Evidence behind the 4-hour rule for initiation of antibiotic therapy in community-acquired pneumonia
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CRD summary
The authors concluded that observational evidence does not confirm that mortality is decreased by early administration of antibiotics in stable adult patients with community-acquired pneumonia. These conclusions did not appear to sufficiently highlight the poor quality of the evidence, which was derived from a small number of potentially biased and poor-quality observational studies.

Authors’ objectives
To determine the effect on mortality rates of administering antibiotics within four hours of presentation compared to after more than four hours among adults being admitted to hospital with community-acquired pneumonia.

Searching
Databases searched: MEDLINE (from inception to August 2007), EMBASE, CINAHL, CENTRAL and Emergency Medical Abstracts (from inception to August 2006). Search strings were reported. The reference lists of relevant articles, editorials and guidelines were checked, as were evidence summaries cited by regulatory guidelines.

Study selection
Prospective and retrospective observational studies of antibiotic therapy for immunocompetent adults admitted to hospital with community-acquired pneumonia were eligible for inclusion, provided that outcomes relating to the timing of therapy were calculable. Studies were required to report outcomes data for a control group defined by later initiation of therapy. Primary outcomes of interest in the review were inpatient and 30-day mortality.

Studies in the review included patients whose clinical status varied with respect to severity, stability, comorbidities and admission to intensive care unit. Methods of diagnosing pneumonia also varied. Most studies measured pneumonia severity, typically using the Pneumonia Severity Index (PSI). Interventions in the review comprised antibiotics initiated either four hours or eight hours after patient presentation versus antibiotics initiated at a later time. About half of the studies measured the time to antibiotic treatment from emergency department triage onwards. In other studies the definition of time of antibiotic administration was imprecise. Most studies reported in-patient and/or 30-day mortality. Three studies reporting length of hospital stay (but not mortality) were also included in the review. Most of the included studies were multicentre cohort studies. The authors did not state how the papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
Aspects of study validity considered in the 10 studies reporting mortality were: whether design was prospective; whether outcomes were adjusted for severity with PSI; whether prospective studies had complete follow up; and whether retrospective studies adhered to published methodological criteria for chart review (Gilbert 1996). The authors did not state how the assessment was performed.

Data extraction
Odds ratios (ORs) were calculated from the numbers of events in the control and intervention groups of each study, with 95% confidence intervals (CIs). Mortality outcomes for one study were adjusted for severity by the review authors using data in the published report to calculate an adjusted OR and 95% CI, with Mantel-Haenszel weights. The authors did not state how the data were extracted for the review nor how many reviewers performed the data extraction.

Methods of synthesis
The data were combined in a narrative synthesis, grouped by intervention and study quality (whether the design was prospective and/or whether the outcomes were adjusted for severity measured by the PSI). Study data were displayed in forest plots but were not pooled.
Results of the review

Thirteen observational studies were included: 12 cohort (n=22,295) and one case-control (n=132). Sample sizes ranged from 96 to 13,771.

Quality (10 cohort studies)

Four studies were prospective (three adjusted for pneumonia severity) and six were retrospective (three adjusted for pneumonia severity). Only three of the retrospective studies adhered to more than two of the eight published chart review standards.

Mortality rate

Four-hour cut-off (seven studies). Findings varied. Two of the seven studies (one prospective without severity adjustment and one retrospective) reported that antibiotics within four hours were associated with a statistically significant reduction in mortality. The reduction ceased to be statistically significant in the prospective study after adjustment for mental status and other variables. Post-hoc analysis of the only prospective study with adjustment for severity (conducted by the review authors) found a statistically significant association between early antibiotic administration and higher mortality (OR 1.99, 95% CI: 1.22 to 13.45, n=409). A possible relationship between study design and the magnitude of observed results was noted overall, with lower-quality studies more likely to indicate a survival benefit associated with early administration.

Eight-hour cut-off (four studies). One study (retrospective without severity adjustment) reported that early antibiotics were associated with a statistically significant reduction in mortality. The other three studies (including one prospective study without severity adjustment) reported no statistically significant difference between the treatment groups.

Results of three additional retrospective studies reporting length of hospital stay were inconsistent.

Authors' conclusions

Observational evidence did not confirm that mortality was decreased by early administration of antibiotics in stable adult patients with community-acquired pneumonia being admitted to hospital.

CRD commentary

The review objectives were not entirely clear, as the review incorporated a clinical scenario that applied only to a subset of participants (those with moderate, stable pneumonia). This was reflected in the conclusions, which refer only to adults with stable pneumonia, although only one of the included studies appeared to be restricted to this population. Relevant sources were searched for studies, but it does not appear that specific attempts were made to retrieve unpublished studies, so the review may be prone to publication bias. It was not stated whether the search was restricted by language. It was also unclear whether steps were taken to minimise the risk of error and bias by having more than one reviewer involved in study selection, data extraction and validity assessment. Study characteristics were reported clearly. Suitable criteria were used to evaluate validity. Potential sources of bias in the primary studies were acknowledged in the text. The use of a narrative synthesis appears appropriate given the clinical and methodological heterogeneity between the studies. Lack of information about review methods makes it difficult to assess the reliability of the findings. Moreover, the authors' conclusions do not appear to sufficiently highlight the poor quality of the evidence, which derives from a small number of potentially biased and poor-quality observational studies.

Implications of the review for practice and research

Practice: the authors stated that prompt diagnosis and treatment of stable patients with community-acquired pneumonia is a worthwhile objective, but should not take priority over treatment of patients with equal or greater severity of illness in the emergency department setting.

Research: the authors did not state any implications for research.

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