Preventive antibiotics for infections in acute stroke: a systematic review and meta-analysis

van de Beek D, Wijdicks EF, Vermeij FH, de Haan RJ, Prins JM, Spanjaard L, Dippel DW, Nederkoorn PJ

CRD summary
The review found that prophylactic antibiotics reduced the risk of infection but did not reduce the mortality rate in adults with acute stroke; larger studies were needed to confirm these findings. In view of the limited search, incomplete reporting of review methods and likely selection bias in the included studies, the authors’ conclusions require cautious interpretation.

Authors' objectives
To evaluate the role of prophylactic antibiotics in adults with acute stroke.

Searching
MEDLINE was searched from 1966 to February 2009. Cochrane databases (unspecified) and reference lists of retrieved studies were searched. Search terms were not reported.

Study selection
Randomised controlled trials (RCTs) that compared prophylactic antibiotics with placebo or control in adults (over 16 years) with acute stroke were eligible for inclusion. Studies were required to report mortality or infection as an outcome.

Most participants in the review had a history of ischaemic stroke. Inclusion criteria for stroke severity in the primary studies were based on National Institute of Health Stroke Scale (NIHSS) or Rankin scale; required NIHSS scores ranged from at least 4 to at least 11. One study excluded participants with a life expectancy of under 90 days. Intervention groups received fluoroquinolones, tetracycline or mezlocillin B-lactam antibiotic with b-lactamase inhibitor, to be started within six to 36 hours of stroke onset. Duration of therapy ranged from three to five days. Primary outcomes varied across the included studies. The primary outcomes in the review were mortality rate and short-term infection rate (infections were defined by the study and occurred within two weeks of symptom onset). Study definitions of infection varied widely. Medication-related adverse events were reported as a review outcome.

The authors stated neither how the papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
Studies were allocated a score for methodological factors such as inclusion criteria, intervention, outcome measures and sample size calculations. Studies were also evaluated using the Jadad scale of adequacy of reported randomisation, double blinding and withdrawals or dropouts. Each study was awarded a Jadad score out of a maximum of 5 points. The authors did not state how many reviewers performed the assessment.

Data extraction
Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from the number of events in the two groups of each study. Data were extracted on an intention to treat basis if possible. The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Studies were combined using the Mantel-Haenszel fixed-effect model to calculate pooled odds ratios and 95% CIs. Heterogeneity was assessed using the Q statistic. The number needed to treat (NNT) was calculated.

Results of the review
Four RCTs were included in the review (n=426). Quality scores ranged from 2 to 5 points out of 5. Three RCTs had adequate allocation concealment, two were double blinded and three reported reasons for withdrawal from the study.
The rate of infection was significantly lower in the intervention group compared to controls (OR 0.44, 95% CI 0.23 to 0.86, NNT 7; three RCTs). The infections prevented by antibiotics were those most commonly reported (pneumonia and urinary tract infection). There was no statistically significant difference between the groups in mortality rate (four RCTs). There was no significant statistical heterogeneity in any analysis. No major harm or toxicity was found to be associated with the intervention (three studies, data not pooled).

Two individual studies reported a statistically significant difference between the groups in their primary outcome that favoured the intervention group. They measured improvement in NIHSS score (p<0.001) and fever rate (p=0.03).

**Authors’ conclusions**
In adults with acute stroke, prophylactic antibiotics reduced the risk of infection, but did not reduce mortality rate. Larger studies were needed to confirm this effect.

**CRD commentary**
The objectives and inclusion criteria of the review were clear. Some relevant sources were searched for studies, but (as the authors noted) the search was not extensive and the review may be subject to publication bias as some RCTs may have been missed. It did not appear that publication bias was formally assessed. It was not stated whether the search was limited by language; if so, the review may also be subject to language bias. It was unclear whether steps were taken to minimise the risk of reviewer bias and error by having more than one reviewer independently select studies, assess validity and extract data. The nature of the intervention received by control groups was not stated clearly. Appropriate statistical techniques were used to combine data and assess for statistical heterogeneity. The authors noted that the included studies had very low mortality rates, which probably reflected selection bias (associated with studies including only participants with a favourable prognosis). The included studies were small and two of the four were of questionable quality. In view of the limited search, incomplete reporting of review methods and likely selection bias in the included studies, the authors’ conclusions require cautious interpretation.

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

**Practice:** The authors stated that antibiotics used to prevent infection after stroke should have a broad antimicrobial action against causative organisms of pneumonia and urinary tract infections. The potential benefit for an individual patient should be weighed against the risk of increasing the antimicrobial resistance rate.

**Research:** The authors stated that the role of prophylactic antibiotics should be assessed in a large RCT (probably involving thousands of participants), which should report functional clinical outcomes and use a standardised definition of infection. Study outcomes should include mortality and health care costs. The authors also stated that ceftriaxone could be investigated for use after stroke, as it has both antibiotic and potentially neuroprotective properties.

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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.