National Essential Medicine List Medication Review Process
Adult Hospital Level
Component: Respiratory

Date: January 2016

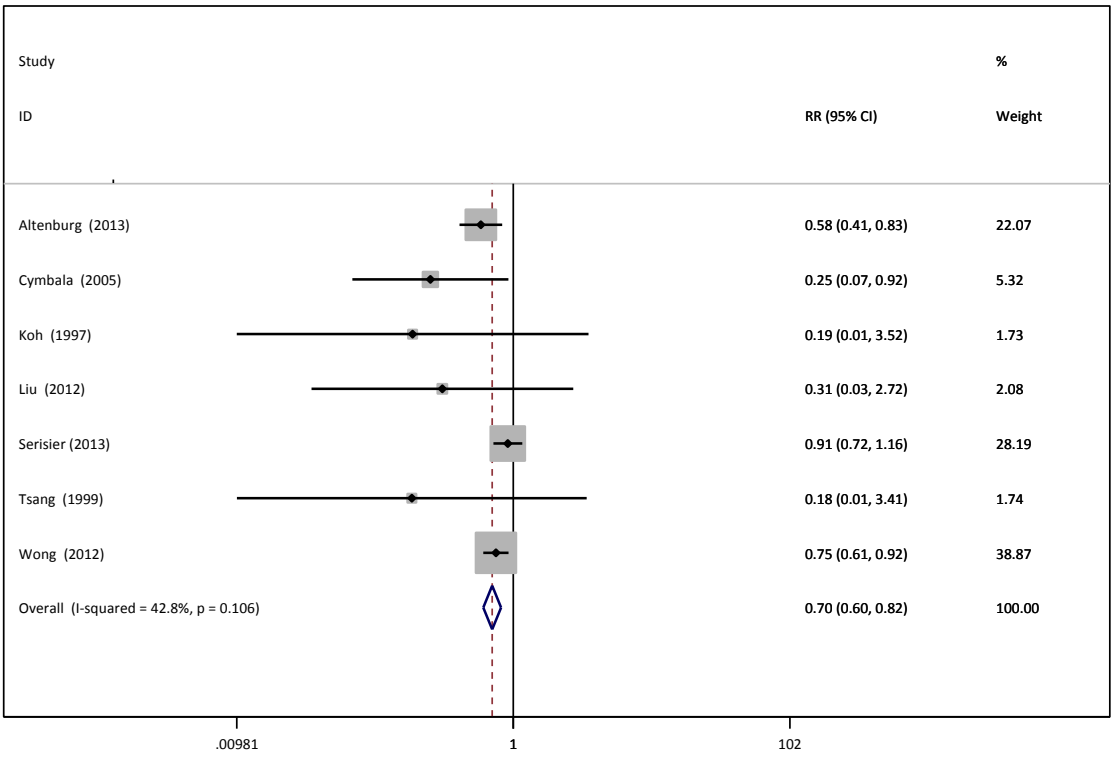
Medication: Macrolides for bronchiectasis

There are two fairly recent meta-analyses, both Chinese, looking at macrolides for bronchiectasis. (Wu et al, Respirology (2014) **19**, 321–329, and Shi et al, Pulmonary Pharmacology & Therapeutics (2014) 171e178) The studies identified were the same except that Shi excluded a small 2012 study by Liu which was not placebo controlled. Event rate for the primary endpoint in the control groups varied from 13% to 82%, and duration of therapy from 3 months to one year. Dose intervals varied from twice daily to three times weekly. All the trials were very small (the largest, Wong, had 70 patients in each arm) and one (Cymbala) was unblinded.

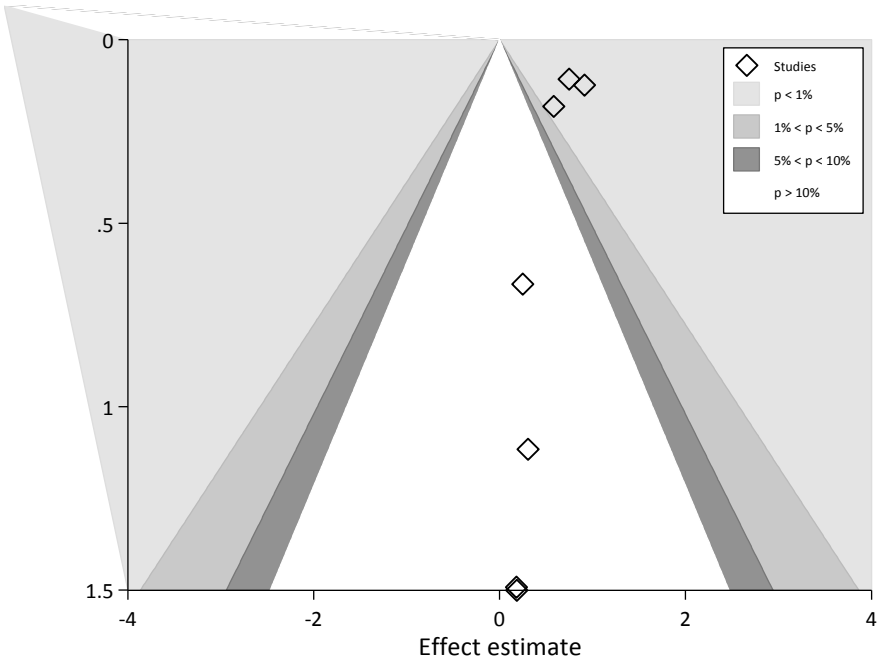
In neither systematic review was the study question particularly clearly delineated. Specifically, the authors definition of exacerbations was not clearly defined in Wu, and in Shi was stated as 'requiring antibiotics for a sustained deterioration in respiratory symptoms', with no clarity on what constituted symptoms, or in who decided antibiotics were required, and on what criteria. Shi made no statement about how bronchiectasis was defined; Wu stated that it was to be based on a CT diagnosis (which would imply most patients were at least reviewed at tertiary centres with a high resolution CT and interpreting radiologist available.)

The primary endpoint of infectious exacerbations:

There is some evidence of heterogeneity (I^2 43%).



A funnel plot shows evidence of a small studies effect:



Wu stated: "Funnel plots for the primary end-points did not indicate noticeable evidence of publication bias and the modified Macaskill's test showed no publication bias for exacerbations (*P* = 0.56)." However the funnel plot was not reproduced in the paper. Tests of publication bias are difficult to interpret with only small numbers of studies, but to see this plot as showing no evidence of small studies effect is wishful thinking.

Sensitivity analysis:

Running the meta-analysis without the two studies at most risk of bias (Jadad 3 or less) reduces power but does little to the effect size (RR 0.74). One of the studies (Koh) was done on children, and its validity in adults is not known, although there is no obvious reason why the information from it cannot be used. Removing Liu (not placebo controlled) then leaves three studies, but the effect size remains stable, really just reflecting the fact that most of the meta-analysis weight is from these three studies in any case, as between them have the majority of events.

Closer scrutiny of the two main trials is of interest:

EMBRACE

(Wong et al Lancet 2012; 380: 660–67)

The trial was small, but of good quality and was adequately powered for all of the co-primary endpoints.. The groups were unbalanced in terms of current smoking status (azithromycin 1%, placebo 6%) and short acting beta2 agonist use (34% vs 47%). The study had three co-primary endpoints: 'event-based exacerbations' (i.e. was given an antibiotic for the episode), pre-bronchodilation FEV1, and St George's respiratory questionnaire total score at six months. Of these three, only the first was statistically significantly different. Gastrointestinal side effects were twice as common in the azithromycin group (27% vs 13%.) During the study period, only four patients in the trial (3 in placebo, one in azithromycin group) required admission due to exacerbations of bronchiectasis.

The trial thus demonstrated that giving continuous antibiotics reduced the need for antibiotics for exacerbations, but with little evidence of improvements in other patient-relevant endpoints. Specifically, there was no difference in symptom-based exacerbations.

BAT

(Altenberg et al. JAMA. 2013;309(12):1251-1259)

Nine criteria could be used to make a diagnosis of a protocol-defined exacerbation (PDE) 'requiring' antibiotics. For instance, the four features of change in sputum consistency, malaise, 'changes in chest sounds' and a complaint of increased wheeze could constitute a PDE. The trial was reported as double blinded, but GIT adverse events happened in 40% of azithromycin patients and only 5% of placebo group patients. Patients in the placebo group were older (mean 64.6 vs 59.9) and had more exacerbations in the year before the study (mean of 5 vs 4.)

Conclusions

In summary there is preliminary evidence in favour of macrolides reducing exacerbations in patients with bronchiectasis. However the primary effect measure is not readily translated into clinically meaningful effects such as reductions in hospitalisations, there is considerable clinical (if not statistical) heterogeneity between study designs, the studies are all small, and the pooled analysis is at risk of a false positive conclusion because of publication bias.