Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis

Paul M, Shani V, Muchtar E, Kariv G, Robenshtok E, Leibovici L

CRD summary
The authors concluded that appropriate empirical antibiotic treatment was associated with a significant reduction in all-cause mortality. The conclusions appear reliable, but the limited search and incomplete reporting of results of quality assessments suggest a need for some caution.

Authors' objectives
To assess the effects of appropriate empirical antibiotic treatment on mortality among adult in-patients with sepsis.

Searching
PubMed was searched (1975 to November 2008). Search terms were reported. Reference lists of identified articles were handsearched. There was no search for unpublished studies. No language restrictions were applied.

Study selection
Prospective cohort studies that compared appropriate (versus inappropriate) empirical antibiotic treatment (further definitions were reported) in adult patients (over 18 years) with sepsis and microbiologically documented infections were eligible for inclusion. Studies with sample sizes of fewer than 50 patients and those that assessed meningitis and endocarditis were excluded (rationale for exclusions was reported). Outcome measures included all-cause 30-day mortality or, where this was not reported, other mortality (at another fixed point in time or in hospital).

Most studies were conducted in high-income countries. Study settings (intensive care unit/non-intensive care unit), spectrum of bacteria (pathogen), definitions of appropriate empirical antibiotic treatment (dose, route, duration) and time of mortality assessments varied (details were reported). Most studies enrolled only bacteraemic patients.

Two reviewers independently selected studies for inclusion.

Assessment of study quality
Two reviewers independently assessed the quality of included studies using a modified version of the Newcastle-Ottawa score to a maximum score of 8 points (higher scores represented a lower risk of bias). Definitions of appropriate and empirical, timing of mortality assessment and prospective components of the study (planning, patient detection and data collection) were documented.

Data extraction
Two reviewers independently collected data on unadjusted and adjusted number of deaths in comparison groups, variances and covariates assessed to enable calculation of odds ratios (ORs) and 95% confidence intervals (CIs). Where there were null values 0.5 was added. Authors of primary studies were contacted where data was missing or unclear. Where there were disagreements a third reviewer extracted the data.

Methods of synthesis
Pooled odds ratios and 95% CIs were calculated using the random-effects models. Heterogeneity was assessed using $X^2$ and $I^2$. Subgroup analysis and meta-regression was done to examine the differential effects of covariates (such as study setting, pathogen, Newcastle-Ottawa score and study year). Publication bias was assessed using funnel plots and Begg and Mazumdar tests. Sensitivity analysis was done by considering separately studies that did not perform multivariate analysis.

Results of the review
Seventy studies were included (n=25,488 patients, range 52 to 3,413). The mean Newcastle-Ottawa score was 6.7.
Inappropriate empirical antibiotic treatment was associated with significantly higher mortality in the unadjusted and adjusted comparisons (adjusted OR 2.05, 95% CI 1.69 to 2.49, $I^2=79.7\%$; 48 studies). Significant benefit of appropriate empirical treatment was maintained in most subgroup and sensitivity analyses. In analyses adjusted for background conditions and sepsis severity, the pooled odds ratio was 1.6 (95% CI 1.37 to 1.86, $I^2=46.3\%$; 26 studies) and the number needed to treat to prevent one fatal outcome was 10 patients (95% CI 8 to 15).

Effect modifiers included study design, time of mortality assessment, reporting methods of the multivariable models and covariates used for adjustment. Septic shock was the only clinical variable found to influence results (was associated with higher ORs).

**Authors’ conclusions**
Appropriate empirical antibiotic treatment was associated with a significant reduction in all-cause mortality; methods used in the observational studies significantly affected reported effect sizes.

**CRD commentary**
The review addressed a well-defined question with explicit study selection criteria. One major database was searched without language restrictions. Limited efforts were made to identify unpublished papers; some relevant papers may have been missed. Review processes were conducted in duplicate, which minimised potential reviewer error and bias. Study quality was assessed using appropriate criteria and results were reported as a mean score without individual study results. The methods used to combine data and account for statistical heterogeneity were appropriate and justified. The authors acknowledged a number of limitations (possible bias due to non-random allocations, heterogeneity, data imputations). A large number of studies with large overall sample size were included.

The authors’ conclusions appear reliable, but the limited search and incomplete reporting of results of quality assessments suggest a need for some caution.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that future studies (both observational and RCTs) should assess 30-day mortality (rather than in-hospital or other unfixed follow-up) and adjust the effect of appropriate antibiotic treatment for underlying disorders, disease severity before infection onset and sepsis severity at onset of infection.

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