Review: antibiotics active against atypical pathogens do not improve community acquired pneumonia more than β lactam antibiotics

Mills GD, Oehley MR, Arroll B. Effectiveness of β lactam antibiotics compared with antibiotics active against atypical pathogens in non-severe community acquired pneumonia: meta-analysis. *BMJ* 2005;**330**:456.

Clinical impact ratings GP/FP/Primary care ★★★★★★☆ Internal medicine ★★★★★★☆ Infectious disease ★★★★★★☆

Q In patients with community acquired pneumonia (CAP), how do antibiotics active against atypical pathogens (AAAAPs) compare with β lactam antibiotics for effectiveness?

METHODS

Data sources: Cochrane Central Controlled Trials Register, Medline, and EMBASE/Excerpta Medica (to December 2003); conference proceedings; registration authorities; reference lists of review articles and retrieved studies; and pharmaceutical companies conducting trials on AAAAPs.

Study selection and assessment: randomised, blinded (investigators, patients, and outcome assessors), controlled trials (RCTs) that compared AAAAPs (fluoroquinolones, macrolides, and ketolides) with β lactam antibiotics (penicillins and cephalosporins) in patients with radiographically confirmed CAP.

Outcomes: failure to achieve clinical cure or improvement and all cause mortality.

MAIN RESULTS

18 RCTs (n = 6749) met the selection criteria. The trials evaluated 9 different fluoroquinolones, 2 macrolides, and 1 ketolide. Time of outcome assessment ranged from the end of treatment to 38–42 days after commencement of antibiotics. No RCT showed a difference between groups in failure to achieve clinical cure or improvement and no significant heterogeneity existed between studies. Pooled analysis showed no overall difference between groups for failure to achieve cure or improvement and no difference when analyses were done separately on type of AAAAP (table). No treatment effect was seen in patients with *Mycoplasma pneumoniae* (13 RCTs) (relative risk [RR] 0.60, 95% CI 0.31 to 1.17) or *Chlamydia pneumoniae* (7 RCTs) (RR 2.32, CI 0.67 to 8.03), but a reduction in failure to achieve cure or improvement with AAAAPs was seen in patients with *Legionella* species (10 RCTs) (RR 0.40, CI 0.19 to 0.85). AAAAPs and β lactam antibiotics did not differ for all cause mortality (RR 1.20, CI 0.84 to 1.71).

For correspondence: Dr G D Mills, Waikato Hospital, Hamilton, New Zealand. millsg@waikatodhb.govt.nz

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CONCLUSION

In patients with community acquired pneumonia, antibiotics active against atypical pathogens and β lactam antibiotics do not differ for achieving clinical cure or improvement.

Commentary

There are 2 ways in which one can interpret the results of the meta-analysis by Mills *et al.* One is that patients with pneumonia of mild to moderate severity (apart from those with Legionnaire's disease) do not need to receive AAAAPs (mainly *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*) because the host response is sufficient to contain this infection. The second interpretation is that the wrong outcome measures were used in the clinical trials. Time to resolution of symptoms and time to return to work are more likely to be responsive to the intervention in patients with very low mortality caused by pneumonia. I suspect that both interpretations may be correct.

2 previous trials suggest a shorter time to resolution of fever in patients with *M pneumoniae* and *Coxiella burnetii* infection treated with AAAAPs.[1–2] Since such outcomes were not addressed in the review, the question of benefit with AAAAPs remains unresolved.

Despite its limitations, this review confirms the findings of observational studies dating back to the original outbreak of Legionnaire's disease[3–4] that indicated that treatment of Legionnaire's disease with AAAAPs improved outcomes. The issue of whether AAAAPs offer an advantage over β lactam antibiotics in patients with CAP needs to be addressed in an RCT using appropriate outcomes.

Thomas J Marrie, MD
University of Alberta
Edmonton, Alberta, Canada

1 Shames JM, George RB, Holliday WB, *et al.* Comparison of antibiotics in the treatment of mycoplasmal pneumonia. *Arch Intern Med* 1970;**125**:680–4.
2 Sobradillo V, Zalacain R, Capelastegui A, *et al.* Antibiotic treatment in pneumonia due to Q fever. *Thorax* 1992;**47**:276-8.
3 Fraser DW, Tsai TR, Orenstein W, *et al.* Legionnaires' disease: description of an epidemic of pneumonia. *N Engl J Med* 1977;**297**:1189–97.
4 Blázquez Garrido RM, Espinosa Parra FJ, Alemany Francés L, *et al.* Antimicrobial chemotherapy for legionnaires disease: levofloxacin versus macrolides. *Clin Infect Dis* 2005;**40**:800–6.

Antibiotics active against atypical pathogens (AAAAPs) *v* β lactam antibiotics in community acquired pneumonia*

Outcome at ⩽42 days	Type of AAAAP	Number of trials (n)	Weighted event rates		RRR (95% CI)	NNT
			AAAAP	β lactam		
Rate of failure to achieve clinical cure or improvement	All	18 (6749)	17.8%	18.4%	3% (−7 to 13)	Not significant
	Macrolide or ketolide	3 (566)	18.1%	19.9%	19% (−14 to 42)	Not significant
	Fluoroquinolone	14 (5375)	17.5%	17.9%	1% (−11 to 12)	Not significant
	Quinolone or macrolide†	1 (808)	22%	23%	5% (−28 to 29)	Not significant

*Abbreviations defined in glossary; weighted event rates, RRR, NNT, and CI calculated from data in article using a fixed effects model.
†Event rates are not weighted.