Title: Effectiveness and safety of antibiotics for preventing pneumonia and improving outcome after acute stroke: systematic review and meta-analysis

Short title: Preventive antibiotics for post-stroke pneumonia

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ABSTRACT

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 randomised controlled trials comparing preventive antibiotics to placebo or no antibiotics after acute stroke. The primary outcome was post-stroke pneumonia. Secondary outcomes were all infections, urinary tract infections, death, dependency, length of hospital stay, and adverse events. Treatment effects were summarised using random-effects meta-analysis.

Results: Six trials (4,111 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 post-stroke pneumonia (RR 0·75, 95%CI 0·57-0·99), and all infections (RR 0.58, 95%CI 0.48-0.69). There was no significant difference in the risks of dependency (RR 0.99, 95%CI 0·88-1·11), or mortality (RR 0·96, 95%CI 0·78-1·19) between the preventive antibiotics and control groups. Preventive antibiotics did not increase the risk of elevated liver enzymes (RR 1.20, 95% CI 0.97-1.49). 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.

INTRODUCTION

Pneumonia is the most common infective complication of acute stroke which occurs in 5%-26% of patients with acute stroke (1-3). Post-stroke 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). Post-stroke pneumonia can lead to respiratory failure requiring mechanical ventilation, prolonged hospitalisation, 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 post-stroke pneumonia include older age, dysphagia, male gender, stroke severity, pre-admission 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 post-stroke pneumonia compared to larger strokes, stroke-associated immunosuppression can increase the risk of post-stroke pneumonia (8).

In some trials, administering preventive antibiotics has been shown to reduce the risk of post-stroke infection (9-18). However, there is uncertainty as to whether preventive antibiotics reduce post-stroke 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, colonisation 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 post-stroke 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 standardised 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 randomised trials, cross-over trials).

Studies were eligible for inclusion if they: (1) were randomised 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 ischaemic and haemorrhagic strokes were considered.

Outcome measures

The primary study outcomes were post-stroke 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 difficile-positive diarrhoea, Methicillin-resistant Staphylococcus aureus (MRSA) colonisation, 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 ≤0.05 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).

The potential for small study effects (publication bias) was assessed by testing the funnel plot asymmetry using the Harbord's test.(27) The quality of evidence was summarized according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines (28). All analyses were conducted using Stata/MP (version 14.2, Stat Corp, College Station, Texas).

Role of funding source

This study had no funding. The corresponding author had access to all data and took final responsibility for submission of this paper.

RESULTS

Selection and description of studies

Six trials including 4,111 stroke patients met the inclusion criteria (Figure 1; Table 1). (11-13, 15-17) The mean age of participants ranged from 67 to 78 years. The proportion of male patients ranged from 35%-57%. The median baseline National Institute of Health Stroke Scale (NIHSS) score ranged from 5 to 17 (Table1).(29) Duration of follow-up ranged from 12 weeks to 24 weeks (11-13, 16, 17). One trial which contributed the maximum patients to this study included patients with less stroke severity unlike all the other trials which included moderate to severe strokes (Table 1) (17). One trial only recruited patients with dysphagia which was not a pre-requisite for inclusion in the other trials (13). Data on dysphagia was available in only three trials (12, 13, 17). In one trial, the proportion of patients with dysphagia was 26-27% (17). In the other two trials, the proportion of patients with nasogastric tubes ranged from 22-67% (12, 13).

The preventive antibiotics evaluated were ceftriaxone, moxifloxacin, mezlocillin plus sulbactam, levofloxacin and penicillin, in five trials (11, 12, 15-17). In two trials penicillins were used and these were semisynthetic derivatives of penicillins, and mezlocillin plus sulbactam (15, 16). In two trials fluoroquinolones were used, levofloxacin and moxifloxacin (11, 12). Ceftriaxone was used in one trial (17). In one trial, a range of antibiotics were used including amoxicillin with or without clarithromycin or with metronidazole or cephalosporins or any suitable antibiotic could be administered (13). In this trial, 78% of patients received amoxicillin with clavulanic acid with clarithromycin (13). In most trials, preventive antibiotics were administered intravenously or orally and commenced in the first 48 hours post-stroke (Table 1). The duration of treatment ranged from 3 to 7 days (11-13, 16, 17). All trials excluded patients currently using antibiotics (11-13, 15-17).

Patients in the control groups received antibiotics if pneumonia or infection was diagnosed. Preventive antibiotics were discontinued, and an appropriate drug initiated in both groups in case of a diagnosed pneumonia or infection in one trial (11). In three trials additional antibiotics were used in case of diagnosed infections in both groups and withdrawal of preventive antibiotics was based on clinical judgement and local antibiotic policy (13, 16, 17). In one trial, though a regimen of intravenous ceftazidime and tobramycin for pneumonia, intravenous vancomycin for bacteraemia/endocarditis and ciprofloxacin for urinary tract infections, in addition to preventive antibiotics or placebo, was pre-defined, if infections were refractory to therapy, study medication was withdrawn and antibiotics started as per clinical judgement (12). All patients in the trials received standard stroke unit care. The primary meta-analysis was performed excluding two trials (11, 13). The STROKE-INF was a cluster randomised trial and the ESPIAS trial did not provide data on post-stroke pneumonia and instead provided data on lower respiratory tract infection (LRTI) (11, 13). Both these trials were excluded from the primary analyses due to methodological differences from the other trials (11, 13). As the ESPIAS trial criteria for LRTI made it likely that a significant number of people with post-stroke pneumonia were included, this trial data, along with STROKE-INF trial data, were included in the sensitivity analyses (11, 13). The sensitivity analysis included all the trials (11-13, 15-17).

Risk of bias

The areas introducing the greatest risk of bias were lack of blinding of patients and investigators to the intervention (Figure 2) (15-17). Patients were not blinded to the intervention in three trials and investigators were not blinded to the intervention in four trials (Figure 2) (13, 15-17). Patients, investigators and outcome assessors were not blinded to the intervention in only one trial (15). One trial was graded as unclear risk of bias for ‘other

forms of bias' due to the problems with cluster randomised design, for example recruitment bias, and differential participant recruitment into clusters (28).

Effects of interventions

Primary outcome measure

Post-stroke pneumonia

Preventive antibiotics reduced the risk of post-stroke pneumonia in the primary analysis (4 trials; 2757 participants; RR 0.75, 95% CI 0.57-0.99, P=0.04; Heterogeneity χ^2=1.83, I^2=0%, P=0.60; certainty of evidence moderate) (Figure 3; Table 2) (12, 15-17). There was no significant difference in preventing post-stroke pneumonia between the antibiotic and control arms when the STROKE-INF trial was included in the sensitivity analysis (5 trials; 3845 participants; RR 0.85, 95% CI 0.59-1.2, P= 0.12; Heterogeneity χ^2=7.32 I^2=45.2%,P=0.4; certainty of evidence moderate) (Figure 4; Table 2) (12, 13, 15-17). One trial did not specify the number of post-stroke pneumonia patients in the data on lower respiratory tract infections and hence it was excluded from this outcome analysis (11).

Secondary outcome measures

All infections

Types of infections included were pneumonia, urinary tract infections, catheter-related phlebitis, tracheobronchitis, and other infections (not specified in the trial data). Preventive antibiotics were better than control in the primary analysis including the (3 trials; 2677 participants; RR 0.58, 95% CI 0.48-0.69, P<0.0001; Heterogeneity χ^2=0.27, I^2=0.0%, P=0.60; certainty of evidence high) (Figure 5; Table 2) (12, 16, 17). In the sensitivity analysis, antibiotics reduced the risk of all infections when compared to control, but with moderate heterogeneity (5 trials; 4030 participants; RR 0.67, 95% CI 0.52-0.85, P=0.001;

Heterogeneity χ^2=9.18, I^2=56.4%,P=0.05; certainty of evidence moderate) (see Supplementary files for forest plot; Table 2) (11-13, 16, 17).

Urinary tract infections

Preventive antibiotics were better than control in the primary analysis (3 trials; 2677 participants; RR 0.49, 95% CI 0.26-0.89, P=0.02; Heterogeneity χ^2=4.80,I^2=58.4%,P=0.09; certainty of evidence high) (Table 2) (12, 16, 17). Preventive antibiotics were better than control in the sensitivity analysis (4 trials; 3894 participants; RR 0.42, 95% CI 0.29-0.62, P<0.0001; Heterogeneity χ^2=4.85, I^2=38.2%, P=0.18; certainty of evidence high) (Table 2) (12, 13, 16, 17).

Dependency at 12 weeks

There was no significant difference between antibiotic use and control for dependency (mRS 3-6) at 12 weeks in the sensitivity analysis including the PASS and STROKE-INF trials (3719 patients) (2 trials; 3719 participants; RR 1.00, 95% CI 0.93-1.08, P=0.91; Heterogeneity χ^2=1.9, I^2=47.4%, P=0.16; certainty of evidence moderate) (Table 2) (13, 17). Primary analysis for this outcome was not possible since there was no data from other trials.

Death at 12 weeks

There was no significant difference between antibiotic use and control for mortality at day 90 in the primary analysis (4 trials; 2733 patients; RR 0.96, 95% CI 0.78-1.19, P=0.75; Heterogeneity χ^2= 2.45, I^2=0%, P=0.48; certainty of evidence moderate) (12, 15-17), or sensitivity analysis (6 trials; 4050 participants; RR 1.08, 95% CI 0.90-1.29, P=0.31; Heterogeneity χ^2=5.86, I^2=14.6%,P=0.32; certainty of evidence moderate) (Table 2) (11-13, 15-17).

Other outcomes

Meta-analysis was not conducted for the European Quality of life scale, Canadian neurological scale, the Barthel Index, length of stay, dependency and death at discharge and within 6 weeks because of absent or insufficient available data for pooling (22-24).

Adverse events

Preventive antibiotics did not increase the risk of elevated liver enzymes (3 trials; 2652 participants; RR 1.20, 95% CI 0.97-1.49, P=0.08; Heterogeneity χ^2=0.34, I^2=12.6%,P=0.84; certainty of evidence moderate) (12, 16, 17). Preventive antibiotics did not increase the risk of drug resistant infections (2 trials; 2591 participants; RR 1.37, 95%CI 0.45-4.16, P=0.57; Heterogeneity χ^2= 0.28, I^2=0.1%, P=0.59; certainty of evidence low) (12, 13, 17). Preventive antibiotics also did not increase the risk of MRSA infection (2 trials; 1296 participants; RR 0.83, 95%CI 0.39-1.77, P=0.63; Heterogeneity χ^2=0.0.69, I^2=0%,P=0.83; certainty of evidence low) (12, 13). Preventive antibiotics did not increase the risk of clostridium difficile diarrhoea (2 trials; 3729 participants; RR 1.12, 95% CI 0.12-10.35, P=0.9; Heterogeneity χ^2=1.79, I^2=44.1%,P=0.18; certainty of evidence low) (13, 17). Only one trial provided data on acute kidney injury, gastrointestinal bleeding, ICU admission, phlebitis, ventilator use, allergic reactions, and drug induced exanthema, and hence meta-analysis was not possible (12, 13, 16, 17).

DISCUSSION

In this systematic review (4,111 patients), preventive antibiotics reduced the risk of pneumonia (primary analysis), infection, and urinary tract infection after stroke (11-13, 15-17). However, there was no reduction in mortality or improved functional outcome with preventive antibiotics. There was no significantly increased risk of elevated liver enzymes, drug resistant infections, MRSA colonisation, or clostridium difficile diarrhoea with a low to moderate certainty of evidence. There was insufficient data available to determine the impact of antibiotics on other adverse events.

Three previous systematic reviews showed that preventive antibiotics reduced the risk of post-stroke infection (6, 10, 30). Only one previous systematic review reported post-stroke pneumonia as an outcome measure (30). In this review, preventive antibiotics did not reduce the risk of post-stroke pneumonia (30). There was no improvement in functional outcome or reduction in mortality in any of the previous systematic reviews (10, 30, 31). Significant adverse events were not reported in previous systematic reviews (10, 30, 31).

The STROKE-INF trial was cluster randomised, making the results difficult to compare to the other randomised trials (13). In the STROKE-INF trial, a range of antibiotics was allowed, and this could have compromised the effectiveness of antibiotics (13). In the STROKE-INF trial, 34% of the patients in the control group received antibiotics while infections were diagnosed in only 24% of them suggesting that control group patients were also receiving preventive antibiotics (13, 32). This could have confounded the results of the trial (13, 32). Being cluster randomised, the STROKE-INF trial could have led to preferential recruitment of patients at risk of post-stroke pneumonia into the preventive antibiotics group, resulting in a negative result for preventive antibiotics (13). However, there was no difference in the baseline characteristics of the two groups in this trial.

The main issue with the PASS trial (2538 patients) contributing the largest number of patients to this systematic review, was the low rate of post-stroke pneumonia compared to scientific literature, and milder strokes compared to other trials included in this study (12, 13, 15-17, 33). This may have reduced the effect of preventive antibiotics on improving outcomes. This trial had 83 % weightage in the primary meta-analysis for post-stroke pneumonia (17). The STROKE-INF trial specified that dysphagia was a pre-requisite for recruitment (13). Only up to 27% patients experienced dysphagia in the PASS trial (17). There was inadequate reporting of dysphagia in the other trials (11, 15, 16). In two trials, patients were lost to follow-up and this could have caused attrition bias reducing the effect of preventive antibiotics (12, 17).

It is possible that post-stroke pneumonia is a respiratory syndrome and a marker of poor outcome, and hence preventive antibiotics have not been shown to improve outcome in this meta-analysis (17). Similarly, it is possible that post-stroke infection is a marker of poor functional outcome (17). Finally, it is likely that stroke unit care has improved so much that preventive antibiotics, in addition, are not superior in improving outcomes from preventing post-stroke pneumonia and post-stroke infections.

The strengths of this study are that it represents a comprehensive overview of the available evidence, with risk of bias assessment, rating certainty of evidence, and inclusion of only randomised controlled trials. We recognise our study has limitations, for the inclusion of trial-level rather than individual patient data which did not allow further analysis according to particular patient characteristics defined by age, sex, stroke severity, or antibiotic type. There was significant clinical heterogeneity in the trials with different antibiotics, variable onset and duration of treatment, and follow-up post-stroke, with inadequate assessment and reporting of adverse events. Although we assessed publication bias using the recommended technique, this test may not have adequate power to distinguish chance from real asymmetry, as there

were fewer than 10 trials included. While the overall trial quality was fair, there were only six trials, and the open nature of four meant that participants were not blinded in three trials and investigators were not blinded in four trials (Table 2) (13, 15-17).

Based on this review, adequately powered double-blinded randomised trials, including moderate to severe acute stroke patients with dysphagia after acute stroke are required to determine whether preventive antibiotics after the onset of acute stroke prevent pneumonia and improve outcome with good safety and cost-effectiveness. There is insufficient evidence to recommend routine provision of antibiotics to prevent post-stroke pneumonia or infection, and uncertainty over the balance of potential benefits and harms of preventive antibiotics. In this study, preventive antibiotics were not superior to standard stroke unit care in improving functional outcomes or reducing mortality. This would indicate that there should be a greater emphasis on stroke unit care for patients with acute stroke to prevent post-stroke pneumonia and improve outcomes in these patients.

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Legends for figures:

Figure 1: PRISMA diagram

Figure 2: Risk of bias assessment of trials included

Figure 3: Forest plot of comparison: Preventive antibiotics versus control after stroke, primary outcome- post-stroke pneumonia (primary analysis)

Figure 4: Forest plot of comparison: Preventive antibiotics versus control after stroke, primary outcome- post-stroke pneumonia (sensitivity analysis)

Figure 5: Forest plot of comparison: Preventive antibiotics versus control after stroke, secondary outcome- all infections (primary analysis)

Supplemental figure (Supplemental files): Preventive antibiotics versus control after stroke- secondary outcome- all infections (sensitivity analysis)