Bundled care for septic shock: an analysis of clinical trials
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CRD summary
The authors' concluded that sepsis care bundles significantly improved survival and use of antibiotics; their effect on other therapies was unclear. The findings should be interpreted cautiously given the limitations of the included studies. The authors' conclusions appropriately considered the limitations of the studies, but potential for bias in the review should be borne in mind.

Authors' objectives
To compare the effects of sepsis bundles versus non-protocolised care in the treatment of septic shock.

Searching
PubMed, EMBASE and The Cochrane Library were searched between January 1980 and July 2008 for English-language articles. Search terms were reported.

Study selection
Clinical trials that compared use of sepsis care bundles (using a central venous oxygen saturation measure to guide therapy) against controls (historical or concurrent) of received non-protocol care for treatment of septic shock (American College of Chest Physicians and Society of Critical Care Medicine Consensus Conference definition) in adults (≥18 years) were eligible for inclusion. The primary outcomes of interest were survival and frequencies in the use of therapies. Eligible studies were required to quantify the use of at least five of the therapies (whether these formed components of the sepsis bundle or not): antibiotics; fluids; vasopressors; inotropic agents; packed red blood cell transfusions; corticosteroids; recombinant human activated protein C (rhAPC); insulin; and mechanical ventilatory tidal volumes.

Included studies were conducted in an emergency department or intensive care unit. Initial treatment times were reported as time in the emergency department or zero to six hours. Study inclusion criteria for sepsis or septic shock in patients had to be consistent with American College of Chest Physicians and Society of Critical Care Medicine Consensus Conference definitions. Systolic blood pressure had to be ≤90mmHg after fluid challenge (the quantity of which differed across studies) and/or mean arterial pressure had to be ≤65mmHg or blood lactate of ≥4. Mean Acute Physiology and Chronic Health Evaluation (APACHE) II scores ranged between 20.4 and 40 in the control groups and between 21.4 and 42 in the bundled care groups. Protocol treatments included early goal-directed therapy and non-protocol treatments and included deep venous thrombosis prophylaxis. Most studies included aids to facilitate protocol care (such as specialised education of health workers, dedicated areas of care, tool kits, quality improvement programmes and department head communications to increase compliance). Mortality was reported in hospital or at 28 days.

The authors did not state how many reviewers screened studies for inclusion.

Assessment of study quality
The authors did not state that they formally assessed study quality, but reported on blinding and comparison of study groups at baseline.

Data extraction
Two reviewers independently extracted survival rates and frequencies in the use of the therapies. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. Time before antibiotic administration (hours) and volume of crystalloid administered (mL) in the intervention and control groups were extracted to calculate mean differences between groups and 95% CIs. Discrepancies were resolved by referral to a third reviewer.

Methods of synthesis
A random-effects model was used to combine odds ratios and 95% CIs. Mean differences and 95% CIs were combined to calculate weighted mean differences (WMDs). Statistical heterogeneity was assessed using $I^2$. Where there was evidence of statistical heterogeneity, sensitivity analysis was performed by removal of one study at a time.

There was insufficient data on insulin therapy and lung protective strategies to enable analysis in the review.

**Results of the review**

Eight studies (n=1,271) were included in the review: one prospective randomised trial and seven before-and-after studies. None of the studies was blinded. Four before-and-after studies reported imbalances in study group criteria at baseline.

Bundled care increased the odds of survival compared to controls (OR 1.91, 95% CI 1.49 to 2.45, $I^2=0%$; eight studies, n=1,271); the difference was statistically significant. Bundled care significantly decreased the time to administration of antibiotics (WMD -0.58 hours, 95% CI -0.85 to -0.33, $I^2=0%$; four studies) and increased the odds of receiving appropriate antibiotics compared with controls (OR 3.05, 95% CI 1.69 to 5.53, $I^2=0%$; five studies).

There was significant statistical heterogeneity among studies that reported on timely administration of antibiotics ($I^2=77%$) and crystalloid use ($I^2=89%$) and studies that reported the number of patients who received vasopressors ($I^2=84%$), inotropes ($I^2=67%$), packed red blood cell transfusions ($I^2=73%$), corticosteroids ($I^2=87%$) and rhAPC ($I^2=88%$).

Sensitivity analyses reduced statistical heterogeneity among studies that reported timely administration of antibiotics, use of inotropes and packed red blood cell transfusions, which indicated that bundle care significantly increased the odds of receiving timely antibiotics compared with controls (OR 3.89, 95% CI 1.98 to 7.64, $I^2=0%$; five studies) and use of inotropes (OR 6.89, 95% CI 2.33 to 20.38, $I^2=0%$; six studies). There were no statistically significant differences between treatment groups in occurrence of packed red blood cell transfusions.

**Authors’ conclusions**

Sepsis care bundles significantly improved survival and use of antibiotic therapy; the effect on other therapies was unclear due to heterogeneity among studies. The findings should be interpreted cautiously given the limitations of the included studies.

**CRD commentary**

The review question and supporting inclusion criteria were clearly stated. The literature search included appropriate electronic databases. The search was limited to English-language publications, so potentially relevant studies may have been missed. The authors undertook data extraction in duplicate, but the process for study selection was not reported and so reviewer error and bias could not be ruled out. No formal quality assessment was undertaken, but the authors acknowledged limitations with the included studies (such as retrospective study design, lack of blinding, potential selection bias, use of unadjusted data and analysis of both randomised and non-randomised studies). As such, it may not have been appropriate to combine the studies. There was evidence of significant statistical heterogeneity for some outcomes; the authors investigated this to some extent. Few patient details were reported and the authors acknowledged the lack of baseline patient data and data on certain outcomes. It was unclear to what extent use of additional aids to facilitate protocol care may have influenced the findings.

The authors’ conclusions seem suitably cautious, but limitations of the included studies and potential for bias in the review should be borne in mind.

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