<tr>
<td>Shapiro et al. (N = 167)</td>
<td>Massachusetts, USA: 1 hospital; academic medical centre Emergency department</td>
<td>Prospective, interventional cohort study with historical controls</td>
<td>Medical, surgical Mean age 59.9 ± 29.4 Apache II not reported</td>
<td>Adapted-SSC bundle: &quot;MUST protocol” Compliance not reported</td>
<td></td>
</tr>
<tr>
<td>Jones et al. (N = 156)</td>
<td>North Carolina, USA: 1 hospital; academic medical centre Emergency department with critical care admissions</td>
<td>Prospective interventional cohort study</td>
<td>Medical, surgical Mean Age 57.6 ± 15.6 Apache II not reported</td>
<td>EGDT only: early resuscitation bundle Compliance not reported</td>
<td>Before: 27% After: 18%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient recruitment location</th>
<th>Study design</th>
<th>Patient types and age</th>
<th>Intervention and time period/time comment/bundle compliance</th>
<th>Hospital mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nguyen et al.32</td>
<td>California, USA: 1 hospital; academic medical centre Emergency department with critical care admissions</td>
<td>Prospective observational cohort; intracohort comparison emergency department bundle compliant vs non-compliant groups</td>
<td>Medical, surgical Mean age = 64.1 ± 20.5 Mean Apache II = 30.9 ± 9.4</td>
<td>6 h modified SSC bundle completed in the emergency department Compliance 51%</td>
<td>Full compliance: 20.8% Partial compliance: 39.5%</td>
</tr>
<tr>
<td>Zambon et al.33</td>
<td>Brussels: 1 hospital Academic medical centre Patients admitted to critical care from emergency department or wards</td>
<td>Prospective interventional cohort study</td>
<td>Not reported</td>
<td>6 month period 6 h and 24 h bundles Compliance 6 h resuscitation: 72.1% 24 h management: 68%</td>
<td>Resuscitation: full compliance: 16%, partial compliance: 41% Management: N/S, full compliance: 23%, partial compliance: 33% Hospital mortality 30% ICU mortality 23%</td>
</tr>
<tr>
<td>Ferrer et al.34</td>
<td>Spain: 77 ICUs throughout Spain Patients admitted to critical care from emergency department or wards</td>
<td>Before/after design;</td>
<td>Medical, surgical Mean Apache II = 21.0 ± 7.5 Mean age 62.4 ± 16.3</td>
<td>2 month standardised educational program at each hospital based on the SSC guidelines Compliance resuscitation: before: 5.3% after: 10% Management: before: 10.9% after: 15.7%</td>
<td>Hospital mortality Before: 44% After: 39.7%</td>
</tr>
<tr>
<td>Orford et al.35</td>
<td>Australia: 1 hospital tertiary ICU Patients admitted to critical care from emergency department or wards</td>
<td>Prospective observational Study before and after an education intervention</td>
<td>Medical, surgical, trauma Mean Apache II Pre protocol 23 ± 7 Post protocol 18.5 ± 6</td>
<td>5 month education program based on the SSC bundles. Compliance not reported Individual components reported only Time frame not stated 6 h bundle Compliance resuscitation 50%</td>
<td>Hospital mortality 23% pre protocol 14% post protocol Sample size too small for statistical significance</td>
</tr>
<tr>
<td>Ellender et al.37</td>
<td>Indianapolis, USA: 1 hospital Urban academic emergency department with critical care admissions</td>
<td>Before/after design</td>
<td>Not reported Apache II score not reported</td>
<td></td>
<td>Hospital mortality Before: 46% After: 16.6%</td>
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</tbody>
</table>
### Table 2 (Continued)

<table>
<thead>
<tr>
<th>Author</th>
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<th>Study design</th>
<th>Patient types mean Apache II and age</th>
<th>Intervention and time period/time comment/bundle compliance</th>
<th>Hospital mortality</th>
<th>Hospital mortality before bundles</th>
<th>28 day mortality</th>
<th>Hospital mortality 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baldwin et al.38</td>
<td>Kent, UK: 1 hospital Emergency department with critical care admissions</td>
<td>Prospective observational audit</td>
<td>Medical, surgical Mean Apache II = 17 ± 5.8</td>
<td>9 month period 6 h bundle Compliance 19%</td>
<td>22%</td>
<td>13%</td>
<td></td>
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</tr>
<tr>
<td>El Solh et al.36</td>
<td>Buffalo, New York: 1 tertiary care centre Both ED and ICU admissions</td>
<td>Observational prospective study with a historical control group Older age ≥65 years</td>
<td>Medical, surgical, trauma septic shock Mean Apache: treatment = 42 ± 18 after 2004; control = 40 ± 16 before 2004 Mean age: 74.6 ± 5.2</td>
<td>May 2004—February 2007 6 h and 24 h bundles</td>
<td></td>
<td>55%</td>
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<tr>
<td>Guo et al.39</td>
<td>Guangdong, China: 1 hospital academic medical centre Emergency department with critical care admissions</td>
<td>Prospective observational cohort; historical cohort comparison</td>
<td>Medical surgical Apache II and age not reported</td>
<td>14 month period 6 h and 24 h bundles Compliance 6 h bundles Hospital mortality Before bundles = 41.9% After = 18.6%</td>
<td></td>
<td>52%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Miguel-Yanes et al.40</td>
<td>Spain, Madrid: 1 hospital academic medical centre Emergency department with critical care admissions</td>
<td>Follow-up study from 2005 as comparison</td>
<td>Medical surgical Mean Apache II = 15.9 ± 6.9 SD Mean age 70.7 years</td>
<td>1 month period 6 h modified SSC bundle completed in the emergency department HDU Compliance 26% compared to 0% in 2005</td>
<td></td>
<td>22% and 16% this study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiel et al.41</td>
<td>St. Louis, WA USA: 1 hospital academic medical centre hospital wide</td>
<td>Retrospective before and after in between education period</td>
<td>Medical, surgical trauma Mean Apache II = before 21.8 (7.0), after 20.2 (6.5) Mean age = before 58.5 (16.7), after 60.5 (15.5) Medical, surgical trauma Mean Apache II = 19</td>
<td>Before period December 2003—May 2005 After May 2005—December 2006 Both SSC bundles modified slightly for an order set Jan 2005—June 2007 Both bundles Compliance increased from 8 to 35%</td>
<td></td>
<td>55.0% vs 39.5% Antibiotic administration 1 h 53% vs 65% p = 0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Girardis et al.42</td>
<td>Italy: 1 hospital academic medical centre Emergency department with critical care admissions</td>
<td>Prospective observational cohort Historical controls</td>
<td>Medical, surgical trauma Mean Apache II = 19</td>
<td>6 h 23% vs 68% 24 h 27% vs 68% (Historical controls)</td>
<td></td>
<td>Hospital mortality</td>
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Table 2 (Continued)

<table>
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<tr>
<th>Author</th>
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<th>Study design</th>
<th>Patient types mean Apache II and age</th>
<th>Intervention and time period/time comment/bundle compliance</th>
<th>Hospital mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artigas et al.43 N = 2796</td>
<td>Spain: 77 participating ICUs Patients admitted to critical care from emergency department or wards</td>
<td>Prospective multicentre observational study</td>
<td>Medical, surgical Mean age 62 years Mean Apache II = 21</td>
<td>Both bundles No compliance reported</td>
<td>Hospital mortality 41% Predictors of survival Antibiotics within 1 h ScvO2 &gt; 70% Blood glucose ≤ 150 mg/dL Protective mechanical vent aPC in organ failure</td>
</tr>
<tr>
<td>Castellanos-Ortega et al.44 N = 96 historical 384 intervention</td>
<td>Spain ICU all admissions academic medical centre</td>
<td>Quasi-experimental prospective study that included a post intervention group and a historical comparison group</td>
<td>Medical, surgical trauma Septic shock Mean age 63 ± 15 Mean Apache II = 23.2 ± 7.3</td>
<td>Educational program June—August 2005 then year data collection Both bundles Compliance 6 h 9% 24 h 10% Partial compliance much greater 50—60%</td>
<td>Hospital mortality Historical group 41% Post intervention 36%</td>
</tr>
<tr>
<td>Jones et al.45 N = 300 (150 each group)</td>
<td>USA: 3 large urban medical centres. Emergency department admissions to critical care</td>
<td>Prospective randomized, parallel group, non blinded, clinical trial</td>
<td>Medical, surgical trauma Mean age 60 ± 17 Report SAPS II not Apache II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levy et al.46 N = 15022</td>
<td>USA, UK, Brazil, Spain, Germany, Canada 165 sites</td>
<td>SSC performance improvement initiative online database</td>
<td>Medical, surgical trauma Apache II not reported</td>
<td>January 2005—March 2008 Both bundles outcome measure was change in compliance with bundle targets over time Compliance 6-h bundle increased linearly from 10.9% first site quarter to 31.3% end of 2 years 24-h bundle started 18.4% in the first quarter, to 36.1% by the end of 2 years</td>
<td>Hospital mortality overall decreased from 37.0% in the first quarter in the Campaign to 30.8% by 2 years</td>
</tr>
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</table>
Severe sepsis bundles as processes of care

the Resuscitation 6 hour Bundle, the Management 24 hour Bundle or both in contrast to individual components of the sepsis bundles. Papers of all languages were accepted with one study in Chinese. Communication with the author by email confirmed data. A total of 23,438 patients were included this meta-analysis.

Statistical analysis

Comprehensive Meta Analysis Version 2 software was used to perform analysis. Of 21 studies, 26 bundle events were calculated and added to the model to assess for heterogeneity. There were no outliers on examination of the forest plot and all studies were included. The Q-value 50.981 p < 0.000 demonstrated moderate heterogeneity with an \( I^2 \) (60.770 as percent (%)) value to support this interpretation. \( I^2 \% \) describes the proportion of total variation (between-study and within-study) in study estimates that is due to heterogeneity.\(^{48}\) A value of 0% indicates no observed heterogeneity, and larger values (up to 100%) show increasing heterogeneity. Hence 60.770% is considered moderate.

A random effect model was needed for analysis due to the studies residual heterogeneity and variations in study design despite all studies being observational cohort studies with cases and controls. With regard to clinical heterogeneity, some of the studies had small samples and slightly modified sepsis bundles because of local issues such as resources and funding. In addition, the host response to infection and sepsis are heterogeneous in nature due to the related infection type, severity and season, age, race, presence of chronic disease and individual genomic patterns, thus supporting the heterogeneity thesis. Clinical heterogeneity has been defined as the variation in study population characteristics, coexisting conditions, co-interventions, and outcomes evaluated across studies.\(^{49}\) Therefore both clinical and statistical heterogeneities were present supporting the use of a random effect model. As a consequence wider confidence intervals produced by the random effects rather than fixed effects were taken into account during the interpretation and during the testing for publication bias due to random effect summaries having higher estimated variances.

The variable of interest (use of the sepsis bundles) was divided into two groups — cases and controls — those patients receiving care compliant to the bundle and those patients receiving care which was either not compliant or before implementation of the bundle. The line at 1 was considered null and no odds of an association between the use of a sepsis bundle and survival. Statistical significance was considered at the \( p = 0.5 \) level. The meta-analysis was then applied to the separate bundles; Resuscitation 6 hour and Management 24 hour and then both bundles together or Complete Bundle, then the separate components of ScvO2 \( \geq 70 \) and blood glucose control 120—150 mg/dL (6.8—8.4 mmol/L) in order to separately examine the contribution each bundle component made to survival.

Results

The 21 studies included in the meta-analysis were distributed broadly internationally. The hospital mortality rates ranged from 58% pre intervention in Spain to 23% pre intervention in Australia confirming the Australian position. The post intervention hospital mortality ranged from 39% in Spain to 13% in Australia. The largest study in the group by Levy et al.\(^{46}\) included USA, United Kingdom, Spain and Germany, demonstrated a hospital mortality benefit from 37% to 30% post intervention. In terms of compliance with the sepsis bundles, this was only achieved in only 50% of patients receiving the complete component of the sepsis bundles. Levy et al.\(^{37}\) reported an increase in compliance from 10% to 36% over a 2 year period demonstrating that there is still some way to go in achieving acceptance into routine clinical practice with the sepsis bundles.

6 hour early resuscitation bundle

The 6 hour Resuscitation Bundle studies\(^{25,26,28,32,33,37,38,40,42,44}\) are presented in the forest plot using a random effect model (Fig. 2) with a pooled odds ratio (OR) of 2.124 (95% CI 1.701—2.651, \( p < 0.000 \)) with a total of 1819 patients. The Resuscitation 6 hour Bundle is two times more likely to be associated with survival to the 0.000 level compared to standard care. There was little heterogeneity within this group of studies (\( Q = 5.640, I^2 = 0.000 \)) suggesting that the application of this bundle was very similar between the 11 studies. There are still studies whose confidence intervals intercept the null line of 1 within the group, again not significant in this association; however, only two of the studies were originally designed to be adequately powered for a nominated decrease in mortality percent; one limitation of these observational studies.

24 hour management bundle

There are only 5 studies which reported the Management 24 hour Bundle\(^{25,26,33,42,46}\) in isolation
from the Resuscitation 6 hour Bundle and both bundles together. The results of a random effect meta-analysis (pooled odds ratio 1.646, 95% CI 1.036—2.614, \( p < 0.035 \)) 16,521 patients (Fig. 3) is statistically significant in terms of an association with survival but only 1.6 times more likely to survive than standard care and should be interpreted with caution. There was considerable heterogeneity within this group of studies (\( Q = 14,960, I^2 = 79.946 \)) suggesting that there was considerable variation in the application of this bundle between the 5 studies. It should also be noted that the confidence intervals for the pooled effects are quite wide and nearly span the null line. This suggests that the strength of the analysis is questionable and as such cannot be recommended or interpreted as a strong survival benefit compared to standard care.

**Sepsis bundles both**

Twelve studies\(^26,27,29,30,34—37,39,41,44,46\) reported survival benefit for the combination of both bundles or Complete Bundle. The random effect meta-analysis pooled odds ratio for both of the bundles together (OR 1.744, 95% CI 1.421—2.141, \( p = 0.000 \)) (Fig. 4) demonstrates that using both bundles patients are 1.7 times more likely to survive than
Both Sepsis Bundles*and survival

<table>
<thead>
<tr>
<th>Study name</th>
<th>Subgroup within study</th>
<th>Statistics for each study</th>
<th>Survived / Total</th>
<th>Odds ratio and 95% CI</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Odds ratio</td>
<td>Lower limit</td>
<td>Upper limit</td>
</tr>
<tr>
<td>Kortgen et al 2006</td>
<td>Both</td>
<td>4.750</td>
<td>1.584</td>
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**Figure 4** Both sepsis bundles and survival.

Sepsis resuscitation bundle component ScvO2

Five studies reported analysis of survival of the components of the Resuscitation 6 hour Bundle. The random effects pooled odds ratio for the ScvO2 (≥70%) component of the Resuscitation 6 hour Bundle with a sample size of 11,530 patients (OR 2.049, 95% CI 1.701–2.651, p < 0.006) (Fig. 6) demonstrates a positive statistical association with survival. Those patients in which the ScvO2 endpoint was used in the resuscitation process were 2 times more likely to survive than at the p < 0.006 level. It was noted prior to analysis that there was considerable heterogeneity (Q = 24.34, I² = 85.575) in this group of studies. This may be due to the different technologies used with either continuous or regular intermittent ScvO2 sample analysis supporting the clinical heterogeneous state. This heterogeneity was considerably reduced using a random effect model (Q = 2.941, I² = 0.000). This demonstrates an outcome that may suggest that the ScvO2 ≥70% endpoint rather than any specific type of technology may have contributed to the increased survival benefit (Fig. 5).

Sepsis management bundle component blood glucose

The random effect pooled odds ratio for the blood glucose component of the Management 24 hour Bundle (maintaining BSLs between 120 and 150 mg/dL or 6.8–8.4 mmol/L) with a sample size of 8437 patients (OR 2.551, 95% CI 1.536–4.238, p < 0.000) (Fig. 6) demonstrates a positive statistical association with survival. Those patients whose blood glucose levels were maintained between the recommended levels were 2.5 times more likely to survive at the p < 0.000 level. It should be noted that this component of the Management 24 hour Bundle has a stronger association with survival than the full bundle, suggesting that there are bundle components that contribute much less to a survival benefit than this component. In addition, this demonstrates an outcome that can confirm to clinicians that blood glucose control but in a conservative approach may contribute to the management best practice in sepsis patients.

Testing for precision and publication bias

The meta-analysis for both bundles together was applied to a funnel plot to determine the state of publication bias (Fig. 7). The funnel plot is asymmetrical suggesting possible publication bias, that is, only positive outcome studies have been published, and the negative studies have been left unpublished. Bias is not the only explanation for funnel plot asymmetry; funnel plots should be seen as a means of examining “small study effects” (the
tendency for the smaller studies in a meta-analysis to show larger treatment effects). The funnel plot is a plot of a measure of study size (usually standard error or precision) on the vertical axis as a function of effect size on the horizontal axis.

The funnel plot asymmetry may be due to publication bias, but it may also result from clinical heterogeneity between studies (for example different control event rates) or methodological heterogeneity between studies (for example failure to conceal allocation or a Hawthorne effect). A Hawthorne effect would skew the funnel plot to the right with greater intensity of treatment in the bundle groups. This is quite a feasible explanation to the described phenomenon as each of the studies was not controlled in terms of blinding before and after interventions. There is also the possibility that publication bias exists but the analysis does not give insight into this situation. Note that the studies missing from publication in terms of bias would be placed per the filled circles.

**Discussion**

The intention of this meta-analysis was to investigate the question of survival benefit of the sepsis bundles as a process of care and what this means in terms of clinical practice. This study reports that the Resuscitation 6 hour Severe Sepsis Care Bundle was associated with consistent and
Severe sepsis bundles as processes of care

Firstly, the ARISE study (2009)\textsuperscript{22} was designed to confirm that Australian critical care practice did not use EGDT or ScvO\textsubscript{2} $\geq$ 70% as a resuscitation endpoint in the ED and debate continues around the need to use this endpoint in Australian clinical practice. One of the most outstanding findings of the Rivers et al.\textsuperscript{14} study was that the mean ScvO\textsubscript{2} on admission to the ED was less than 50% in both the standard therapy and the EGDT groups. These ScvO\textsubscript{2} values are extremely low since the normal ScvO\textsubscript{2} is about 75%. Recent studies have found much higher ScvO\textsubscript{2} values in septic shock patients either in the ED or on admission to the ICU. In two of these studies\textsuperscript{52,53} the mean ScvO\textsubscript{2} was 72—74%; in one of them, only 8 out of 125 patients (6%) had a ScvO\textsubscript{2} value below 60% and only 1 patient had a ScvO\textsubscript{2} below 50%. The authors of these studies\textsuperscript{52—54} have commented that their sepsis patients were seemingly less critically ill at presentation compared with those of Rivers et al.\textsuperscript{14} However this meta-analysis confirms the benefit of optimising ScvO\textsubscript{2} in sepsis patients to an endpoint of $\geq$ 70% with its large sample but cannot extrapolate further.

In regard to blood glucose protocol endpoints since the publication of the NICE-SUGAR study\textsuperscript{24} it seems that clinicians need clarification. For several years intensive insulin therapy endpoints of blood glucose levels have remained less than 108 mg/dL or 6 mmol/L. Since the NICE SUGAR study, two meta-analyses\textsuperscript{55,56} of intensive insulin therapy have reported a similar outcome of increased mortality with intensive insulin therapy and tight glycaemic control thought to be due to the large amount of adverse events of hypoglycaemia. In the Sepsis Management Bundle, the blood glucose component maintains glycaemic control at (120—150 mg/dL) or (6.8—8.4 mmol/L). This is far more a conservative range than the NICE-SUGAR study control arm (blood glucose level 6.1—8.3 mmol/L). The more conservative range of the Sepsis Management Bundle has a survival benefit in sepsis patients as reported by this study and should give clinicians the confidence to consider the more moderate blood glucose levels in sepsis patients.

In regard to limitations these include lack of methodological rigor in the studies analysed (lack of blinding,\textsuperscript{25—42} before—after study designs,\textsuperscript{25—30,31,34} retrospectively identified historical controls,\textsuperscript{27—29,38} potential selection bias,\textsuperscript{25—28,33—41} duration of sepsis,\textsuperscript{36,38} completeness of data collection,\textsuperscript{27,36,40} use of unadjusted data\textsuperscript{42}), which may confound their findings. Variation in factors, such as participating healthcare workers and patients studied, as well as the natural trend for general care to improve over time in hospitals, may have favoured better outcomes.
with bundled care, and as such in isolation have not made an impact on the critical care fraternity who look for evidence that is higher in quality, such as randomized control trials. However, this meta analysis brings together a large enough sample (23,438 patients) to outweigh the issues regarding study design and used a random effects model to counteract the bias routinely found in observational studies.

In conclusion, the sepsis bundles still have a place in clinical practice but as clinicians seeking to improve the treatment of patients with severe sepsis they may choose to implement the Surviving Sepsis Campaign Bundles in their entirety because even the most conservative conclusion from the current report is that doing so is unlikely to cause harm; indeed, increased awareness as a result of the campaign may be partly or even predominantly responsible for the survival benefit observed. Others who are less convinced by the primary evidence may take a more conservative approach and await the results of ongoing trials. We should welcome the fact that baseline mortality appears to be decreasing, but there is still much work to be done. A beneficial effect of the sepsis bundles on patients’ outcomes is not yet of sufficient understanding and quality in Australia to promote the guidelines as a global standard of care.

References

22. Australasian Resuscitation in Sepsis Evaluation investigators (ARISE) are recruiting for a randomised control trial (Registered Clinical Trial number ACTRN12608000053325) of EGDT versus current practice. This is in conjunction with ProCESS (Protocolized Care for Early Septic Shock), US based trial Register Clinical Trial (NCT00510835), and ProMISE (Protocolised Management in Sepsis, UK based trial).

Severe sepsis bundles as processes of care


