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CLINICAL

Antibiotic prophylaxis is ineffective in preventing pneumonia post-stroke

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TITLE Prophylactic antibiotics after acute stroke for reducing pneumonia in patients with dysphagia (STROKE-INF): a prospective, cluster-randomised, open-label, masked endpoint, controlled clinical trial

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SUMMARY

STROKE-INF aimed to evaluate whether prophylactic antibiotics could prevent the development of pneumonia in patients with dysphagia after acute stroke. The study was a prospective cluster-randomised open-label controlled trial. Patients were enrolled within 48 hours of stroke onset. In total, 48 stroke units across the UK were randomly assigned to deliver standard stroke unit care with prophylactic antibiotics or standard stroke unit care alone. The antibiotic regimens were left to the discretion of the investigators but largely consisted of a β-lactam (amoxicillin or co-amoxiclav) with or without clarithromycin. The primary outcome measure was the development of pneumonia in the first 14 days, defined using a criteria-based algorithm and also as diagnosed by a physician. Suspected infections could be treated with additional antibiotics.

During the study period, 1,224 patients across 48 stroke units were randomly assigned; 24 units to standard stroke unit care with prophylactic antibiotics (intervention group) and 24 units to standard stroke unit care alone (control). Within 14 days of randomisation, 11 units and 7 patients withdrew, leaving 1,217 patients (615 patients in intervention group, 602 in control) across 37 units.

Based on the diagnostic algorithm, incidence of post-stroke pneumonia was 71 of 564 (13%) in the intervention group compared with 52 of 524 (10%) in the control group; marginal adjusted odds ratio (OR) 1.21 [95% CI 0.72–2.08], p = 0.49. The incidence of physician-diagnosed pneumonia was 101 of 615 (16%) compared with 91 of 602 (15%), adjusted OR 1.01 [95% CI 0.61–1.68], p = 0.96. Incidence of adverse effects were low and similar between the two groups although infections not related to post-stroke pneumonia were less common in the intervention group (22 of 615, 4%) than the control group (45 of 602, 7%). Patients assigned to antibiotic treatment were significantly more likely to die during follow-up than patients in the control group, hazard ratio 1.33 (1.01–1.75, p=0.045).

The authors concluded that prophylactic antibiotics in patients with acute stroke and dysphagia did not reduce the development of post-stroke pneumonia and this treatment should not be used.

OPINION

Post-stroke pneumonia is common in patients with dysphagia following acute stroke with an incidence of 16–19%.[1] Infections following stroke have been associated with less favourable outcomes, although to what extent this merely reflects stroke severity is difficult to ascertain. A meta-analysis of randomised controlled trials of prophylactic antibiotics post-stroke (n = 506) has suggested preventative antibiotics could reduce the incidence of infections following stroke by 14% in the short term, although the effect on long-term outcome was unclear.[2] Results from the Preventative Antibiotics in Stroke Study (PASS) earlier this year suggest that prophylactic intravenous ceftriaxone for 4 days reduced the incidence of (mainly urinary) infections with ad hoc subgroup analyses suggesting that prophylaxis was associated with improved neurological outcomes in patients who had received thrombolysis for acute ischaemic stroke.[3] However, therapy did not appear to prevent development of pneumonia.

The results of STROKE-INF again failed to provide convincing evidence of benefit from prophylactic antibiotics following acute stroke, with the only difference between the intervention and control groups being a reduction in infections other than pneumonia,

mainly urinary tract infections. Functional outcomes were similar between the two groups, and in fact time to death was shorter in the antibiotic group. Overall, there were no significant differences in incidence of pneumonia as diagnosed by algorithm or physician despite prophylaxis.

Most cases of post-stroke pneumonia occur following aspiration or micro-aspiration of organisms from the oropharynx. Reducing the incidence of pneumonia in patients with dysphagia requires the employment of various strategies, including optimal patient positioning, frequent suctioning of oropharyngeal secretions and diet modifications.[4] It appears that prophylactic antibiotic therapy adds little to these measures, which are offered as part of routine stroke unit care.

Lack of obvious benefit is likely to be further compounded when clinicians have a low threshold for starting antimicrobial therapy in this patient group. This is demonstrated by the large number of patients (207 of 602, 34%) in the control group who received at least one dose of an antibiotic in the first 7 days despite only 10% (52 of 524) having an algorithm diagnosis of pneumonia, suggesting that the distinction between 'prophylactic' and 'early' treatment is perhaps not clear.

It is surprising that patients in the intervention group had longer hospital stays than controls and even died significantly earlier than controls. Possible causes for the delayed discharge include delay in diagnosis of infection due to a masking effect of prophylaxis, initial perceived adequacy of prophylactic therapy regimen (more patients in the control group received second line antimicrobials) or infections due to organisms resistant to first line therapy. Data on the latter were not specifically collected as part of the STROKE-INF study. These reasons may also have contributed to an increased risk of death, although other studies have shown increased risk of mortality after administration of antibiotics, particularly macrolides which were widely used in this study.[5,6]

Although poorly defined, the possibility of a 'post-stroke respiratory syndrome', a complex interplay of chemical, bacterial and immunological factors unaffected by antimicrobial therapy, has been suggested previously. It may be that a greater proportion of these patients have non-infective pathology, such as a chemical pneumonitis following aspiration, than was previously recognised.[7]

In the era of evolving antimicrobial resistance and *Clostridium difficile* infection, prudent antibiotic use is becoming increasingly important. Combining this with the lack of demonstrable benefit, there remains no evidence to support the use of antimicrobial prophylaxis following acute stroke.

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