How good is the evidence for the recommended empirical antimicrobial treatment of patients hospitalized because of community-acquired pneumonia? A systematic review

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Background: For years, monotherapy with a β-lactam antibiotic (penicillin, amoxicillin or second-generation cephalosporin) was recommended as empirical therapy for patients with community-acquired pneumonia (CAP). A combination of a β-lactam and a macrolide antibiotic was only recommended for patients with severe CAP needing intensive care treatment or when atypical pathogens, i.e. Legionella pneumophila, Mycoplasma pneumoniae and Chlamydia pneumoniae, were strongly suspected. However, new guidelines recommend a combination of a β-lactam antibiotic plus a macrolide or monotherapy with a fluoroquinolone for all patients hospitalized with CAP. We evaluated whether treatment with a β-lactam plus macrolide or quinolone monotherapy is truly superior to β-lactam treatment alone.

Methods: We systematically reviewed available studies, retrieved from MEDLINE and by hand-searching reference lists from recent reviews and guidelines on the effectiveness of recommended empirical antimicrobial treatment of patients hospitalized because of CAP.

Results: Eight relevant studies were selected. In six studies significant reductions in mortality were found, in one study a reduction in hospital length of stay was found and in one study no beneficial effects could be demonstrated for treatment regimens with fluoroquinolone monotherapy or combinations of β-lactams and macrolides. The beneficial value of macrolides or fluoroquinolones might be the result of a large and mainly unrecognized role of atypical pathogens in the aetiology of CAP, anti-inflammatory effects of macrolides or resistance to β-lactams of the most important pathogens. However, the studies supporting the recommended treatment regimen were designed as non-experimental cohort studies. As a consequence, the results may have been influenced by confounding by indication. In addition, the outcomes showed several inconsistencies.

Conclusions: A randomized controlled trial is warranted to circumvent the methodological flaws in the designs of the currently available studies. Since the addition of macrolides or treatment with fluoroquinolones may lead to enhanced antibiotic resistance, increased side effects and healthcare-related costs, such a fundamental change in the treatment of CAP should be based on valid data.

Keywords: macrolide antibiotics, fluoroquinolones, β-lactam antibiotics, mortality, length of stay

Introduction

Initial therapy for patients with community-acquired pneumonia (CAP) is mostly empirical. Previous British and North American guidelines recommended initial treatment with benzyl penicillin, amoxicillin or another β-lactam antibiotic for uncomplicated pneumonia. The addition of a macrolide to the initial management was not recommended unless there was either a strong suspicion of atypical pneumonia caused by Legionella pneumophila, Mycoplasma pneumoniae or Chlamydia pneumoniae, or severe pneumonia requiring admission to an intensive care unit (ICU).1-3

Recent North American publications, however, have suggested that combination therapy consisting of a β-lactam antibiotic plus a macrolide or monotherapy with one of the newer fluoroquinolones in the initial management of all patients hospitalized with CAP who do not require admission to an ICU reduces both mortality rates and length of hospitalization. Based on these findings, the British and American Thoracic Societies and the Infectious Diseases Society of America (IDSA) have revised their guidelines for the treatment for CAP, and now recommend either treatment with a β-lactam antibiotic plus a macrolide or treatment with a fluoroquinolone for all patients hospitalized because of CAP.4-7 However, such a strategy...
could lead to an increase in costs, adverse events related to antibiotic use and the induction of antibiotic resistance. Here, we will discuss whether there is sufficient scientific evidence to justify such a fundamental change in the empirical treatment of patients admitted with CAP. We review recent peer-reviewed reports to determine whether, compared with monotherapy with \( \beta \)-lactams, initial therapy with a \( \beta \)-lactam plus a macrolide or quinolone monotherapy reduces mortality or length of stay (LOS) among adult patients hospitalized with CAP. In addition, we explore possible aetiological explanations for the results.

Materials and methods

We performed a systematic MEDLINE search in which the following MESH terms were used: ‘community-acquired pneumonia’ or ‘pneumococcal pneumonia’ in combination with either ‘antibiotics, empiric’, ‘antibiotics, combinations’, ‘antibiotics macrolides’, or ‘antibiotics, quinolones’ combined with ‘mortality’, ‘length of stay’ or ‘treatment outcome’. In addition, we hand-searched references of relevant articles and guidelines.

We only included original peer-reviewed articles published in the period between January 1997 and April 2003 regarding adult patients hospitalized because of CAP and dealing with the question of whether treatment with \( \beta \)-lactam plus macrolide or quinolone monotherapy is associated with a reduction in mortality or LOS compared with \( \beta \)-lactam treatment alone. We are not aware of any relevant studies before January 1997.

We excluded articles in which children were the subject of study, articles in which no clear comparisons were made between fluoroquinolones or \( \beta \)-lactams plus macrolide and \( \beta \)-lactam treatment alone, articles on CAP in HIV-infected patients, nosocomial pneumonia or CAP managed in an outpatient setting.

In addition, we explored possible aetiological reasons that may explain the results and assigned quality levels as defined by Sackett to the reviewed studies.

Results

The initial literature search yielded 135 articles. One hundred and sixteen studies were excluded based on their titles and abstracts and another 11 were excluded after the original articles had been reviewed. The reasons for exclusion are given in Figure 1. Eventually, we found eight studies dealing with the question of whether atypical coverage by means of combinations of macrolides and \( \beta \)-lactams or fluoroquinolones in the initial treatment of patients requiring hospitalization because of CAP is associated with better outcomes. These studies are summarized in Table 1. Six studies found a significant reduction in all-cause mortality for patients treated with combinations of \( \beta \)-lactams plus macrolides or with monotherapy with a fluoroquinolone. In one study no mortality reduction could be demonstrated, and in another study, including 76 patients, a significant reduction in hospital LOS was found for the 12 patients treated with a macrolide. In addition, Dudas et al. found a reduction in LOS for patients treated with combination therapy in multivariate analysis. Reductions in LOS could not be demonstrated in two other studies and were not analysed in the remaining studies. The role of atypical pathogens in the aetiology of CAP was not addressed in any study and the susceptibility of causative microorganisms to antimicrobial therapy was analysed in only two studies. Possible disadvantages resulting from increased macrolide or fluoroquinolones use, such as an increase in costs, an increase in side effects as a result of antibiotic usage and an increase in the development of resistance, were not investigated in any study.
<table>
<thead>
<tr>
<th>Reference</th>
<th>No. patients</th>
<th>Patient category</th>
<th>Study design</th>
<th>Endpoints</th>
<th>Results</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Mufson &amp; Stanek (1999)</td>
<td>423</td>
<td>bacteraemic <em>S. pneumoniae</em></td>
<td>retrospective non-experimental cohort study</td>
<td>30 day mortality</td>
<td>mortality&lt;sup&gt;a&lt;/sup&gt; regimens with macrolide versus regimens without macrolide 1983–1987: OR 0.56 (95% CI 0.06–5.57) 1988–1992: OR 0.27 (95% CI 0.03–2.36) 1993–1997: OR 0.16 (95% CI 0.03–0.86)</td>
<td>aetiology: no data on atypical pathogens resistance: no data on susceptibility of <em>S. pneumoniae</em> severity of CAP related to choice of antibiotics: no data LOS: no data level of evidence: III</td>
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<tr>
<td>Gleason et al. (1999)&lt;sup&gt;12&lt;/sup&gt;</td>
<td>12945</td>
<td>65 years of age or older, patients selected from databases of healthcare finance organization</td>
<td>retrospective non-experimental cohort study</td>
<td>30 day mortality</td>
<td>compared to third generation cephalosporin second generation cephalosporin + macrolide: OR 0.71 (95% CI 0.52–0.96) third generation cephalosporin + macrolide: OR 0.74 (95% CI 0.60–0.92) quinolone: OR: 0.65 (95% CI 0.43–0.94) β-lactam/β-lactamase inhibitor + macrolide: OR 1.77 (95% CI 1.28–2.46)</td>
<td>aetiology: no data on atypical pathogens resistance: no data severity of CAP related to choice of antibiotics: cephalosporin plus macrolide more often prescribed in low risk pneumonia, β-lactam antibiotics more often prescribed in high risk CAP LOS: no differences in length of stay level of evidence: III</td>
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<tr>
<td>Stahl et al. (1999)&lt;sup&gt;13&lt;/sup&gt;</td>
<td>76</td>
<td>patients selected from chart review</td>
<td>retrospective non-experimental cohort study</td>
<td>LOS</td>
<td>regimens with macrolide versus regimens without macrolide: 2.75 days versus 5.3 days (P = 0.1)</td>
<td>aetiology: limited data on atypical pathogens resistance: no data severity of CAP related to choice of antibiotics: no data level of evidence: III</td>
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<td>Reference</td>
<td>No. patients</td>
<td>Patient category</td>
<td>Study design</td>
<td>Endpoints</td>
<td>Results</td>
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<td>Dudas et al.</td>
<td>2963</td>
<td>physician-presumed CAP, but for inclusion no infiltrate on chest X-ray was necessary</td>
<td>prospective, non-experimental cohort study</td>
<td>mortality</td>
<td>mortality $\beta$-lactam/$\beta$-lactamase inhibitor plus macrolide versus $\beta$-lactam: OR: 0.4 (95% CI: 0.2–0.8)</td>
<td>aetiology: no data; resistance: no data; severity of CAP related to choice of antibiotics: lower age, lack of ICU admittance and short delay to administration of antibiotics were also associated with lower mortality; LOS: $\beta$-lactam/$\beta$-lactamase inhibitor plus macrolide independently associated with decreased LOS</td>
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<tr>
<td>Burgess &amp; Lewis</td>
<td>213</td>
<td>patients selected from databases of health-care finance organization</td>
<td>retrospective non-experimental cohort study</td>
<td>mortality</td>
<td>mortality $^a$ third generation cephalosporin with macrolide versus third generation cephalosporin without macrolide: OR: 0.27 (95% CI: 0.03–2.67)</td>
<td>aetiology: no aetiological investigations performed; resistance: no data; severity of CAP related to choice of antibiotics: patients treated with macrolide had a significant lower age; LOS: third generation cephalosporin plus macrolide versus third generation cephalosporin; 5.2 ± 2.8 days versus 5.2 ± 3.4 days (not significant); level of evidence: III</td>
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<td>Houck et al.</td>
<td>10,069</td>
<td>65 years of age or older, patients selected from databases of health-care finance organization</td>
<td>retrospective non-experimental cohort study</td>
<td>mortality</td>
<td>mortality (1993) $\beta$-lactam plus macrolide versus standard therapy: OR: 0.42 (95% CI: 0.25–0.69); no favourable effect in 1995 and 1997</td>
<td>aetiology: no aetiological investigations performed; resistance: no data; severity of CAP related to choice of antibiotics: no data; LOS: no data; level of evidence: III</td>
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Table 1. (Continued)

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<thead>
<tr>
<th>Reference</th>
<th>No. patients</th>
<th>Patient category</th>
<th>Study design</th>
<th>Endpoints</th>
<th>Results</th>
<th>Comment</th>
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<tr>
<td>Waterer <em>et al.</em> (2001)</td>
<td>225</td>
<td>positive blood culture for <em>S. pneumoniae</em></td>
<td>retrospective non-experimental cohort study</td>
<td>mortality</td>
<td>mortality monotherapy versus dual therapy: OR: 3.0 (95% CI: 1.2–7.6)</td>
<td>aetiology: all cases. <em>S. pneumoniae</em>; no data on atypical pathogens; resistance: all strains were susceptible for initiated therapy; severity of CAP related to choice of antibiotics; no data; LOS: no data; level of evidence: III</td>
</tr>
<tr>
<td>Martinez <em>et al.</em> (2003)</td>
<td>409</td>
<td>positive blood culture for <em>S. pneumoniae</em></td>
<td>retrospective non-experimental cohort study</td>
<td>mortality</td>
<td>mortality receipt of empirical macrolide therapy versus no receipt of empirical macrolide therapy: OR: 0.4 (95% CI: 0.17–0.92)</td>
<td>aetiology: all cases. <em>S. pneumoniae</em>; no data on atypical pathogens; resistance: 17% erythromycin resistance, 18% penicillin resistance, 8% both erythromycin and penicillin resistance; severity of CAP related to choice of antibiotics; patients receiving macrolide more often in shock and admitted to ICU, other adverse prognostic features more prevalent in patients not receiving macrolide; LOS: no data; level of evidence: III</td>
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OR, odds ratio; CI, confidence interval; CAP, community-acquired pneumonia; LOS, length of stay.

*Odds ratios were recalculated based on data given in the publications.*
Design and patient selection

Seven studies9,10,12–16 were designed as retrospective cohort studies. Only Dudas et al.11 studied patients prospectively. In this study, the diagnosis of CAP was based on a chest X-ray, made within 72 h of hospitalization, but an infiltrate was not required for a definite diagnosis of pneumonia.11 Furthermore, accurate patient inclusion can also be questioned in the studies by Gleason et al.12 and Houck et al.13 because administrative databases of health-care insurance companies were used to identify patients with possible pneumonia. Three other studies used culture results to select patients.14,16,17

Validation of available studies

We assigned evidence levels to the reviewed studies based on the definitions of Sackett.8 (Table 2). Based on these evidence levels, a graded recommendation can be formulated for the treatment regimen under study. Considering the non-randomized design, the results of the reviewed studies should be categorized as level III evidence. Since newly formulated recommendations for the initial therapy of CAP are supported only by level III studies, they should be graded as level D recommendations.

Discussion

Patient selection bias

A potential drawback of retrospective studies is that the reported beneficial effects of empirical coverage of atypical pathogens could be the result of confounding by indication that may be present when patients are selected for certain prescribed antibiotic regimens based on the severity of their clinical condition.18,19 Except for L. pneumophila, atypical pneumonia tends to follow a less severe course and is more often found in younger persons than bacterial pneumonia. Therefore, it is possible that physicians considered atypical microorganisms as causative agents and added macrolides or fluoroquinolones to the empirical treatment in cases of milder presentation or in relatively younger persons. Clues to this form of confounding bias can be found in the study of Gleason et al.12 Antibiotic regimens containing macrolides were more often prescribed in patients with a low risk of mortality. Regimens containing a β-lactam/β-lactamase inhibitor without a macrolide were more often prescribed in high-risk patients. In contrast, in Burgess & Lewis’10 study, combination therapy was more often prescribed in high-risk patients. In the Gleason et al.12 study, combinations of β-lactam/β-lactamase inhibitors plus a macrolide were associated with high risk of mortality, whereas combinations of cephalosporins and macrolides were associated with a better survival. Although statistical corrections were made, these cannot correct entirely for this form of confounding bias.18 The outcomes suggest that cephalosporins are more effective than penicillins, but another observational study of 460 patients with pneumococcal pneumonia suggested the opposite.20 Furthermore, in the Martinez et al.9 study, a beneficial effect of macrolides was not demonstrated in univariate analysis, but was revealed only after using a stepwise logistic regression method including all putative prognostic factors. Patients receiving macrolide treatment were more often in shock and more often admitted to an ICU. However, other adverse prognostic features, such as ultimately or rapidly underlying fatal disease, having received cancer chemotherapy, comorbidity and nosocomial infection, were more prevalent in patients receiving treatment without a macrolide.9

Other reports did not confirm the findings of these retrospective analyses: in a prospective randomized study a newer fluoroquinolone (moxifloxacin) was more effective than co-amoxiclav with or without a macrolide. However, a significant survival benefit in these 628 patients was not found. There were no data on how many and which patients received macrolides.21 In addition, in a recent Scandinavian study, initial therapy with narrow-spectrum antibiotics was not associated with worse outcomes.22 The question of whether treatment with monotherapy with a β-lactam agent is inferior to the

Table 2. Description of levels of evidence and grading of guideline statements (according to Sackett8)

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Definition</th>
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<tbody>
<tr>
<td>I</td>
<td>large, randomized trials with clear-cut results; low risk of false-positive error or false-negative error</td>
</tr>
<tr>
<td>II</td>
<td>small, randomized trials with uncertain results; moderate to high risk of false-positive and/or false-negative error</td>
</tr>
<tr>
<td>III</td>
<td>non-randomized, contemporaneous controls</td>
</tr>
<tr>
<td>IV</td>
<td>non-randomized, historical controls and expert opinion</td>
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<tr>
<td>V</td>
<td>case series, uncontrolled studies and expert opinion</td>
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<tr>
<th>Grading of guideline statement</th>
<th>Definition</th>
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<tr>
<td>A</td>
<td>supported by at least two level I investigations</td>
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<tr>
<td>B</td>
<td>supported by only one level I investigation</td>
</tr>
<tr>
<td>C</td>
<td>supported by level II investigations only</td>
</tr>
<tr>
<td>D</td>
<td>supported by at least one level III investigation</td>
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<tr>
<td>E</td>
<td>supported by level IV or V evidence</td>
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</table>
combination with a macrolide or monotherapy with a quinolone therefore remains unanswered.

Possible explanations for the reported outcomes

**Atypical pathogens.** The causative role of atypical pathogens in the aetiology of CAP is relatively unknown, but could be substantial. A recent report found that CAP was associated with the presence of atypical pathogens in 20% of patients. Many other prospective studies, however, failed to identify an important role of atypical pathogens, despite extensive serological testing. Moreover, annual variation of, for example, *L. pneumophila* and *M. pneumoniae*, possibly as a result of epidemics, could have influenced the results of Houxk et al.'s study, in which the additional value of macrolides was not consistent over the years.

Several arguments can be formulated against the hypothesis that undiagnosed (co-)infections with atypical microorganisms are responsible for the benefits of this broad-spectrum empirical coverage.

First, the increased mortality associated with treatment with a macrolide plus a β-lactam/β-lactamase inhibitor, as found in one study, is contradictory to this hypothesis. Secondly, the absence of such a benefit for patients treated with a quinolone, as found in another study, also fails to confirm such a hypothesis. Thirdly, a number of prospective randomized trials reported no benefit for treatment of macrolides or quinolones as compared with β-lactam antibiotics.

Whether treatment of atypical pathogens is the explanatory mechanism for the favourable results therefore remains undetermined.

**Resistance to antibiotics.** The survival benefit and reduced LOS associated with regimens with combination therapy could also be explained by resistance of *Streptococcus pneumoniae* to β-lactam antibiotics. Unfortunately, in only two of the seven studies was the susceptibility of microorganisms to initiated therapy determined. In one of these, all streptococci were susceptible to prescribed monotherapy. In the USA, 30% of pneumococci show reduced susceptibility to penicillin in some areas, but this does not seem to influence survival in patients with pneumonia. In previous studies of bacteraemic pneumococcal pneumonia, mortality risks for patients treated with β-lactams were comparable for those infected with susceptible and non-susceptible pneumococci. Furthermore, for β-lactams, it has been shown that maintaining serum levels above the MIC for ~40% of the dosing interval achieves a good clinical cure for *S. pneumoniae*. As penicillin resistance is not an absolute resistance, this can be achieved with higher dosages of β-lactam antibiotics. It is therefore unlikely that β-lactam resistance can explain the favourable results. In areas with limited resistance, like the Netherlands and the UK, decreased susceptibility or resistance to *S. pneumoniae* will hardly be relevant. In fact, resistance to macrolides is probably a greater and more rapidly increasing problem. Importantly, clinical failure due to resistance arising during treatment has already been reported for the newer fluoroquinolones, and may jeopardize the use of this class of agents in the future.

**Synergy.** The favourable outcomes could also be explained by synergy of macrolides and β-lactam antibiotics. However, such a synergistic effect has never been demonstrated, and in an animal model this combination even showed antagonism. In theory, antagonism could have led to the high mortality rate for the combination of β-lactam/β-lactamase inhibitors and macrolides in the Gleason study but combinations of other β-lactam antibiotics and macrolides were associated with a reduction of mortality in this study. Synergy is therefore not a likely explanation for the reduction in mortality seen in the studies.

**Anti-inflammatory effect of macrolides.** Macrolides show anti-inflammatory effects; this property is used, for example, in the treatment of diffuse panbronchiolitis. The mechanism that causes the modulation of inflammation in the acute phase is not yet entirely clear. *In vitro*, macrolides can decrease the production of pro-inflammatory cytokines and expression of endothelin-1, inhibit the production of superoxide and diminish the adherence of pneumococci to respiratory epithelium. Whether or not the favourable outcome of short-term macrolide treatment in CAP results from anti-inflammatory effects, however, remains unknown. Moreover, unless quinolones have similar anti-inflammatory properties, the survival benefit associated with quinolone treatment would remain unexplained.

**Conclusions**

In the studies discussed above, treatment with a macrolide plus a β-lactam antibiotic or monotherapy with a quinolone showed reductions in mortality or LOS. However, the non-experimental design of the studies reviewed may have resulted in confounding by indication, and this may have influenced the results significantly. The current advice to use empirical treatment with either a β-lactam/macrolide combination or monotherapy with a new quinolone for patients hospitalized with CAP is based on studies with level III evidence. Moreover, the results are inconsistent and do not reveal a mechanism that explains the favourable results. Therefore, given the current evidence it cannot be concluded that the addition of a macrolide or monotherapy with one of the newer fluoroquinolones should become the standard of care for patients admitted to the hospital with CAP. In addition, possible disadvantages, such as an increase in costs, an increase in side effects as a result of antibiotic usage and an increase in the development of resistance, were not investigated. Widespread implementation of treatment regimes including unnecessary use of macrolides and fluoroquinolones could lead to an increase in antibiotic pressure, which may enhance antibiotic resistance dramatically. To determine the costs and benefits of adding a macrolide or a fluoroquinolone to the initial treatment of patients with CAP, large, prospective, randomized studies are necessary.

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lides. Drugs 63, 181–205.


42. Johansen, H. K., Jensen, T. G., Dessau, R. B. et al. (2000). Antagonism between penicillin and erythromycin against Streptococcus

