β-Lactam/macrolide dual therapy versus β-lactam monotherapy for the treatment of community-acquired pneumonia in adults: a systematic review and meta-analysis

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Received 17 December 2013; returned 4 January 2014; revised 16 January 2014; accepted 27 January 2014

Objectives: Several studies have compared the clinical effect of β-lactam/macrolide (BLM) dual therapy versus β-lactam (BL) monotherapy in community-acquired pneumonia (CAP) patients. However, the results remain controversial. Thus, we did this meta-analysis to determine which treatment was more effective.

Methods: Databases comprising PubMed, Embase and the Cochrane Register of Controlled Trials were searched to find relevant studies. The primary outcome was mortality. The Newcastle–Ottawa scale was used to evaluate the methodological quality of included studies. Multivariable-adjusted ORs with 95% CIs were pooled in the random effects model.

Results: Four prospective cohort studies and 12 retrospective cohort studies were included (n = 42942). Compared with BL monotherapy, BLM dual therapy was significantly associated with reduced mortality (adjusted OR 0.67, 95% CI 0.61–0.73, P < 0.001, I² = 3%). Subsequent subgroup analyses confirmed that BLM dual therapy was statistically superior to BL monotherapy in reduction of mortality. Sensitivity analyses strengthened the validity of the results.

Conclusions: In comparison with BL monotherapy, BLM dual therapy might reduce mortality risk in patients with CAP. Because this finding is based on observational studies, randomized controlled trials are required to demonstrate the usefulness of BLM dual therapy in the treatment of CAP.

Keywords: mortality, antibiotics, lung infections

Introduction

Community-acquired pneumonia (CAP) is a common disease and is still characterized by significant morbidity and mortality. Antibiotics are the most important drugs in the treatment of CAP. However, the optimal empirical antibiotic therapy is an often-debated issue. Chinese guidelines recommended dual therapy consisting of a β-lactam plus a macrolide (BLM) or β-lactam (BL) monotherapy for patients hospitalized with CAP in a ward. British Thoracic Society (BTS) and Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines recommend BLM dual therapy but not BL monotherapy in treating these patients. All these recommendations are based on observational studies. These observational studies, however, showed results ranging from beneficial to no effect. To our knowledge, no meta-analysis has been designed to determine the effects of two therapies on mortality in patients with CAP. Thus, the clinical effect of BLM dual therapy versus BL monotherapy in CAP patients has remained unclear. Asadi et al. conducted a meta-analysis to compare macrolide-based regimens with other treatment regimens for the treatment of CAP. They found a reduction in mortality risk with macrolide use. However, a comparison between BLM dual therapy and BL monotherapy was not performed in that meta-analysis.

The aim of this meta-analysis was to summarize all the available evidence and compare the efficacy of BLM dual therapy with that of BL monotherapy for CAP patients.

Methods

Literature search

PubMed, Embase and the Cochrane Register of Controlled Trials were searched for relevant studies published up to January 2014. No language restrictions were imposed. References from relevant articles, including review papers, were also reviewed. Details of the search strategy are given in the Supplementary data available at JAC Online.
**Study selection**
To be included, the studies were required to have a randomized controlled trial (RCT) or cohort design and to compare BLM dual therapy with BL monotherapy in adult patients with CAP. The primary outcome was mortality and was selected in the protocol. The secondary outcome was resistance induced by the use of antibiotics. Details of the studies selected are given in the Supplementary data available at JAC Online.

**Data collection and methodological quality assessment**
Two authors extracted the data in standardized data-collection forms and assessed study quality. The Newcastle–Ottawa scale (NOS) was used to evaluate methodological quality. Details are described in the Supplementary data available at JAC Online.

**Statistical analysis**
We estimated the OR with 95% CI for mortality. The multivariable-adjusted ORs with 95% CIs were pooled in our analysis. We used a random-effects model. Statistical heterogeneity among studies was evaluated using the Q and I² statistics. Meta-regression was used to assess the effect of age on treatment efficacy. Subgroup analyses and sensitivity analyses were performed. Publication bias was investigated by the funnel plot method. Funnel plot asymmetry was assessed using Egger’s linear regression test. If publication bias was detected, the effect of such bias was assessed with the fail-safe number method. All statistical analyses were performed with STATA software (version 12.0, Stata Corporation, College Station, TX, USA). Details are provided in the Supplementary data available at JAC Online.

**Results**

**Literature search**
A total of 2946 publications were identified in the initial search, and 2 publications were identified by manual searching. Based on screening the titles or abstracts, 2470 records were excluded. Full-text articles were retrieved only for 113 publications and assessed for eligibility. Of these 113 publications, 97 were excluded (74 studies did not use BL monotherapy or BLM dual therapy, 8 studies did not report adjusted ORs, 12 studies did not provide mortality data, 2 studies were duplicates and 1 study included CAP patients infected with HIV). Finally, 16 studies were included in the meta-analysis.

![Figure 1](image.png)

*Figure 1.* Flow chart of study identification, inclusion and exclusion.
Study characteristics

Four prospective cohort studies and 12 retrospective cohort studies were included. Seven studies were conducted in wards, one study was conducted in an intensive care unit (ICU) and eight studies were conducted in both wards and ICUs. Five studies included patients with bacteremic pneumococcal pneumonia (BPP). ICD-9-CM (International Classification of Disease, Ninth Edition, Clinical Modification) codes were used to identify CAP in three studies. Unfortunately, no study provided information on resistance induced by antibiotics. All studies were assessed using the NOS. The quality scores ranged from 7 to 8, suggesting that methodological quality was generally high. The characteristics of each study are presented in Table 1 and Table S1 (available as Supplementary data at JAC Online).

Quantitative data synthesis

There were 42,942 patients involved in these 16 cohort studies. Compared with BL monotherapy, BLM dual therapy was associated with significantly reduced mortality (adjusted OR 0.67, 95% CI 0.61–0.73, P<0.001; Figure 2). There was low heterogeneity between included studies (I² = 3%).

In the subgroup analysis by the site of care (Table 2), BLM dual therapy was associated with decreased mortality risk in wards (OR 0.64, 95% CI 0.55–0.73, P<0.001, I² = 39%) and in ICUs (OR 0.64, 95% CI 0.62–0.89, P=0.008, I² = 0%). In terms of BPP, we found a significant association between BLM dual therapy and decreased mortality risk (OR 0.57, 95% CI 0.35–0.94, P=0.03, I² = 27%). In the analysis stratified by severity, a statistically significantly decreased mortality risk was found among patients with mild to moderate CAP (OR 0.73, 95% CI 0.58–0.93, P=0.01, I² = 0%), and was also found among severe CAP patients (OR 0.66, 95% CI 0.58–0.76, P<0.001, I² = 27%). A subgroup analysis of patients with Streptococcus pneumoniae showed a beneficial effect of BLM dual therapy on mortality (OR 0.59, 95% CI 0.37–0.95, P=0.03, I² = 33%).

We used meta-regression to examine variation in treatment effect attributable to age. Treatment effect was not associated with increased age (P=0.867).

Sensitivity analyses

A sensitivity analysis showed no substantial modification of the estimates after exclusion of individual studies (data not shown). In an analysis limited to prospective studies, the result was still statistically significant (OR 0.64, 95% CI 0.44–0.93, P=0.02, I² = 19%). A statistically similar result was obtained after excluding the studies using ICD-9-CM data (OR 0.61, 95% CI 0.52–0.71, P<0.001, I² = 13%). In addition, no significant change in the result was shown when excluding studies with small sample size (OR 0.71, 95% CI 0.64–0.79, P<0.001, I² = 0%). When we limited the meta-analysis to studies that controlled for severity and underlying diseases, a significant association between BLM dual therapy and reduced mortality remained (OR 0.73, 95% CI 0.62–0.86, P<0.001, I² = 0%). Results of the sensitivity analyses are listed in Table 3.

Publication bias

The funnel plot showed obvious asymmetry (Figure S1, available as Supplementary data at JAC Online). Egger’s test
suggested that publication bias was present ($P=0.02$). Fail-safe methods showed that, to nullify our estimated effect size, 436 studies with non-significant findings would be needed.

**Discussion**

This meta-analysis revealed that BLM dual therapy might be more effective than BL monotherapy. Empirical BLM dual therapy was
Results from this meta-analysis were stable and reliable. First, the large number of patients provided adequate statistical power to detect a treatment effect. Second, in order to avoid the potential influence of differences in study design, we carried out a sensitivity analysis by excluding retrospective studies. Other factors that could potentially influence the results of this meta-analysis, such as the use of ICD-9-CM codes, small sample size and without adjusting for severity and underlying diseases, were also evaluated. Furthermore, omitting a single study each time did not alter the results significantly, suggesting the reliability of our results. Third, no significant heterogeneity was found in this meta-analysis. Finally, although Egger's test detected significant publication bias, the fail-safe number was large (n=436). It was highly improbable that such a large number of similar studies would have gone unpublished or have been missed by our extensive search strategy.

The present meta-analysis had some limitations. First, the absence of RCT data was a major limitation. As a meta-analysis of observational studies, it was prone to the bias (e.g. recall and selection bias) inherent in the original studies. Therefore, the observed reduced mortality may be a result of confounding, especially confounding by indication. Patients suspected of harbouring atypical pneumonia are probably younger and have less severe pneumonia than patients in whom a pneumococcal infection is suspected. Thus, physicians may tend to prescribe macrolides to younger patients or patients with milder presentation. Although a multivariable logistic regression was performed in all the included studies, this method could not remove confounding by factors not selected in the model. Propensity analysis could overcome problems with confounding. Paul et al. used this method to adjust for differences between patients. No beneficial effect of BLM dual therapy was found in their study. Since only 54 patients were included in the propensity analysis in that study, more studies using propensity analysis are needed in the future. Second, due to the lack of relevant information in the original reports, we could not assess the side effects of these two therapies. Subgroup analyses according to other pathogens (including no identified pathogen) of CAP also could not be performed. Finally, Leibovici et al. suggested that all systematic reviews of antibiotic treatment should address the induction of resistance. We could not address this issue because the data were insufficient.

In conclusion, compared with BL monotherapy, BLM dual therapy might reduce mortality risk in patients with CAP. A large-scale, high-quality, double-blind RCT comparing BLM dual therapy with BL monotherapy for CAP is urgently needed.
Supplementary data

Supplementary methods, Table S1 and Figure S1 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References