SUPPLEMENTARY DETAILS (FOR ONLINE REPOSITORY)

Other discussion points

1. It would be desirable to know the percentage of patients captured in the study as a proportion of all patients hospitalised with CAP at study sites during the study period. However, it is extremely difficult to obtain a true denominator due to inaccuracies in current hospital coding systems – estimates from various local audits indicate that up to 50% of episodes coded as CAP are inaccurate. For this audit, Trusts were asked to submit data on all patients admitted with CAP within the audit period. Some Trusts had prospective audit systems in place, reliant on the identification of relevant patients at the time of hospital admission, while other Trusts retrieved medical notes from all patients with a discharge code for pneumonia and screened for eligibility. Each Trust may have missed a proportion of patients admitted with CAP during the study period. However, overall, given the large dataset and the number of institutions involved, we do not anticipate any systematic bias in one particular direction in terms of case selection.

2. Narrow spectrum beta-lactams, such as amoxicillin or benzylpenicillin, differ in terms of antibiotic coverage of Gram negative infections compared to broad spectrum beta-lactams, such as co-amoxiclav. However, Gram negative organisms are seldom implicated (<2%) in patients hospitalised with CAP in the UK. Furthermore, narrow spectrum beta-lactams were more commonly prescribed in the combination therapy group compared to the single agent therapy group. Therefore, it is unlikely that superior antibiotic coverage of such infections, or co-infections, accounts for the differences observed.

3. Antibiotics prior to hospital admission are associated with better clinical outcomes. Therefore, if pre-treated patients were more likely to receive combination therapy, this may partially account for the observed differences in mortality. Unfortunately, data on pre-hospital treatment were not available to test this hypothesis. However, in most clinical practice in the UK, the decision whether to give combination empirical antibiotic therapy at the time of hospital admission is not dependent on pre-hospital treatment. Therefore, it seems unlikely that there would be a strong association between pre-treatment and empirical combination therapy, though this cannot be discounted.

Supplementary Table A

Clinical characteristics of study cohort (n=5240)

	Beta-lactam therapy (n=2001)	Beta-lactam/macrolide combination therapy (n=3239)	p value
Age*	76 (59-85)	73 (56-84)	**0.001**
Male	967 (48.3)	1646 (50.8)	**0.042**
CCF	162 (8.1)	234 (7.2)	0.135
Stroke disease	208 (10.4)	288 (8.9)	**0.04**
Liver disease	30 (1.5)	35 (1.1)	0.115
Renal disease	154 (7.7)	197 (6.1)	**0.014**
Active Malignancy	166 (8.3)	203 (6.3)	**0.003**
COPD	397 (19.8)	648 (20.0)	0.457
IV antibiotic use	1463(73.1)	2817(87.0)	**<0.001**
ICU admission	136(6.8)	282(8.7)	**0.009**
Need for MV	58(2.9)	93(2.9)	0.508
Need for INS	42(2.1)	88(2.7)	0.095
Median LOS*†	5(2-10)	6(3-11)	0.094
Time to death*†	5(2-10)	5(2-11)	0.550
CURB65 0-1	908(45.4)	1339(41.3)	**0.002**
CURB65 2	561(28.0)	919(28.4)	0.409
CURB65 3-5	532(26.6)	981(30.3)	**0.002**

IQR-Inter-quartile range, CCF-Congestive cardiac failure, COPD-Chronic obstructive pulmonary disease, ICU-Intensive care unit, MV-mechanical ventilation, INS-Inotropic support, LOS-length of stay

All values given as n(%) unless stated otherwise

*Values given as median(IQR)

†Measured in number of days

Supplementary Table B

Antibiotics other than a beta-lactam or beta-lactam/macrolide combination prescribed for patients in the national dataset (n=1072)

Antibiotic	n	%
Macrolide	552	51.5
Tetracyclines	252	23.5
Fluoroquinolones	114	10.6
Sulphonamides	21	2.0
Chloramphenicol	26	2.4
Aminoglycosides	16	1.5
Vancomycin/Teicoplanin	69	6.4
Metronidazole	8	0.7
Rifampicin	2	0.2
No antibiotic data available	63	5.9

Supplementary References

- Kent, Surrey and Sussex NHS Trust-What a difference a year makes (2010-2011); Available from:http://www.enhancingqualitycollaborative.nhs.uk/index.php?option=com_docman&task=doc_download&gid=1&Itemid=19 (accessed 31/05/2012).
- V´azquez EG, Mensa J, Mart´ınez JA, et al. Lower mortality among patients with community-acquired pneumonia treated with a macrolide plus a beta-lactam agent versus a beta-lactam agent alone. Eur J Clin Microbiol Infect Dis 2005;24:190-5.
- Houck PM, MacLehose RF, Niederman MS, et al. Empiric antibiotic therapy and mortality among medicare pneumonia inpatients in 10 Western states 1993, 1995, and 1997. Chest 2001;119:1420-6.
- Gleason PP, Meehan TP, Fine JM, et al. Associations between initial antimicrobial therapy and medical outcomes for hospitalized elderly patients with pneumonia. Arch Intern Med 1999;159:2562-72.
- Martı´nez JA, Horcajada JP, Almela M, et al. Addition of a macrolide to a b-lactam–based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. Clin Infect Dis;36:389-95.
- Weiss K, Low D, Cortes L, et al. Clinical characteristics at initial presentation and impact of dual therapy on the outcome of bacteremic streptococcus pneumoniae pneumonia in adults. Can Respir J 2004;11(8):589-93.
- Paul M, Nielsen AD, Gafter-Gvili A, et al. The need for macrolides in hospitalised community-acquired pneumonia: Propensity analysis. Eur Respir J 2007;30:525-31.
- Aspa J, Rajas O, Rodriguez de Castro F, et al. Impact of initial antibiotic choice on mortality from pneumococcal pneumonia. Eur Respir J 2006;27:1010-9.
- Blasi F, Iori I, Bulfoni A, et al. Can CAP guideline adherence improve patient outcome in internal medicine departments? Eur Respir J 2008;32:902-10.
- Schouten JA, Hulscher MEJL, Trap-Liefers J, et al. Tailored interventions to improve antibiotic use for lower respiratory tract infections in hospitals: A cluster-randomized, controlled trial. Clin Infect Dis 2007;44:931-41.
- Sharpe BA. Guideline-recommended antibiotics in community-acquired pneumonia:Not perfect, but good. Arch Intern Med 2009;169(16):1462-4.
- Martin-Loeches I, Lisboa T, Rodriguez A, et al. Combination antibiotic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia. Intensive Care Med 2010;36:612-20.
- Metersky ML, Ma A, Houck PM, et al. Antibiotics for bacteremic pneumonia improved outcomes with macrolides but not fluoroquinolones. Chest 2007;131:466-73.
- Livermore DM, Reynolds R, Stephens P, et al. Trends in penicillin and macrolide resistance among pneumococci in the UK and the Republic of Ireland in relation to antibiotic sales to pharmacies and dispensing doctors. Int J Antimicrob Agents 2006;28:273-9.
- Guillota L, Tabarya O, Nathana N, et al. Macrolides: New therapeutic perspectives in lung diseases. Int J Biochem Cell Biol 2011;43:1241-6.
- Wise MP, Williams DW, Lewis MA, et al. Macrolides and community-acquired pneumonia: Is quorum sensing the key? Crit Care 2010;14(181):1-3.

- Healy DP. Macrolide immunomodulation of chronic respiratory diseases. Curr Infect Dis Rep 2007;9(1):7-13.
- Bartlett JG. Is activity against “atypical” pathogens necessary in the treatment protocols for community-acquired pneumonia? Issues with combination therapy. Clin Infect Dis 2008;47:S232-6.
- Robenshtok E, Shefet D, Gafter-Gvili A, et al. Empiric antibiotic coverage of atypical pathogens for community-acquired pneumonia in hospitalized adults. Cochrane Database Syst Rev 2008(1). Epub 14 April 2010.