AUDIT, RESEARCH AND GUIDELINE UPDATE

# Single versus combination antibiotic therapy in adults hospitalised with community acquired pneumonia

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▶ Additional supplementary data are published online only. To view this file please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2012-202296)

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Received 18 June 2012
Accepted 21 September 2012
Published Online First 16 October 2012



▶ http://dx.doi.org/10.1136/thoraxjnl-2012-202425

**To cite:** Rodrigo C, Mckeever TM, Woodhead M, *et al*. *Thorax* 2013;**68**: 493–495.

## ABSTRACT

The benefits of β-lactam/macrolide combination therapy over β-lactam therapy alone for the treatment of hospitalised community-acquired pneumonia (CAP) in relation to pneumonia severity are uncertain. We studied 5240 adults hospitalised with CAP from 72 secondary care trusts across England and Wales. The overall 30-day inpatient (IP) death rate was 24.4%. Combination therapy was prescribed in 3239 (61.8%) patients. In a multivariable model, combination therapy was significantly associated with lower 30-day IP death rate in patients with moderate-severity CAP (adjusted OR 0.54, 95% CI 0.41 to 0.72) and high-severity CAP (adjusted OR 0.76, 95% CI 0.60 to 0.96) but not low-severity CAP.

## BACKGROUND

For patients hospitalised with moderate-severity and high-severity CAP, national guidelines recommend empirical combination antibiotic therapy comprising β-lactam and macrolide antibiotics.[1] In some CAP observational cohort studies, macrolide and β-lactam combination therapy has been associated with a lower death rate compared with single-agent antibiotic therapy,[2] while other studies have reported no differences. A meta-analysis of studies comparing macrolide-based regimens with other treatment regimens (not just single-agent β-lactam therapy) found a reduction in death rate with macrolide use;[3] this benefit was felt to be due to guideline concordance rather than antibiotic choice. This uncertain evidence base may partially explain the relatively poor adherence to CAP antibiotic recommendations observed by some investigators. Concerns that broad-spectrum antibiotics promote antimicrobial resistance, medication side effects, cost and nosocomial infections may also limit adherence.

Beginning in 2009, the British Thoracic Society (BTS) conducted the largest national audit of adult CAP management in the UK.[4] These data were analysed to determine the 'real-world' variation in the use of single versus combination antibiotic therapy in CAP, and whether observed differences in antibiotic use are related to clinical outcomes stratified by pneumonia severity.

## METHOD

All trusts across England and Wales were invited to participate in the BTS adult CAP national audit. Sites were asked to include consecutive immunocompetent adults hospitalised with CAP during the periods 1 December 2009–31 January 2010 and 1 December 2010–31 January 2011. Inclusion criteria were age over 16 years, new infiltrates on admission chest x-ray (CXR) consistent with CAP, symptoms suggestive of a lower respiratory tract infection and treatment given as for CAP. Patients previously discharged from hospital within 10 days of admission were excluded. Following admission, patients were treated at the discretion of the admitting clinical team and data entered anonymously using a secure web-based system. The audit protocol was approved by the BTS Professional and Operational Standards Committee which determined that ethical approval was not required for the conduct of the audit.

For this analysis, patients who received either empirical single-agent therapy with β-lactam antibiotics (defined as any penicillin or cephalosporin antibiotic) or combination therapy with β-lactam and macrolide (defined as erythromycin, clarithromycin or azithromycin) antibiotics were considered. Patients who received other classes of antibiotics such as fluoroquinolones, either alone or in combination with β-lactam or macrolide antibiotics, were excluded. The primary outcome measure was 30-day in-patient (IP) death rate. Secondary outcome measures were length of stay (LOS), intensive care unit (ICU) admission, need for mechanical ventilation (MV), need for inotropic support (INS), time to death and 30-day readmission.

### Statistical analysis

Analyses were performed using SPSS V.20.0. Pearson's $\chi^2$ test was used to compare categorical variables, perform univariate analyses and generation of ORs and 95% CIs. Mann–Whitney U test was used to compare non-parametric continuous variables. The association between combination antibiotic therapy and 30-day IP death rate was examined using a logistic regression model adjusting for the following variables: age, sex, binary variables within the CURB65 pneumonia severity score excluding age (confusion, urea>7 mmol/litre, respiratory rate≥30/min, blood pressure<90 mm Hg systolic or ≤60 mm Hg diastolic), individual comorbidities, intravenous antibiotic use, nursing home residency and ICU admission. A similar model was used to examine the associations between combination antibiotic therapy and secondary outcomes, except ICU

admission was not included in the model when assessing need for MV, INS and ICU admission. Subgroup analysis according to pneumonia severity based on the CURB65 score was performed following adjustment for sex, individual comorbidities, intravenous antibiotic use and nursing home residency. Statistical significance was defined as a p value <0.05. Results are expressed as the OR with 95% CI.

## RESULTS

There were 6312 patients in the national audit dataset; 1072 (17%) received an antibiotic other than a β-lactam or a β-lactam/macrolide combination, leaving 5240 for analysis. The commonest β-lactam antibiotic prescribed was co-amoxiclav (42.7%), followed by amoxicillin (23.3%), benzylpenicillin (17.6%), piperacillin with tazobactam (12.8%) and cephalosporins (3.6%). Combination therapy was prescribed in 3239 (61.8%) patients; the commonest macrolide prescribed was clarithromycin (96.1%), followed by erythromycin (3.7%) and azithromycin (0.2%). Narrow spectrum β-lactams (amoxicillin, bezylpenicillin) were more commonly prescribed in the combination compared with single-agent therapy group (44.2% vs 31.5%, p<0.001).

Patients who received combination therapy were significantly younger (median age 73 years (IQR 56–84) vs 76 years (IQR 59–85), p=0.001) and had significantly less coexisting stroke disease, renal disease and active malignancy compared with patients who received β-lactam therapy alone (see online supplementary table A). Of 4207 patients in whom data on residency were available, 194 (12.2%) in the β-lactam group were admitted from nursing or residential care compared with 222 (8.5%) in the combination therapy group (OR 0.66, 95% CI 0.54 to 0.81, p<0.001). ICU support (8.7% vs 6.8%; OR 1.3, 95% CI 1.05 to 1.6, p=0.009) and intravenous antibiotic use (87.0% vs 73.1%, p<0.001) were commoner in the combination therapy group.

### Outcome measures

The overall 30-day IP death rate was 24.4% (1281/5240). On univariate analysis, 30-day IP death rate was lower in the combination versus single-therapy group (23.0% vs 26.8%; OR 0.81, 95% CI 0.72 to 0.93, p=0.001). On multivariate analysis, combination therapy remained significantly associated with lower 30-day IP death rate (adjusted OR 0.72, 95% CI 0.60 to 0.85, p<0.001) but not with secondary outcomes of ICU admission rate, need for MV, need for INS or 30-day readmission rate (adjusted OR=0.908, 95% CI 0.70 to 1.19, p=0.48) (table 1).

When stratified by pneumonia severity, combination therapy was significantly associated with lower 30-day IP death rate in moderate-severity CAP (adjusted OR 0.54, 95% CI 0.41 to 0.72, p<0.001) and high-severity CAP (adjusted OR 0.76, 95% CI 0.60 to 0.96, p=0.025), but not in low-severity CAP (table 1). Combination therapy was not significantly associated with secondary outcomes following stratification according to pneumonia severity.

## DISCUSSION

This is the largest multicentre study of the 'real world' management of adult CAP in the UK. A striking finding is the relatively high death rate observed (24%). This is similar to results from a large database study (n>500 000) of UK hospital data comprising all admissions with pneumonia from 1997 to 2005 (30-day death rate 24.8–28.2%)[5] and from a regional quality improvement programme of patients hospitalised with CAP (n=7352, in-hospital crude death rate 27%) (see references in online supplement). In contrast, the death rate from previous prospective cohort studies conducted in the UK has been lower (5–14%).[1] This discrepancy may be due to selection bias with fitter individuals being recruited into prospective cohort studies.

Combination therapy compared with β-lactam therapy alone was significantly associated with lower death rate after adjustment for demographic factors, pneumonia severity and treatment factors in patients with moderate-severity and high-severity CAP. Previous studies of CAP have also demonstrated a reduction in death rate associated with β-lactam/macrolide combination therapy compared with other antibiotic regimens (see references in online supplement). In particular, Tessmer *et al*[2] (n=1854) reported a significantly lower 14-day death rate only in patients with moderate-severity CAP (CURB65 score of 2) treated with β-lactam/macrolide combination antibiotics compared with single-agent β-lactam antibiotics. The much larger dataset of the current study confirms and extends these findings.

Mechanistic explanations for the superiority of β-lactam/macrolide combination therapy in the treatment of CAP include broader coverage of unidentified infection with atypical

**Table 1** Multivariate analyses of the association between antibiotic therapy and clinical outcomes

| Outcome measures | Total (n=5240) | β-lactam therapy (n=2001) | β-lactam/ macrolide combination therapy (n=3239) | Adjusted OR (95% CI) | p Value |
|---|---|---|---|---|---|
| 30 day IP death rate | 1281 (24.4) | 536 (26.8) | 745 (23.0) | 0.72 (0.60 to 0.85)* | <0.001 |
| ICU admission | 419 (8) | 136 (6.8) | 282 (8.7) | 0.94 (0.72 to 1.22)† | 0.635 |
| Need for MV | 151 (2.9) | 58 (2.9) | 93 (2.9) | 0.99 (0.71 to 1.38)† | 0.508 |
| Need for INS | 130 (2.5) | 42 (2.1) | 88 (2.7) | 0.87 (0.55 to 1.38)† | 0.544 |
| 30-day IP death rate stratified by pneumonia severity | | | | | |
| Low severity (CURB65=0–1) | 201/2247 (8.9) | 95/908 (10.5) | 106/1339 (7.9) | 0.80 (0.56 to 1.16)‡ | 0.238 |
| Moderate severity (CURB65=2) | 370/1480 (25) | 171/561 (30.5) | 199/919 (21.7) | 0.54 (0.41 to 0.72)‡ | <0.001 |
| High severity (CURB65≥3) | 710/1513 (46.9) | 270/532 (50.8) | 440/981 (44.9) | 0.76 (0.60 to 0.96)‡ | 0.025 |

Values given as n (%).
*OR adjusted for age, sex, binary variables within CURB65 excluding age (confusion, urea>7 mmol/l, respiratory rate ≥30/min, systolic blood pressure<90 mmHg or diastolic blood pressure ≤60 mmHg), individual comorbidities, intravenous antibiotic use, nursing home residency and ICU admission.
†OR adjusted for age, sex, binary variables within CURB65 excluding age (confusion, urea>7 mmol/l, respiratory rate ≥30/min, systolic blood pressure<90 mmHg or diastolic blood pressure ≤60 mmHg), individual comorbidities, intravenous antibiotic use and nursing home residency.
‡OR adjusted for sex, individual comorbidities, intravenous antibiotic use, nursing home residency and ICU admission.
ICU, intensive care unit; IP, inpatient; MV, mechanical ventilation; INS, inotropic support.

pathogens and macrolide-specific immunomodulatory, quorum sensing or alveolar epithelial effects.

A striking 37.9% of patients with moderate-severity CAP and 35.2% with high-severity CAP were not prescribed a macrolide, despite current UK guidance advocating combination therapy in these patients. This may reflect reluctance among physicians to prescribe macrolides in frailer patients, an interpretation supported by the observed differences between single and combination therapy groups in age, residency status and comorbid illnesses. Treatment restriction in frailer patients, such as a higher threshold for ICU admission, may have contributed to bias in the results. These confounders were adjusted for in the multivariate analyses; however, residual confounding cannot be completely discounted. Differences in β-lactam antibiotic coverage between the groups are unlikely to explain the observed treatment effect; narrow spectrum β-lactam antibiotic use was commoner in the combination therapy group.

Other limitations of the study include the absence of additional details related to antibiotic therapy (including prior antibiotic administration and duration of therapy) and absence of information about other aspects of care (such as the use of supplemental oxygen or venous thromboembolic prophylaxis). Therefore, the possibility that combination antibiotic therapy is simply a surrogate for other or multiple aspects of better quality care could not be explored in this study.

Given the observed size of effect and the consistency of results across many studies, it is likely that the association of combination therapy with reduced death rate in moderate-severity and high-severity CAP is a true effect, though the true effect size may be smaller than that observed in this study. An adequately powered randomised controlled trial of β-lactam/macrolide combination therapy versus β-lactam single-agent therapy in patients with moderate-severity and high-severity CAP would valuably inform this issue. In the meantime, the available evidence indicates that efforts should be made to improve guideline implementation and adherence in clinical practice, especially given the current unsystematic use of combination therapy highlighted by this study.

**Acknowledgements** The authors would like to thank the British Thoracic Society audit team, including Sally Welham, Chris Routh, Kerry Reid and Christine Bucknall, for their invaluable efforts in conducting the audit. This paper has been prepared by the authors on behalf of the British Thoracic Society, and the efforts by clinicians across the UK in data collection and participation in this audit are gratefully acknowledged.

**Contributors** This paper has been prepared by the authors on behalf of the British Thoracic Society.

**Competing interests** None.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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