Effectiveness and Safety of Antibiotics for Preventing Pneumonia and Improving Outcome after Acute Stroke: Systematic Review and Meta-analysis

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Background: Pneumonia is a common complication after stroke which increases morbidity and mortality. This systematic review was conducted to evaluate the efficacy and safety of antibiotics for the prevention of pneumonia after acute stroke. *Methods:* Medline, EMBASE, and Cochrane databases were searched for randomized controlled trials comparing preventive antibiotics to placebo or no antibiotics after acute stroke. The primary outcome was poststroke pneumonia. Secondary outcomes were all infections, urinary tract infections, death, dependency, length of hospital stay, and adverse events. Treatment effects were summarized using random effects meta-analysis. *Results:* Six trials (4111 patients) were eligible for inclusion. The median National Institute of Health Stroke Scale score in included trials ranged from 5 to 16.5. The proportion of dysphagia ranged from 26% to 100%. Preventive antibiotics were commenced within 48 hours after acute stroke. Compared to control, preventive antibiotics reduced the risk of poststroke pneumonia (RR .75, 95%CI ·.57-.99), and all infections (RR .58, 95%CI .48-.69). There was no significant difference in the risks of dependency (RR 0.99, 95%CI 0·80-1·11), or mortality (RR .96, 95%CI .78-1.19) between the preventive antibiotics and control groups. Preventive antibiotics did not increase the risk of elevated liver enzymes (RR 1.20, 95% CI .97-1.49). Preventive antibiotics had uncertain effects on the risks of other adverse events. *Conclusion:* Preventive antibiotics reduced the risk of post-stroke pneumonia. However, there is insufficient evidence to currently recommend routine use of preventive antibiotics after acute stroke.

Key Words: Preventive antibiotics—Post-stroke pneumonia—Acute stroke—Systematic review—Meta-analysis

Pneumonia is the most common infective complication of acute stroke which occurs in 5%-26% of patients with acute stroke.[1-3] Poststroke pneumonia is a pneumonia occurring after acute stroke, usually being hospital acquired and occurring early (in the first 4 weeks) after acute stroke or late (after 4 weeks).[2] Poststroke

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pneumonia can lead to respiratory failure requiring mechanical ventilation, prolonged hospitalization, and delayed mobilisation.[2,3] Thus, post-stroke pneumonia is associated with significant morbidity, mortality, and poses an economic burden.[4-7] Risk factors associated with poststroke pneumonia include older age, dysphagia, male gender, stroke severity, preadmission dependency, coronary artery disease, congestive cardiac failure, and chronic obstructive pulmonary disease.[3,7] While lacunar strokes are less likely to predispose patients to developing poststroke pneumonia compared to larger strokes, stroke associated immunosuppression can increase the risk of poststroke pneumonia.[8]

In some trials, administering preventive antibiotics has been shown to reduce the risk of poststroke infection.[9-18] However, there is uncertainty as to whether preventive antibiotics reduce poststroke dependency or mortality, with some studies suggesting improvement, and others showing no difference in outcome compared to standard stroke unit care.[9-18] Antibiotic use may lead to complications such as allergic reactions, adverse effects, colonization with drug-resistant organisms such as methicillin-resistant staphylococcus aureus, or Clostridium difficile diarrhoea.[13,17] Therefore, this systematic review was conducted to evaluate the efficacy and safety of prophylactic antibiotics in poststroke pneumonia.

Methods

This systematic review was conducted according to Cochrane methods and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[19,20] The protocol was registered in the International prospective register of systematic reviews (PROSPERO) www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016053133.

Search Strategy and Selection Criteria

Medline (Medical Literature Analysis and Retrieval System Online) via Ovid, EMBASE (Excerpta Medical Database) and CENTRAL (Cochrane Central Register of Controlled Trials) were searched from inception to December 2016 (See supplementary files for search strategy). In addition, clinical trial registers, reference lists of relevant review articles, systematic reviews, and treatment guidelines were searched for published and ongoing trials. Missing, incomplete or unpublished data from clinical trials were requested from the respective investigators by email. The following data were extracted using a standardized form: patient demographic details, study design and conduct, rate of outcome events, and adverse events. The methodological quality of each study was assessed using the risk of bias assessment tool developed by the Cochrane Bias Methods Group.[20] The following eight items were assessed: 1. random sequence generation; 2. allocation concealment; 3. blinding of participants; 4. blinding of investigators; 5. blinding of outcome assessors; 6. incomplete outcome data; 7. selective outcome reporting; 8. any other bias (e.g. insufficient rationale, study design e.g. cluster randomized trials, crossover trials).

Studies were eligible for inclusion if they:[1] were randomized controlled trials;[2] involved adult patients (age ≥18 years) admitted within 30 days of acute ischemic or hemorrhagic stroke; and[3] compared prophylactic antibiotics for the prevention of pneumonia with placebo, no treatment or standard care. There were no language restrictions or study size exclusions. Trials including populations with ischemic and hemorrhagic strokes were considered.

Outcome Measures

The primary study outcomes were poststroke pneumonia after acute stroke. Secondary outcomes were all infections, and urinary tract infections after acute stroke, length of hospital stay, dependency and death at discharge, 6 weeks and 12 weeks after acute stroke. The authors' criteria for the diagnosis of pneumonia, all infection and urinary tract infection were accepted. All assessment scales for dependence and stroke severity were accepted, including modified Rankin scale (mRS) score, Barthel Index, Canadian Neurological Scale, European Quality of life scale (See Supplementary files for description of scales).[21-24] Adverse events included clostridium difficilepositive diarrhea, Methicillin resistant Staphylococcus aureus (MRSA) colonization, intensive care unit (ICU) admission, ventilator requirement, elevated hepatic enzymes, acute kidney injury, allergic reactions, drug induced exanthema, drug resistant infections and phlebitis.

Data Extraction and Quality Assessment

Titles and abstracts were screened independently for potentially eligible studies by two investigators (M.S.B and Z.Z). The same authors independently extracted data and assessed risk of bias using the risk of bias assessment tool developed by the Cochrane Bias Methods Group.[20]

Data Synthesis and Analysis

The numbers of dichotomous outcomes were summarized and mean values with standard deviations were collated for continuous outcomes. Risks ratios with 95% confidence intervals were calculated for dichotomous outcomes. Pooled risk ratios (RR) with 95% confidence intervals (CI) were estimated for primary and secondary dichotomous outcomes using the DerSimonian and Laird random effects model.[25] In every case a two-sided P value of ≤.05 was deemed significant. Q and I^2 statistics were used to estimate heterogeneity across studies. An I^2 values of 25%, 50% and 75% were regarded as evidence of low, moderate and high levels of heterogeneity respectively.[26]