Empiric antibiotic therapy for suspected ventilator-associated pneumonia: a systematic review and meta-analysis of randomized trials

Aarts MA, Hancock JN, Heyland D, McLeod RS, Marshall JC

CRD summary
The review concluded that antibiotic monotherapy was not inferior to combination therapy in the empirical treatment of ventilator-associated pneumonia and that no superior empirical regimen could be identified; further, no robust evidence for equivalence was found. The review was generally well conducted; the authors’ conclusions reflected the limited evidence available and appear likely to be reliable.

Authors’ objectives
To compare specific antibiotic regimens and compare monotherapy with combination therapy for the empirical treatment of ventilator-associated pneumonia.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to January 2007 for studies in any language; search terms were reported. Bibliographies of studies and reviews were searched for additional trials. Unpublished studies were sought by contacting experts in the field and authors of identified trials.

Study selection
Randomised controlled trials (RCTs) of empirical treatment for ventilator-associated pneumonia in adults were eligible if they compared a parenteral antibiotic regimen with placebo or comparison parenteral antibiotic. A suspicion of ventilator-associated pneumonia was defined as a new or progressive infiltrate in association with fever, leukocytosis and/or purulent secretions in patients ventilated for more than 48 hours. Trials were excluded if fewer than 50% of patients were ventilated or if culture results were available before initiation of antibiotics. The primary outcome was 28- or 30-day all-cause mortality.

A very broad range of antibiotics was used in the included studies (most regimens included sufficient coverage for Gram-positive, Gram-negative and anaerobic organisms). Some studies included additional antibiotics to experimental and control groups; no studies used placebo. Around of half the studies described a strategy to alter antibiotics following availability of culture results. Most studies were of intensive care unit patients. Studies were conducted between 1984 and 2006.

Two review groups independently conducted searches and reviewed abstracts; methods used to assess full papers were not reported.

Assessment of study quality
Study quality was assessed by reviewers in duplicate, with disagreements resolved through consensus. Criteria were: blinding of patients, physicians and outcome assessors; allocation concealment; losses to follow-up; use of intention-to-treat analysis; and use of sample size calculation.

Data extraction
Data were extracted (preferably for the intention-to-treat population) in duplicate (with disagreements resolved through consensus) to enable calculate relative risks (RR) with 95% confidence intervals (CI). Authors were contacted for further information when necessary.

Methods of synthesis
Meta-analyses of pooled relative risks were performed using a random-effects model (weighted by inverse variance). Subgroup analyses compared monotherapy with combination therapy and examined the treatment effect for patients with microbiologically-confirmed infection. Sensitivity analyses assessed the effect of study quality and of enrolling only ventilated patients.
Results of the review
Forty-one RCTs were included (n=7,015). The overall quality of studies was low. Thirteen studies blinded outcome assessors and 23 used adequate methods for allocation concealment. Around half of the studies used a power calculation. Around half of the studies had complete follow-up of participants. Only two studies were powered to detect a difference in mortality.

Mortality: There were no differences in mortality (30 RCTs) between any of the regimens, including subgroup analysis that compared monotherapy with combination therapy (eight RCTs).

Treatment failure: Meropenem appeared better than combination ceftazidime/aminoglycoside in terms of treatment failure (RR 0.70, 95% CI 0.53 to 0.93, I²=0%; two RCTs); a similar effect was seen in patients with microbiologically-confirmed infection (RR 0.51, 95% CI 0.33 to 0.80; three RCTs).

Superinfection and adverse events: Twelve of the 13 studies that could not be pooled showed no differences between groups for treatment failure. Of 26 RCTs that reported superinfections and adverse events, only one trial (for each outcome) reported significant differences between groups.

Sensitivity analyses were reported (and yielded similar results).

Authors' conclusions
Monotherapy was not inferior to combination therapy in the empirical treatment of ventilator-associated pneumonia. Available data neither identified a superior empirical regimen nor conclusively concluded that available regimens resulted in equivalent outcomes.

CRD commentary
The review addressed a clear question and was supported by appropriate inclusion criteria. Attempts to identify all relevant studies in any language were undertaken by searching electronic databases and checking references. Efforts were made to identify unpublished studies. Suitable methods were employed to reduce risks of reviewer error and bias for the processes of data extraction and study quality assessment; the authors did not report on whether such methods were used to select studies for inclusion. Study quality was assessed and was used in interpreting the results of the review. Basic study details were provided. An appropriate synthesis of the data was undertaken and this included assessment of heterogeneity and subgroup and sensitivity analyses.

This review was generally well-conducted; the authors' conclusions reflected the limited evidence available and appear likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that in the absence of strong evidence of safety for delayed therapy, they would recommend that patients with a high clinical suspicion of ventilator-associated pneumonia be started on empirical antibiotic therapy.

Research: The authors stated that high-quality adequately powered trials to determine the best treatment for suspected ventilator-associated pneumonia were needed; these should address the appropriate timing of initiation, duration and de-escalation of therapy following identification of a pathogen and the overall utility of early and aggressive empirical antibiotic therapy.

Funding
Physician's Services Incorporated Foundation of Ontario.

Bibliographic details
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.