Critical Review Form
Meta-analysis

Bundled care for septic shock: An analysis of clinical trials
Crit Care Med 2000: 38:668-678

Objective: **"To examine the effect of bundle institution on survival and the application of individual bundle components." (p, 669)**

Methods: **Meta-analysis investigators conducted an English-language electronic data base search of PUBMED, EMBASE and Cochrane from January 1980 to July 2008 to find human studies of adults ≥ 18 years old with American College of Chest Physicians and Society of Critical Care Medicine consensus conference defined sepsis or septic shock using $Scv0_2$ monitoring to guide therapy. Included studies had to have a control group and record mortality rates as well as quantify usage of at least five to nine therapies: antibiotics, fluids, vasopressors inotropic agents, packed RBC transfusions, corticosteroids, recombinant human activated protein C, insulin or mechanical ventilatory tidal volumes.**

The following search terms were used: sepsis, septic shock, treatment, guidelines, protocols early goal directed therapies, and bundles. Two investigators independently reviewed included studies using a standardized data collection form. Survival and frequency of use of outlined therapies were the outcomes of interest. Discrepancies were resolved by a third investigator. The authors also recorded study design and setting, prognostic imbalances between bundle-care and control-groups, presence of educational or other co-intervention with bundled care, "septic shock" and "appropriate antibiotic" definitions, treatments monitored and time over which treatment was assessed and whether target hemodynamic goals were measured.

No individual trial quality assessment (Jadad) was performed. Heterogeneity was assessed with Breslow-Day test and I^2 statistic. Using a random-effects model the Mantel-Haenszel test was employed to generate summary odds ratio with 95% CI's. When significant heterogeneity was noted, a jackknife sensitivity analysis was conducted by sequentially removing individual studies and re-computing summary odds ratios to determine whether a non-heterogeneous meta-analysis summary estimate could be described.

Guide	Question	Comments
I	***Are the results valid?***	
1.	Did the review explicitly address a sensible question?	Yes – is there scientific merit for IHI and CMS "all or none" performance measures when managing septic shock with bundled care? Also, what research supports the individual elements of sepsis bundles?
2.	Was the search for relevant studies details and exhaustive?	No. The meta-analysis authors ignored the non-English literature and did not hand-search bibliographies or scientific abstracts. They did not search the gray literature or contact industry experts or trial leaders for additional unpublished data. In an era transitioning to electronic medical records (EMRs) and computer physician order entry (CPOE), industry may have substantial input on bundled care which fits nicely with computerized packages being sold to hospitals.
3.	Were the primary studies of high methodological quality?	No. As demonstrated in Table 2 (p. 670) 7/8 trials were before-after designs without prospective data collection or randomization to equally distribute unmeasured confounding variables. Although the meta-analysis authors do not rate quality using any validated metric (such as the Jadad scale), if they did these seven articles would receive the lowest quality sores.
4.	Were the assessments of the included studies reproducible?	Unknown. The authors do not describe who or how the articles were selected for inclusion. They do not use a valid/reliable article – quality rating metric (i.e. Jadad) so readers remain uncertain whether two experts reading these eight papers would take them of similar or dissimilar quality.
II.	***What are the results?***	

1.	What are the overall results of the study?	• From 981 identified trials eight met inclusion criteria and seven of those were before/after design. The eight trials were Rivers 2001, Trzeciak 2006, Kortgen 2006, Shapiro 2006, Micek 2006, Nguyen 2007, Jones 2007, and El Solh 2008. • Only Kortgen was not based initially in the ED. • Four trials had baseline prognostic imbalances between groups and statistical methods to adjust for these imbalances are not described. • As demonstrated in Table 3 (p. 670) inclusion criteria across trials varied, but four trials used Rivers EGDT inclusion criteria. • APACHE II baseline scores ranged from 20 to 40 (Table 2, p. 670) • Six trials used co-interventions with bundled care including educational programs, sepsis carts/tool kits, sepsis nursing flow sheets, and "dedicated lines of communication to infectious disease experts or surgical services". (p. 669) • Bundled care improved survival (OR 1.91, 95% CI 1.49 – 2.45, p <0.001, I^2 = 0%) across all eight studies. • Bundled care significantly decreased the time to antibiotics (weighted mean difference – 0.58 hours, p < 0.001, I^2 = 0%) across the four studies reporting this outcome. Bundled care also increased the odds of receiving culture-defined appropriate antibiotics (OR 3.06, 95% CI 1.69 – 5.53, p = 0.0002 I^2 = 0%). • Significant heterogeneity was noted in the use of the following interventions with bundled care: abx within a specified time period (I^2 = 77%), crystalloids (I^2 = 89%), vasopressors (I^2 = 84%), inotropes (I^2 = 67%), PRBC (I^2 = 73%), corticosteroids (I^2 = 87%), and rhAPC (I^2 = 88%). • With the exception of antibiotics within a specified time period, each of the bundled interventions with significant heterogeneity is based on lower quality evidence (as judged by the GRADE criteria) and have on-going RCT's to further evaluate individually (Table 7 and Table 8, pp 674-675). • Removal of individual studies failed to eliminate heterogeneity for fluids, vasopressors, corticosteroids, or rhAPC. However, removal of one

		study did eliminate heterogeneity and yield significant effect sizes for receiving antibiotics within a specified time (OR 3.89, 95% CI 1.98 – 7.64) and use of inotropes (OR 6.89, 95% CI 2.33 – 20.38).
2.	How precise are the results?	The odds ratio 95% CIs remain quite wide for each bundle component so the overall impact and NNT for each intervention remain uncertain.
3.	Were the results similar from study to study?	No. As described above significant heterogeneity was noted for the interventions based upon lower quality evidence (vasopressors, PRBC, corticosteroids, and rhAPC). "Although these agents may benefit some septic patients, until such subgroups are clear, their inclusion in care bundles is inappropriate" (p. 675)
III.	***Will the results help me in caring for my patients?***	
1.	How can I best interpret the results to apply them to the care of my patients?	Bundled care consistently improves survival. The leading interventional component of bundled care based upon the highest quality evidence and the results of this meta-analysis time to antibiotics and appropriateness of initial antibiotics selected. Other interventions sometimes proposed for sepsis bundles need higher quality (RCT) data before they should be incorporated into sepsis bundles or using as quality indicators or pay-for-performance metrics for CMS.
2.	Were all patient important outcomes considered?	No POEMs other than survival were considered. Future trials should consider such patient-oriented outcomes as functional recovery, ICU/hospital LOS, and time to full-recovery.
3.	Are the benefits worth the costs and potential risks?	No cost-benefit analyses were reported or hypothesized. As the components of high-quality evidence-based sepsis bundles are derived and tested in the future, cost analyses from various perspectives (patient, provider, payer, society) should be assessed.

Limitations

1) **Incomplete search strategy (bibliographies, industry, researcher, gray literature, etc.)**

2) **Failure to grade evidence quality using validated metric (Jadad).**

3) **Failure to reference or use QUOROM or MOOSE guidelines.**

4) **No POEMS or cost-effectiveness assessed or hypothesized.**

Bottom Line

Lesser quality (non-RCT) designs and the absence of trials reporting compliance with early goal directed therapy at baseline or therapy-specific responses of hemodynamic benchmarks ($Scv0_2$, CVP, etc) all severely restrict astute clinician's ability to interpret clinical trials of sepsis bundled care. Future trials are needed to individually assess the effectiveness of components like rhAPC, PRBC, vasopressors, and lung protection mechanical ventilation before these interventions become part of sepsis bundled care pathways. Before IHI or CMS or JC incorporate bundled care "all or none" reimbursement pathways, ongoing trials' evidence should be obtained. Future trials will also need to assess bundled care effectiveness and cost-effectiveness in heterogeneous settings in the era of EMR's and CPOE.