Antibiotic- and Fluid-Focused Bundles Potentially Improve Sepsis Management, but High-Quality Evidence Is Lacking for the Specificity Required in the Centers for Medicare and Medicaid Service's Sepsis Bundle (SEP-1)

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Abstract

Objective: To address three controversial components in the Centers for Medicare and Medicaid Service's sepsis bundle for performance measure (SEP-1): antibiotics within 3 hours, a 30 mL/kg fluid infusion for all hypotensive patients, and repeat lactate measurements within 6 hours if initially elevated. We hypothesized that antibiotic- and fluid-focused bundles like SEP-1 would probably show benefit, but evidence supporting specific antibiotic timing, fluid dosing, or serial lactate requirements would not be concordant. Therefore, we performed a meta-analysis of studies of sepsis bundles like SEP-1.

Data Sources: PubMed, Embase, ClinicalTrials.gov through March 15, 2018.

Study Selection: Studies comparing survival in septic adults receiving versus not receiving antibiotic- and fluid-focused bundles.

Data Extraction: Two investigators (D.J.P., P.Q.E.).

Data Synthesis: Seventeen observational studies (11,303 controls and 4,977 bundle subjects) met inclusion criteria. Bundles were associated with increased odds ratios of survival (odds ratio [95% CI]) in 15 studies with substantial heterogeneity ($I^2 = 61\%$; $p < 0.01$). Survival benefits were consistent in the five largest (1,697–12,486 patients per study) (1.20 [1.11–1.30]; $I^2 = 0\%$) and six medium-sized studies (167–1,029) (2.03 [1.52–2.71]; $I^2 = 8\%$) but not the six smallest (64–137) (1.25 [0.42–3.66]; $I^2 = 57\%$). Bundles were associated with similarly increased survival benefits whether requiring antibiotics within 1 hour ($n = 7$ studies) versus 3 hours ($n = 8$) versus

no specified time ($n = 2$); or 30 mL/kg fluid ($n = 7$) versus another volume (2 L, $n = 1$; 20 mL/kg, $n = 2$; 1.5–2 L or 500 mL, $n = 1$ each; none specified, $n = 4$) ($p = 0.19$ for each comparison). In the only study employing serial lactate measurements, survival was not increased versus others. No study had a low risk of bias or assessed potential adverse bundle effects.

Conclusions: Available studies support the notion that antibiotic- and fluid-focused sepsis bundles like SEP-1 improve survival but do not demonstrate the superiority of any specific antibiotic time or fluid volume or of serial lactate measurements. Until strong reproducible evidence demonstrates the safety and benefit of any fixed requirement for these interventions, the present findings support the revision of SEP-1 to allow flexibility in treatment according to physician judgment.

Keywords

bundle; management; performance measure; sepsis; septic shock; treatment

The Centers for Medicare and Medicaid Services (CMS) develops performance measures (PMs) to enhance the recognition and management of clinical problems and thereby improve outcomes (1). Despite these goals, the complexity of CMS's original sepsis bundle PM (SEP-1) raised concerns that it hindered management, so it was simplified in 2017 (2–8) (Appendix Table 1, Supplemental Digital Content 1, http://links.lww.com/CCM/E730). However, questions persist regarding the benefit of SEP-1's continuing requirement for all patients to receive antibiotics within 3 hours, for all hypotensive patients to receive a 30 mL/kg fluid infusion, and for obtaining a second lactate measurement if initially elevated (7, 9–12).

Compliance with SEP-1 requires all components be completed, and hospitals must report their compliance through CMS's In-hospital Quality Reporting program (4). CMS now publicly compares hospitals' SEP-1 compliance, influencing where consumers spend healthcare dollars (13, 14). Although CMS does not presently base hospital reimbursement directly on SEP-1 compliance, this could occur in the future (15). As an increasingly mandated PM, SEP-1 should conform to National Quality Forum (NQF, which endorses PMs for CMS) and CMS standards and only include proven therapies because pressure for hospitals to demonstrate compliance with it carries risks (16, 17). For example, injudicious antibiotic use to meet SEP-1's time requirements in patients with noninfectious etiologies may produce antibiotic-associated toxicities (e.g., renal toxicity or *Clostridium difficile* or resistant nosocomial infection) (7, 9, 18–20). Requiring fixed fluid volumes without adjusting for patients' comorbidities and volume status risks under- or overtreatment (21–24). Finally, serial lactate measurements to guide resuscitation are of unproven benefit and safety (8, 25, 26).

We previously examined and found that the quality of evidence supporting individual hemodynamic components in the original version of SEP-1, including a fixed 30 mL/kg volume infusion, serial lactate measurements, and bedside cardiac ultrasound and fluid responsiveness testing was low (8). We now hypothesize that bundles with elements like the revised SEP-1 and including early antibiotics and fluid administration would likely show a survival benefit, but there would be no concordant data from these bundles supporting

when or how these two therapies should be delivered or that serial lactate measurements be obtained. To test this hypothesis, a systematic review of sepsis bundles similar to SEP-1 was performed, and different from our prior study, we examined the overall effect of these bundle components on mortality as well as whether variation in the administration of the components altered the bundles' outcome.

METHODS

This systematic review was registered on International Prospective Register of Systematic Reviews (PROSPERO) December 18, 2017. A completed Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist and complete methods are provided in the supplementary methods (Supplemental Digital Content 1, http://links.lww.com/CCM/E730) (27).

Data Sources and Searches

We searched PubMed, Embase, Scopus, Web of Science, and ClinicalTrials.gov (Appendix Fig. 1, Supplemental Digital Content 1, http://links.lww.com/CCM/E730; legend, Supplemental Digital Content 2, http://links.lww.com/CCM/E731) through March 15, 2018, using terms previously described to examine SEP-1 (8).

Study Selection

We included studies that compared mortality between subjects receiving versus not receiving a focused sepsis bundle that included antibiotic and fluid administration, with or without vasopressors. Studies evaluating prior SEP-1 interventions no longer required in the revised 2018 version were excluded (2–4).

Bundle Group				
Fluids		Other Interventions		
Timing	Volume	Adjunctive Aids	Other	Control Group
NS	NS	Yes	—	No sepsis alert
1 hr	NS	Yes	O₂ therapy 1 hr; measure urine output 1 hr	No bundle
30 min	20 mL/kg bolus	Yes	—	No bundle
1 hr	20 mL/kg	Yes	VP/I	No bundle
NS	30 mL/kg	Yes	—	No bundle
30 min	500 mL	No	Hemoglobin of 7–9 g/dL; VP/I	Bundle uncompleted
2 hr	2 L	Yes	—	No bundle
NS	30 mL/kg bolus	Yes	—	No bundle
1 hr	NS	Yes	—	No bundle
30 min	30 mL/kg bolus	Yes	—	Bundle uncompleted
30 min	30 mL/kg bolus	Yes	—	Bundle uncompleted
30 min	30 mL/kg bolus	Yes	—	Bundle uncompleted
3 hr	30 mL/kg	Yes	—	No bundle

Bundle Group				
Fluids		**Other Interventions**		
Timing	**Volume**	**Adjunctive Aids**	**Other**	**Control Group**
NS	NS	No	VP/I	Bundle uncompleted
2 hr	1.5–2 L	No	—	Bundle uncompleted
NS	30 mL/kg bolus	No	VP/I	Bundle uncompleted
NS	500–1000 mL bolus, titrate up to 30 mL/kg	Yes	VP/I	No bundle

Endpoints

The overall survival effects of bundles were examined, followed by whether survival effects differed for bundles stipulating: differing antibiotic treatment times, 30 mL/kg fluid volumes versus other volumes, or obtaining versus not obtaining serial lactate measurements. The effects of bundles on antibiotic and fluid administration were assessed.

Data Extraction and Quality Assessment

Data extracted (Appendix Table 2, Supplemental Digital Content 1, http://links.lww.com/CCM/E730) included the following: study design, baseline characteristics, bundle requirements, proportion of subjects receiving interventions within stipulated time goals, amount of fluids infused, proportion of subjects with infection sensitive to administered antibiotics, and adverse effects related to bundle use. Bundles were defined as either stipulating 30 mL/kg fluid, another volume, or no specific volume. Bundle groups were considered favored if subjects were younger, had fewer comorbidities or decreased illness severity, or had fewer pulmonary or abdominal infections. Adjunctive aid use was examined and risk of bias assessed (28, 29).

Data Synthesis and Analysis

For survival or proportion of patients receiving interventions, odds ratio (OR) and 95% CIs were calculated. Reported median and interquartile range (IQR) values were converted to mean difference and SEs (30). Outcome summary estimates used random-effects models (31).

RESULTS

Literature Search

Fifteen publications encompassing 17 studies measuring survival for a sepsis bundle versus control (32–46) were identified (Appendix Fig. 1, Supplemental Digital Content 1, http://links.lww.com/CCM/E730; and legend, Supplemental Digital Content 2, http://links.lww.com/CCM/E731). One report analyzed three cohorts representing three individual studies designated here by each cohort's final enrollment year (i.e., Leisman et al [41], 2012; Leisman et al [41], 2014; and Leisman et al [41], 2015).

Study Characteristics

Table 1 and Appendix Tables 2 and 3 (Supplemental Digital Content 1, http://links.lww.com/CCM/E730) summarize study characteristics. All studies used observational designs, including 10 before/after cohort control studies (7,515 preintervention control and 8,568 postintervention bundle subjects) and seven concurrent cohort control studies (11,303 control and 4,977 intervention bundle subjects). Thirteen studies retrospectively enrolled control or control and bundle subjects, respectively. Three before/after studies employed *International Classification of Diseases* (ICD) codes to identify septic subjects, one employed an administrative data set, and six were quality improvement programs. Only four studies provided adjusted survival estimates, and in four studies, significant baseline differences in severity of illness favored bundle subjects (i.e., higher systolic blood pressure or reduced organ injury).

Summary of Bundles Studied

Antibiotics were required within 1 hour in seven studies, 3 hours in seven, within 3 hours in the emergency department, or 1 hour for inpatients in one (considered 3 hr in analysis), and two studies did not report times (Table 2; and Appendix Tables 4–6, Supplemental Digital Content 1, http://links.lww.com/CCM/E730). The fluid volume required was 30 mL/kg in seven studies, greater than or equal to 2 L in one, greater than or equal to 20 mL/kg in two, and 1.5–2 L or 500 mL in one study each. Four studies did not stipulate a volume. Only one study required serial lactate measurements. Table 2 shows control treatments.

Effect of Bundle Treatment on Survival

Appendix Table 3 (Supplemental Digital Content 1, http://links.lww.com/CCM/E730) shows mortality endpoints of studies. Compared with controls, bundle treatment was associated with increased ORs of survival in 15 of 17 studies (statistically significant in nine), but there was substantial heterogeneity overall ($I^2 = 61\%$; $p < 0.01$). Categorizing studies by enrolled numbers isolated this heterogeneity to smaller trials (Fig. 1). Stratified into terciles based on enrollment numbers, the OR increased consistently in the five largest (1,697–12,486 subjects per study) (1.20 [1.11–1.30]; $I^2 = 0\%$; $p = 0.65$) and six medium-sized studies (167–1,029) (2.03 [1.52–2.71]; $I^2 = 8\%$; $p = 0.36$), but with significant heterogeneity in the six smallest studies (64–137) (1.25 [0.42–3.66]; $I^2 = 57\%$; $p = 0.04$). Bundle survival effects were fairly consistent in before/after studies ($n = 10$ studies) (1.20 [1.02–1.40]; $I^2 = 21\%$; $p = 0.25$), but not cohort-controlled ones ($n = 7$) (1.73 [1.21–2.48]; $I^2 = 76\%$; $p < 0.01$) in which three large and three small studies increased heterogeneity. A funnel plot using Egger regression analysis could not rule out publication bias ($p = 0.10$) (Appendix Fig. 2, Supplemental Digital Content 1, http://links.lww.com/CCM/E730; legend, Supplemental Digital Content 2, http://links.lww.com/CCM/E731). Survival estimates with bundles adjusted for severity of illness or other characteristics were increased in the four studies providing data.

Bundles were associated with similarly increased survival ($p = 0.19$) whether they specified antibiotic administration within 1 hour ($n = 7$ studies) (1.92 [0.92–4.00]; $I^2 = 57\%$; $p = 0.03$), 3 hours ($n = 8$) (1.34 [1.11–1.61]; $I^2 = 56\%$; $p = 0.03$), or without a specified time ($n = 2$) (1.21 [0.69–2.13]; $I^2 = 0$; $p = 0.77$) (Fig. 2) Two of the 1-hour antibiotic studies had

survival effects on the side of harm ($I^2 = 0$), and for one study, this approached significance. Bundles were also associated with increased survival whether they specified 30 mL/kg fluid infusions ($n = 7$ studies) (1.23 [1.09–1.39]; $I^2 = 38\%$; $p = 0.14$), a volume other than 30 mL/kg ($n = 6$) (1.70 [0.94–3.05]; $I^2 = 41\%$; $p = 0.13$) or did not specify a volume ($n = 4$) (1.30 [0.17–10.13]; $I^2 = 77\%$; $p < 0.01$) (Fig. 3). Bundle survival effects were similar ($p = 0.70$) comparing studies specifying volumes other than 30 mL/kg ($n = 6$) versus those with individualized volumes ($n = 4$), and the overall survival effect of bundles in these 10 studies (1.62 [1.03–2.55]; $I^2 = 59\%$; $p < 0.01$) was not significantly different ($p = 0.19$) compared with studies requiring 30 mL/kg (1.23 [1.09–1.39]). This difference was also not significant ($p = 0.27$) when the one study requiring a fluid volume greater than or equal to 2 L was combined with those requiring 30 mL/kg. Finally, in the only bundle study requiring serial lactate measurements, survival (1.14 [1.03–1.27]) was no greater than all others (1.50 [1.20–1.87]; $I^2 = 58\%$; $p < 0.01$).

Effect of Bundle Treatment on Antibiotic and Fluid Administration

In the 13 studies reporting antibiotic administration data, compared with controls, bundle treatment was associated with increased OR of receiving timely antibiotics (i.e., within the bundle's targeted time) in 12 of 12 studies (10 significantly) (12.5 [2.4–65.6)]; $I^2 = 94\%$; $p < 0.01$) and reduced times to antibiotic administration (shown as a negative mean difference [95% CI]) in six of six studies (five significantly) (–42.0 min [–70.0 to –14.1]; $I^2 = 99\%$; $p < 0.01$) (Fig. 4; and Appendix Table 4, Supplemental Digital Content 1, http://links.lww.com/CCM/E730). Only four studies reported subjects with positive cultures, and no study reported antibiotic microbial sensitivities. In 13 studies providing fluid data (Fig. 4; and Appendix Table 5, Supplemental Digital Content 1, http://links.lww.com/CCM/E730), bundles were associated with increased OR of receiving timely fluids in nine of nine studies (eight significantly) (29.9 [1.9–483.2]; $I^2 = 95\%$; $p < 0.01$) and with reduced times to fluid administration in five of five studies (–42.4 min [–65.8 to –18.9]; $I^2 = 98\%$; $p < 0.01$). Variability in antibiotic and fluid administration measures was not related to study size. In the only two studies reporting administered fluid volumes, one requiring 30 mL/kg fluid and one 1.5–2.0 L, bundle patients received more fluid than controls but administered volumes varied widely for both groups in each study (milliliters; mean [SD], 1,900 [1,200] vs 1,800 [1,200]; and median [IQR], 1,500 [1,000–2,000] vs 220 [160–628], respectively) (Appendix Table 5, Supplemental Digital Content 1, http://links.lww.com/CCM/E730). Three studies reported proportions of patients receiving vasopressors, and one the time to vasopressors and were not analyzed further (Appendix Table 6, Supplemental Digital Content 1, http://links.lww.com/CCM/E730).

No significant ($p \geq 0.50$) relationships (slope ± SE) were demonstrated between the log OR of survival and receipt of either timely antibiotics (–0.004 ± 0.028) or fluids (0.007 ± 0.011) with bundle treatment or with reduced time to antibiotic (0.001 ± 0.001) or fluid administration (–0.005 ± 0.004).

Other Findings

Bundle treatment was associated with increased ORs of obtaining initial lactate measurements and blood cultures (Appendix Fig. 3, Supplemental Digital Content

1, http://links.lww.com/CCM/E730 [legend, Supplemental Digital Content 2, http://links.lww.com/CCM/E731] and Appendix Table 6, Supplemental Digital Content 1, http://links.lww.com/CCM/E730). Thirteen studies included educational and/or priority-care adjunctive aids (Appendix Table 7, Supplemental Digital Content 1, http://links.lww.com/CCM/E730). No study had a low risk of bias or assessed adverse effects of bundle treatment (Appendix Tables 7 and 8, Supplemental Digital Content 1, http://links.lww.com/CCM/E730).

DISCUSSION

We previously reported that some hemodynamic elements of the CMS SEP-1 performance improvement metric had only low-quality supporting evidence (8). We now report our study of other elements of this sepsis metric in the 17 observational studies analyzed here. In 15 of these studies, focused sepsis bundles combining antibiotic and fluid administration like SEP-1 had survival effects on the side of benefit and there were consistent significant beneficial effects across the five largest and six medium-sized studies. However, bundles had similar survival effects whether the required time to antibiotics was 1 or 3 hours or was not stated. Also, bundle effects on survival and antibiotic administration were not significantly related. There was substantial heterogeneity across studies of the 1- and 3-hour antibiotic treatment times ($I^2 = 57$ and 56%), and two of the 1-hour antibiotic studies had survival effects on the side of harm with an $I^2 = 0$, with one approaching significance. Bundles stipulating 30 mL/kg fluid did not have a significantly different or larger survival effect compared with bundles directing other volumes or allowing individualized volumes. Only one study requiring 30 mL/kg reported volumes delivered to patients and these varied greatly. Finally, survival was no better in the only study with a bundle requiring serial lactates than other studies. Antibiotics and cardiovascular resuscitation with fluids are essential sepsis therapies. Overall, the present studies are consistent with the notion that antibiotic- and fluid-focused bundles improve sepsis survival. But they do not provide concordant evidence that any specific time to antibiotic treatment or fluid volume was better or safer than any other tested or that serial lactate measurements are needed.

Consistent with these findings, other studies have suggested that decreasing the time from sepsis diagnosis to antibiotic administration improves survival (47–55). A retrospective analysis of SEP-1's earlier version found that only antibiotic compliance was potentially associated with improved survival (56). However, at present, there is no high-quality evidence (i.e., randomized controlled trials [RCTs]) demonstrating that stipulating a specific time to antibiotics like 3 hours, either by itself or in a bundle, is more effective than a more flexible timeframe based on patients' sepsis severity. Although most would agree that antibiotics should be administered rapidly in patients with septic shock, hastily administered antibiotics to patients less likely to have bacterial infection or not requiring emergent therapy can increase risks (e.g., renal toxicity or *C. difficile* or resistant nosocomial infection) (7, 9, 18–20). It is also accepted that septic shock patients require fluid and vasopressor support to prevent organ injury and death. But in the present studies, there was considerable variability in the fluid volumes targeted, ranging from 500 to 1,000 mL up to 30 mL/kg, and survival was increased whether bundles required lower or higher volumes or did not stipulate a volume. The actual volumes administered in the only two studies providing data

varied markedly among patients suggesting fluids were titrated and no single volume was used for all patients. Experts debate the best volume and rate of fluid for sepsis, and a government-sponsored, multicenter trial enrolling septic shock patients (critically examined by C.N., P.Q.E.) is based on the premise that appropriate fluid management for early sepsis is unknown (23, 48, 57–59).

Importantly, none of the 17 analyzed studies reported or clearly investigated bundle-associated adverse events such as toxicities related to inappropriate antibiotic administration in subjects without documented infection, or cardiopulmonary complications related to inadequate or excessive fluid administration. Many subjects meeting systemic inflammatory response or organ failure assessment criteria for focused sepsis bundle administration are eventually found to not have sepsis. The potential harm of these interventions when administered in bundles to nonseptic patients or when comorbidities are unaccounted for has not been quantified.

We understand that important limitations undermine the conclusions regarding the efficacy of the bundles studied. All studies were observational non-RCTs and did not meet NQF standards for high-quality evidence which requires well-conducted RCTs (16). The NQF endorses PMs for CMS including SEP-1. These studies also do not meet NQF criteria for moderate-quality evidence, requiring that observational studies control for possible confounders. Thirteen studies (76%) enrolled patients retrospectively, and no study was at low risk of bias. Thirteen included educational or priority-care adjunctive aids potentially benefiting survival. Only four studies reported adjusted survival, yet the recent analysis of cases managed with the original SEP-1 found that although crude mortality was lower in compliant versus noncompliant patients, the groups did not differ after adjustment for clinical characteristics and illness severity (56). Ten studies (59%), including the largest, were before/after ones, and evidence indicates that increasing sepsis awareness will boost enrollment of less ill sepsis cases over time with this study design (60, 61). This problem may be more pronounced with studies using sepsis coding (e.g., ICD codes) and administrative datasets to identify septic patients, which four studies including the two largest did. In the seven concurrent-control studies, noncompliance in control patients may have been due to less evident sepsis symptomatology at patient presentation, a variable potentially increasing mortality independent of treatment (62). The funnel plot and Egger analysis cannot exclude publication bias. Finally, there was no measurable relationship between bundle effects on time to treatments and improved survival. Thus, multiple factors besides bundle interventions potentially influenced the observed survival improvements across the 17 studies. Observational studies designed similar to those analyzed here, some larger than the present ones, reported that sepsis bundles including early goal-directed therapy (EGDT) improved survival (49). However, subsequent well-conducted RCTs showed that EGDT was no more beneficial but more costly than usual care (63).

We previously showed that there was only low-quality evidence supporting the safety or benefit of serial lactate measurements to manage septic patients (8). The present study demonstrates that there is also no evidence that serial lactate measurements increase the effectiveness of focused sepsis bundles.

Two large retrospective studies examining focused bundles did not meet our inclusion criteria requiring a direct comparison between a bundle and nonbundle group. One examined whether there was a "correlation" between the time the components of a sepsis bundle were administered and survival (48). The other examined whether over 2 years of study, there were "temporal trends" in the initiation of a sepsis protocol, compliance with a sepsis bundle, or survival and then whether there was an association between the two former two measures and survival (64).

Sepsis is one of the most common causes of hospital mortality and may warrant care that is optimized by a PM. The best available data are consistent with the notion that bundles focusing on the two essential initial interventions for septic shock patients, antibiotics for infection and fluids for cardiovascular resuscitation, benefit care. But multiple factors limit how specific these bundle recommendations should be. Notably, there has been considerable variability in the volume of fluids and timing of antibiotics studied in focused bundles so far. Furthermore, studies have not examined bundle-associated adverse effects and lack rigorous methodology. Therefore, these studies are not fully informative or definitive. In sepsis, clinical experience and the belief that delays in treatment for most clinical conditions are detrimental support starting antibiotics for infection and resuscitating with fluids and vasopressors to normalize physiology as soon as possible. Patients with septic shock require prompt antibiotic therapy and hemodynamic support. A framework for the administration of these therapies, like a 3-hour window for antibiotic administration, will benefit some patients and could be part of a PM. However, consistent with the observations of others in the field of sepsis, as CMS further revises SEP-1, it should take into account that without high- or even moderate-quality evidence to support the benefit and safety of one specific antibiotic treatment time or volume of fluid, there is no justification for not allowing clinicians to adjust these treatments' delivery as risk-benefit calculations require in individual cases (10–12). Although emphasizing the importance of early care for septic patients, flexibility is also necessary because it is unlikely that there will ever be definitive data showing a specific antibiotic time or fluid volume that fits all sepsis cases. Without high- or moderate-quality evidence, serial lactate measurements should also be guided by providers' assessment. When revising SEP-1, broad input from all medical disciplines employing the measure may help ensure the measure is followed because there would be a consensus that it represents optimal medical care. A sepsis PM should focus care on the septic patient. However, without high-quality evidence for its safety and benefit, it should not preempt a qualified clinician's judgment or hinder the clinician's medical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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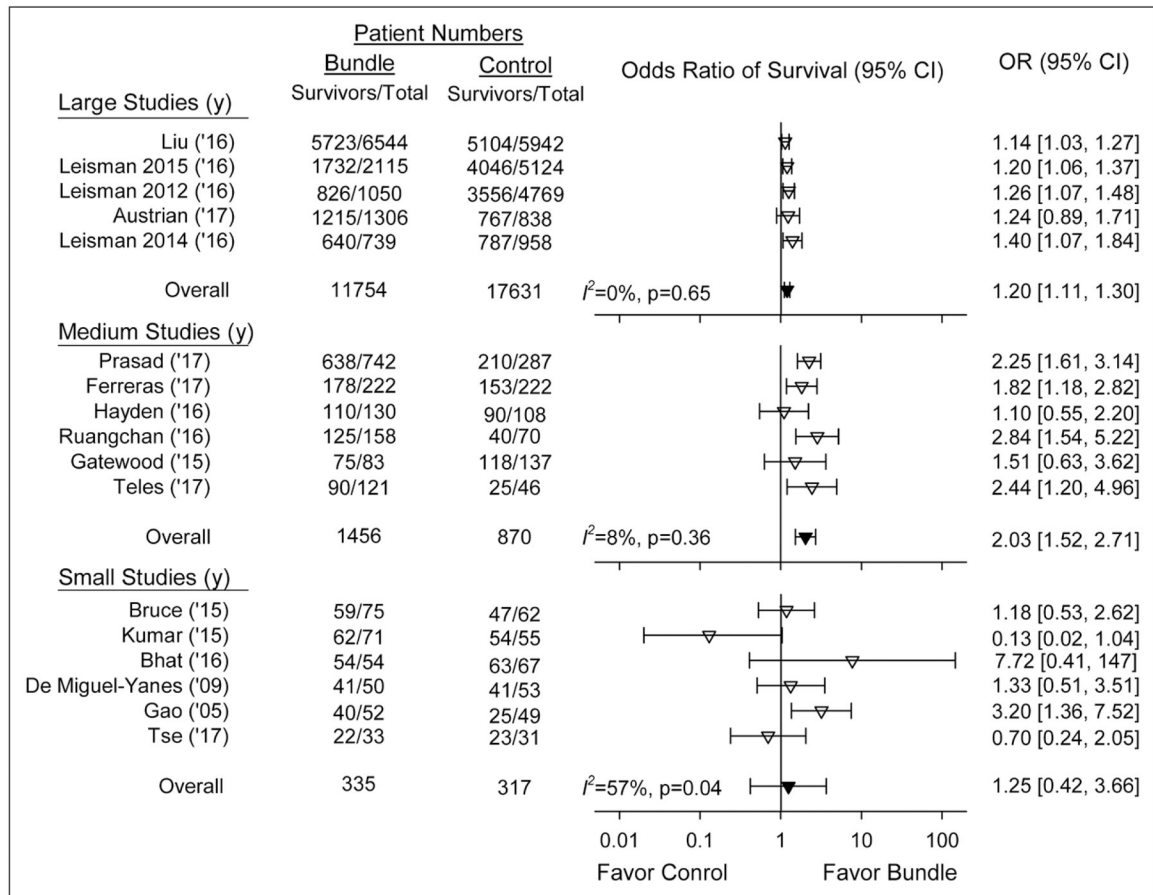
| Large Studies (y) | Patient Numbers | | Odds Ratio of Survival (95% CI) | OR (95% CI) |
	Bundle Survivors/Total	Control Survivors/Total		
Liu ('16)	5723/6544	5104/5942		1.14 [1.03, 1.27]
Leisman 2015 ('16)	1732/2115	4046/5124		1.20 [1.06, 1.37]
Leisman 2012 ('16)	826/1050	3556/4769		1.26 [1.07, 1.48]
Austrian ('17)	1215/1306	767/838		1.24 [0.89, 1.71]
Leisman 2014 ('16)	640/739	787/958		1.40 [1.07, 1.84]
Overall	11754	17631	I^2=0%, p=0.65	1.20 [1.11, 1.30]
Medium Studies (y)				
Prasad ('17)	638/742	210/287		2.25 [1.61, 3.14]
Ferreras ('17)	178/222	153/222		1.82 [1.18, 2.82]
Hayden ('16)	110/130	90/108		1.10 [0.55, 2.20]
Ruangchan ('16)	125/158	40/70		2.84 [1.54, 5.22]
Gatewood ('15)	75/83	118/137		1.51 [0.63, 3.62]
Teles ('17)	90/121	25/46		2.44 [1.20, 4.96]
Overall	1456	870	I^2=8%, p=0.36	2.03 [1.52, 2.71]
Small Studies (y)				
Bruce ('15)	59/75	47/62		1.18 [0.53, 2.62]
Kumar ('15)	62/71	54/55		0.13 [0.02, 1.04]
Bhat ('16)	54/54	63/67		7.72 [0.41, 147]
De Miguel-Yanes ('09)	41/50	41/53		1.33 [0.51, 3.51]
Gao ('05)	40/52	25/49		3.20 [1.36, 7.52]
Tse ('17)	22/33	23/31		0.70 [0.24, 2.05]
Overall	335	317	I^2=57%, p=0.04	1.25 [0.42, 3.66]

0.01   0.1   1   10   100

Favor Conrol   Favor Bundle

Figure 1.

Effect of treatment with a sepsis bundle on the odds ratio (OR) of survival (95% CI) in the 17 individual studies analyzed (*inverted open triangles*). Studies are shown stratified by terciles into the five studies with the largest-sized number of patients enrolled (1,697–12,486 patients, 29,385 total), the six studies with medium-sized number of patients (167–1,029, 2,326 total), and the five studies with the smallest number of patients enrolled (64–137, 652 total). The overall ORs (95% CI) and I^2 are shown for each of these three groups (*inverted closed triangles*).
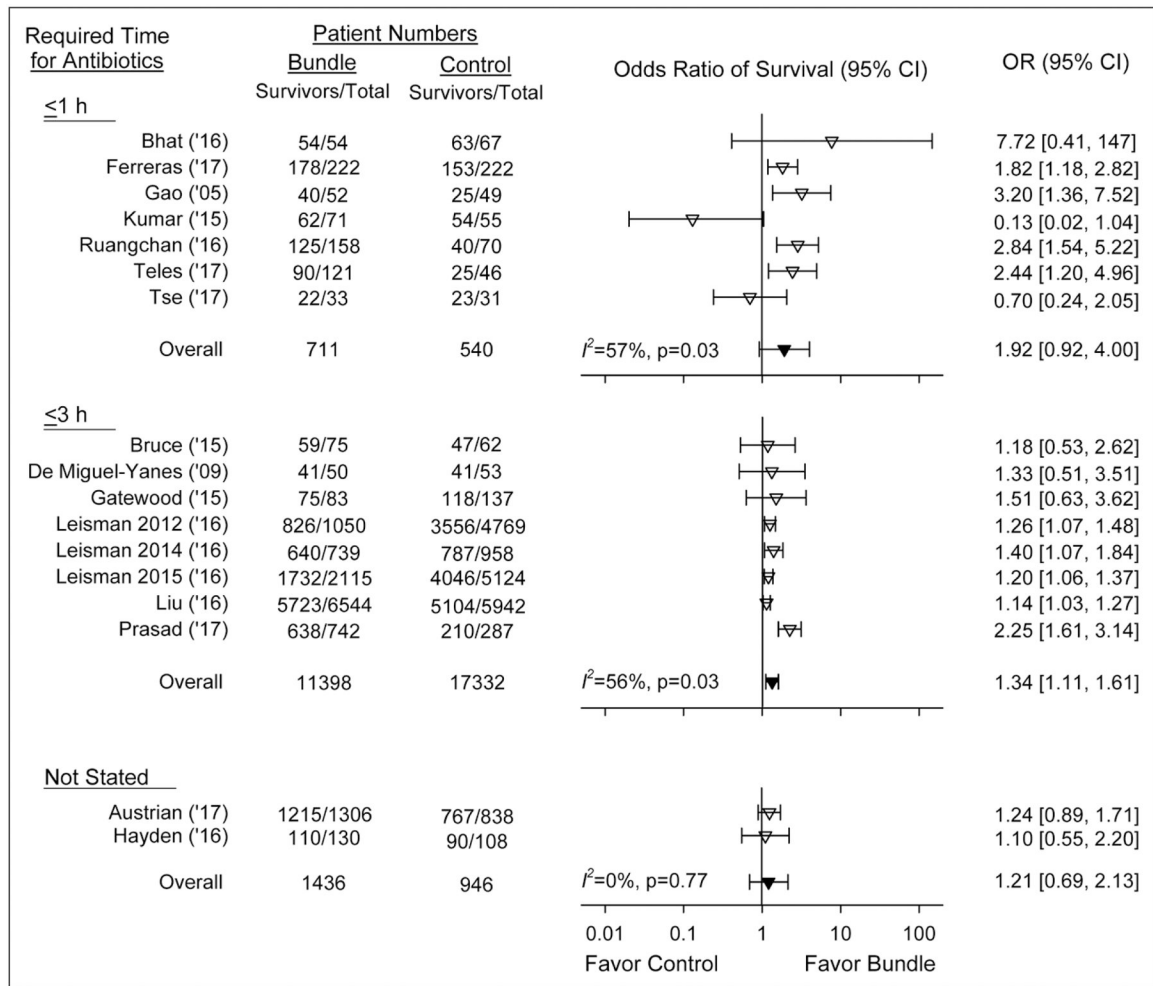
Figure 2.
Effect of treatment with a sepsis bundle on the odds ratio (OR) of survival (95% CI) in studies grouped based on whether the bundles studied required antibiotics be administered (*inverted open triangles*). in less than or equal to 1 hr or less than or equal to 3 hr or the bundle did not state when antibiotics should be administered. The overall ORs (95% CI) and I^2 are shown for each of these three groups. The overall effects of bundles did not differ significantly ($p = 0.19$) comparing the three groups (*inverted closed triangles*).
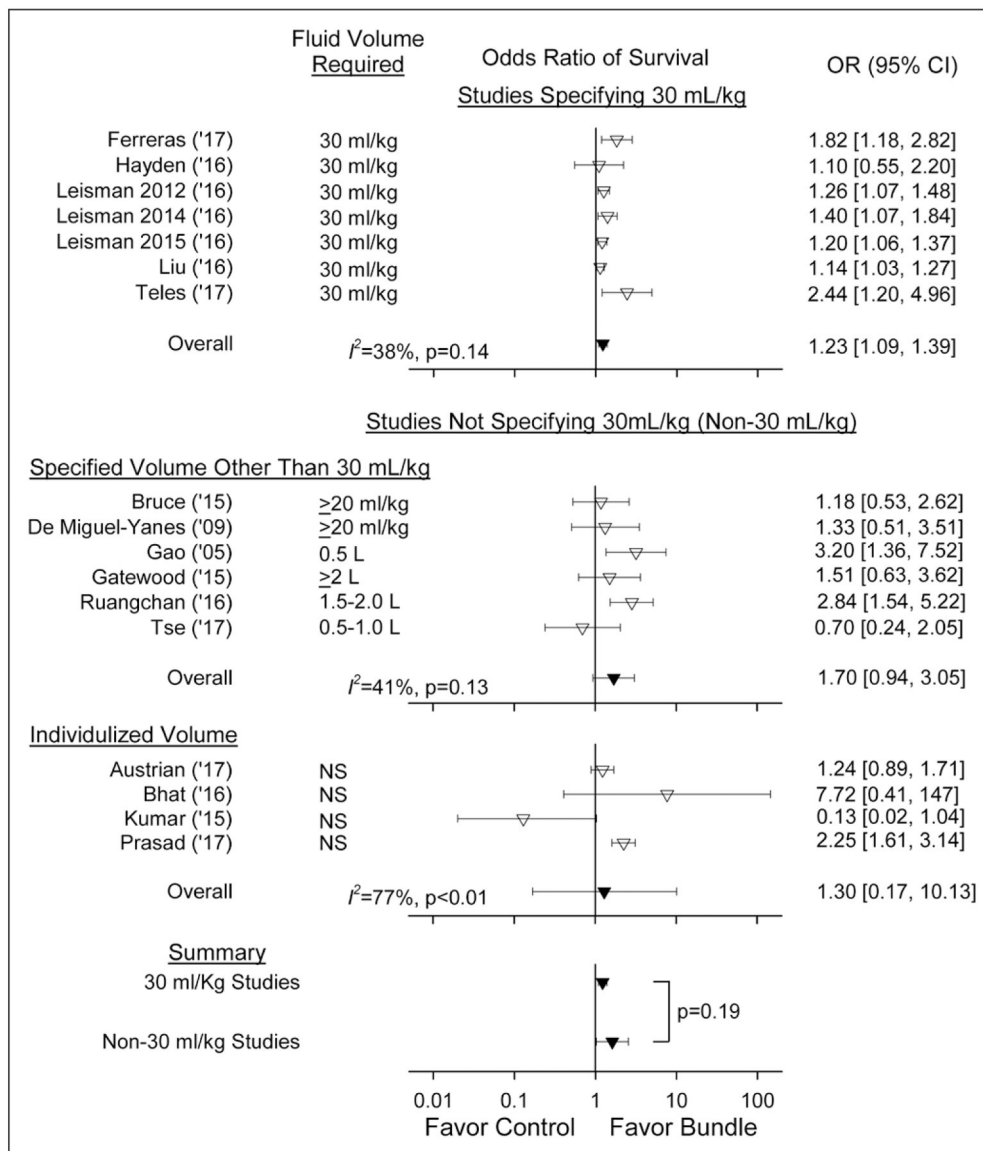
Figure 3.
Effect of treatment with a sepsis bundle on the odds ratio (OR) of survival (95% CI) in studies grouped based on whether the bundles studied specified that 30 mL/kg fluid be administered, that a volume other than 30 mL/kg be given as shown in the figure, or that did not specify what volume be administered (i.e., an individualized volume) (*inverted open triangles*). The overall ORs (95% CI) and I2 are shown for each of these three groups (*inverted closed triangles*). The overall effects of bundles did not differ significantly (*p* = 0.19) comparing studies requiring 30 mL/kg to all other studies not requiring this volume. This difference was also not significant (*p* = 0.27) when the one study requiring a fluid volume greater than or equal to 2 L was combined with those requiring 30 mL/kg and compared with all other studies. NS = not significant.
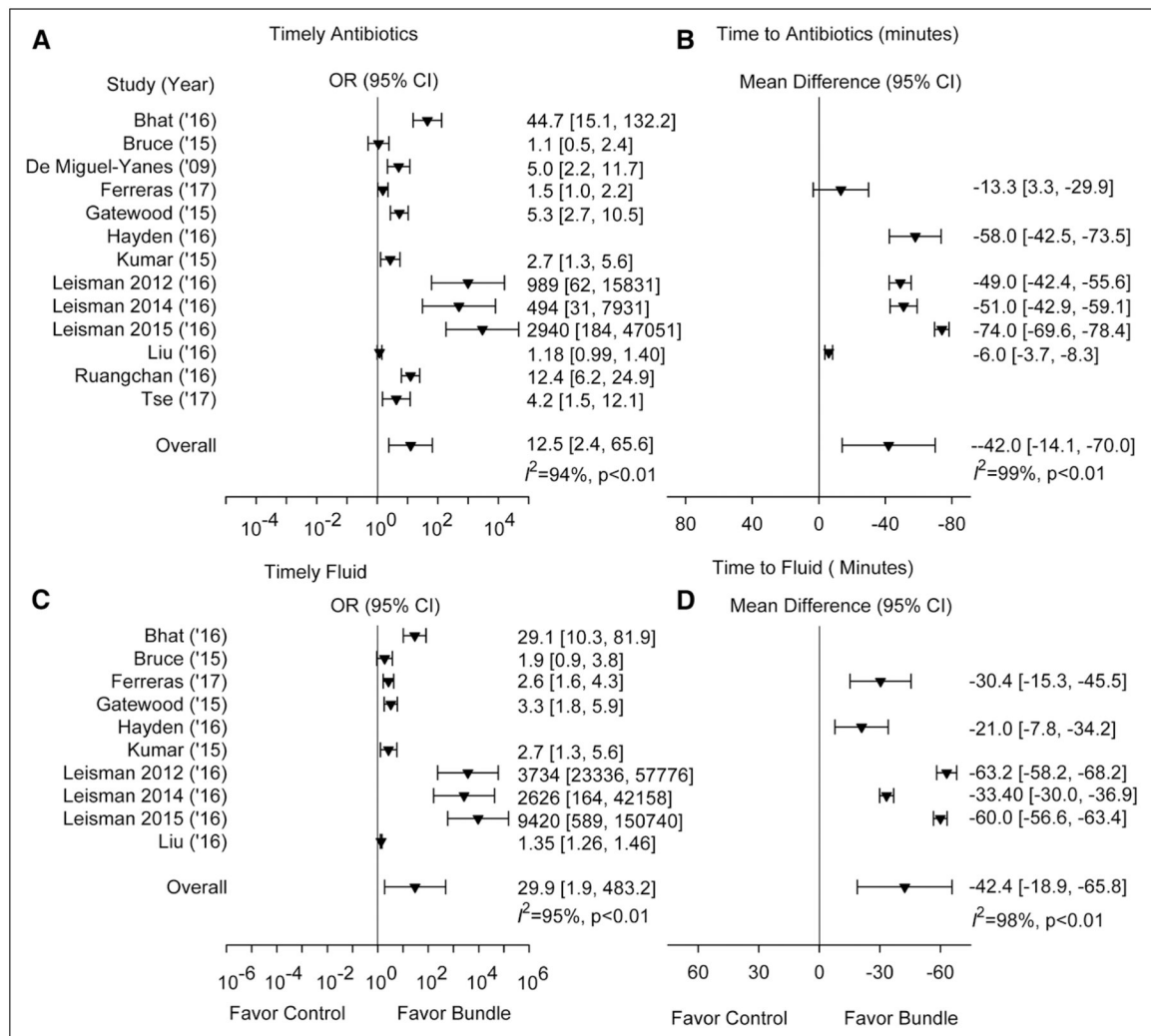
Figure 4.

This figure shows whether bundle treatment increased the proportion of patients receiving timely antibiotics or fluids or decreased the mean time to antibiotics or fluids compared to no bundle treatment in studies providing data. **A** and **C**, The effect of treatment with a sepsis bundle on the odds ratio (OR [95% CI]) of patients receiving timely (i.e., within a prespecified time period) antibiotics or fluids is shown. **B** and **D**, The effect of treatment with a sepsis bundle on the time to (calculated as the mean difference in time [95% CI]) antibiotics or fluids is shown. Both individual and overall ORs are shown as *inverted solid triangles*.

TABLE 1.

Summary of the Patient Numbers in Control and Bundle Groups, Study Designs, Sepsis Types, Location of Enrolled Patients, Country of Study, and the Number of Study Sites in the 17 Studies

Reference	No. of Patients			Study Design		Sepsis Type	Location of Patients	Study Country	No. of Study Sites
	Control	Bundle		Control	Bundle				
Austrian et al (32)	838	1,306	BACC[a,b]	Retrospective	Retrospective	SS/SSh	ED	United States	1
Bhat et al (33)	67	54	BACC[b]	Retrospective	Retrospective	Sepsis	Hospital	United Kingdom	1
Bruce et al (34)	62	75	BACC	Retrospective	Retrospective	SS/SSh	ED	United States	2
De Miguel-Yanes et al (35)	53	50	BACC[b]	Retrospective	Prospective	Sepsis/SS/SSh	ED	Spain	1
Ferreras Amez et al (36)	222	222	BACC[a,b]	Retrospective	Prospective	Sepsis/SSh	ED	Spain	6
Gao et al (37)	49	52	CCC	Prospective	Prospective	SS/SSh	ED + wards	United Kingdom	2
Gatewood et al (38)	137	83	BACC[a,b]	Retrospective	Prospective	SS/SSh	ED	United States	1
Hayden et al (39)	108	130	BACC	Retrospective	Retrospective	Sepsis/SSh	ED	United States	1
Kumar et al (40)	55	71	BACC	Retrospective	Prospective	Sepsis	ED	New Zealand	1
Leisman et al (41) (2012)[c]	4,769	1,050	CCC[b]	Prospective	Prospective	SS/SSh	ED + ICU	United States	11
Leisman et al (41) (2014)[c]	958	739	CCC[b]	Prospective	Prospective	SS/SSh	ED + ICU	United States	1
Leisman et al (41) (2015)[c]	5,124	2,115	CCC[b]	Prospective	Prospective	SS/SSh	ED + ICU	United States	9
Liu et al (42)	5,942	6,544	BACC[a,b]	Retrospective	Retrospective	Sepsis	ED + ICU	United States	21
Prasad et al (43)	287	742	CCC[b]	Retrospective	Retrospective	SS/SSh	ED + ICU	United States	1
Ruangchan et al (44)	70	158	CCC	Retrospective	Retrospective	SS	Hospital	Thailand	1
Teles et al (45)	46	121	CCC	Retrospective	Retrospective	Sepsis	ICU + wards	Brazil	1
Tse et al (46)	31	33	BACC	Retrospective	Prospective	SS	ED	Hong Kong	2

BACC = before-after cohort control, CCC = concurrent cohort control, ED = emergency department, SS = severe sepsis, SSh = septic shock.

[a] Employed *International Classification of Diseases*, 9th Edition, codes or administrative data sets to identify septic patients.

[b] Study described as part of a program to improve patient care quality (i.e., quality improvement).

[c] One publication included comparisons of control and intervention patients from each of three distinct patient populations admitted to study hospitals over periods ending in either 2012, 2014, or 2016, and each group and comparison was analyzed as a single study here.

TABLE 2.

Bundle Components to Be Administered in Bundle Groups and Management in the Control Groups of the 17 Studies

References	Overall Bundle Time	Reported Time Zero	Bundle Group			
			Laboratory Data		Antibiotics	
			Lactate	Blood Culture	Timing	Type
Austrian et al (32)	NS	NR	Yes	Yes	NS	Appropriate
Bhat et al (33)	1 hr	Sepsis diagnosis	Yes, 1 hr	Yes, 1 hr	1 hr	NS
Bruce et al (34)	3 hr	Sepsis diagnosis	Yes	Yes	NS	BS
De Miguel-Yanes et al (35)	3 hr	Sepsis diagnosis	Yes	Yes	3 hr	NS
Ferreras Amez et al (36)	3 hr	ED arrival	Yes	Yes	1 hr	NS
Gao et al (37)	6 hr	Sepsis criteria met[a]	—	Yes	1 hr	NS
Gatewood et al (38)	3 hr	ED triage	Yes	Yes	3 hr	NS
Hayden et al (39)	NS	ED arrival	Yes	Yes	NS	BS
Kumar et al (40)	1 hr	Initial nursing assessment	Yes, 1 hr	Yes, 1 hr	1 hr	NS
Leisman et al (41) (2012)[b]	3 hr	Sepsis criteria met[c]	Yes	Yes	3 hr	BS
Leisman et al (41) 2014[b]	3 hr	Sepsis criteria met[c]	Yes	Yes	3 hr	BS
Leisman et al (41) 2015[b]	3 hr	Sepsis criteria met[c]	Yes	Yes	3 hr	BS
Liu et al (42)	3 hr	Initial lactate test results obtained	Yes[d]	NS	3 hr	NS
Prasad et al (43)	3 hr	Sepsis criteria met[e]	Yes	Yes	3 hr in ED; 1 hr inpatient	NS
Ruangchan et al (44)	NS	Sepsis diagnosis	—	Yes	1 hr	Empiric
Teles et al (45)	3 hr	Sepsis diagnosis	Yes	Yes	1 hr	BS
Tse et al (46)	NS	ED registration	Yes	Yes	1 hr	NS

BS = broad-spectrum antibiotics, ED = emergency department, lactate = initial lactate, NR = not reported, NS = not stated, VP/I = vasopressor and/or inotrope for persistent hypotension.

[a] All the following fulfilled: signs and symptoms of infection, documented source of infection, and ≥ 1 organ dysfunction.

[b] See text for description of these three cohorts.

[c] Time of laboratory result or time of vital sign measurement causing the patient to meet sepsis criteria.

[d] Obtained second lactate value.

[e] Time at which two systemic inflammatory response syndrome criteria and one sign of organ failure in the presence of known or suspected infection met.