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CLINICAL RESEARCH STUDY

Efficacy of Short-Course Antibiotic Regimens for Community-Acquired Pneumonia: A Meta-analysis

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ABSTRACT

PURPOSE: There is little consensus on the most appropriate duration of antibiotic treatment for community-acquired pneumonia. The goal of this study is to systematically review randomized controlled trials comparing short-course and extended-course antibiotic regimens for community-acquired pneumonia.

METHODS: We searched MEDLINE, Embase, and CENTRAL, and reviewed reference lists from 1980 through June 2006. Studies were included if they were randomized controlled trials that compared short-course (7 days or less) versus extended-course (>7 days) antibiotic monotherapy for community-acquired pneumonia in adults. The primary outcome measure was failure to achieve clinical improvement.

RESULTS: We found 15 randomized controlled trials matching our inclusion and exclusion criteria comprising 2796 total subjects. Short-course regimens primarily studied the use of azithromycin (n = 10), but trials examining beta-lactams (n = 2), fluoroquinolones (n = 2), and ketolides (n = 1) were found as well. Of the extended-course regimens, 3 studies utilized the same antibiotic, whereas 9 involved an antibiotic of the same class. Overall, there was no difference in the risk of clinical failure between the short-course and extended-course regimens (0.89, 95% confidence interval [CI], 0.78-1.02). In addition, there were no differences in the risk of mortality (0.81, 95% CI, 0.46-1.43) or bacteriologic eradication (1.11, 95% CI, 0.76-1.62). In subgroup analyses, there was a trend toward favorable clinical efficacy for the short-course regimens in all antibiotic classes (range of relative risk, 0.88-0.94).

CONCLUSIONS: The available studies suggest that adults with mild to moderate community-acquired pneumonia can be safely and effectively treated with an antibiotic regimen of 7 days or less. Reduction in patient exposure to antibiotics may limit the increasing rates of antimicrobial drug resistance, decrease cost, and improve patient adherence and tolerability.

KEYWORDS: Antibiotics; Community-acquired pneumonia; Pneumonia; Short-course

Community-acquired pneumonia is one of the leading causes of morbidity and mortality in the world. In the United States, an estimated 2-3 million cases of community-acquired pneumonia occur annually, resulting in an estimated 10 million physician visits and 600,000 hospitalizations, with a total annual cost of over $20 billion.[1-3] The most commonly isolated pathogen is *Streptococcus pneumoniae*, especially in bacteremic and hospitalized patients. Other common causes of community-acquired pneumonia include *Haemophilus influenzae* and the "atypical" pathogens, which include *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella pneumophilia*. The atypical organisms cannot be differentiated from other etiologies on the basis of clinical symptoms or radiographic appearance and are infrequently isolated in clinical practice. Overall, the bacteriologic etiology of community-acquired pneumonia is undetermined in 40%-60% of clinical studies and in the vast majority of cases in actual practice.[1,2,4-7]

Without adequate clinical trials, the empiric treatment of community-acquired pneumonia continues to be challenging, with a myriad of recommendations on the length of

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treatment and types of antibiotics.[1,3,8-12] The drawbacks of antibiotic overuse are becoming increasingly apparent and include growing antibiotic resistance, rising costs, and potentially severe side effects such as *Clostridium difficile* infections. Recent studies have already begun to question the need for additional antimicrobial agents to cover atypical organisms in community-acquired pneumonia.[6,13] Another method to decrease antibiotic usage is to decrease the length of antibiotic treatment. Currently, a range of recommendations can be found regarding the duration of treatment, most encompassing a treatment course of 5-14 days.[1,7-9,14] Several recent studies have suggested the clinical effectiveness and benefits of shorter duration antimicrobial therapy for lower-respiratory tract infections and community-acquired pneumonia.[15-20] In order to further define the appropriate length of antibiotic treatment for community-acquired pneumonia, we performed a meta-analysis of randomized-controlled trials comparing short-course (≤7-day) versus extended-course (>7-day) antibiotic regimens.

CLINICAL SIGNIFICANCE

- Adults with mild-moderate community-acquired pneumonia can be effectively treated with an antibiotic regimen of 7 days or less.
- This result is consistent among the 4 antibiotic classes studied (macrolide, fluoroquinolone, beta-lactam, and ketolide).
- There is a trend toward decreased adverse events with antibiotic regimens of 7 days or less.

METHODS

Search Strategy

We used the Cochrane Central Register of Controlled Trials, Medline, and Embase to find publications from 1980 through June 2006. In the Cochrane database, the record title was searched for the keyword "pneumonia." Articles in Medline and Embase were found by searching for clinical studies or trials with the word "pneumonia" in the title and without the following keywords in the title: "pneumocystis," "aspiration," "aspirate," "nosocomial," "ventilator," "ventilation," "ventilated," "pediatric," "paediatric," "child," "childhood," and "children." In addition, we reviewed the reference lists from review articles and the identified clinical trials, as well as medication inserts and drug manufacturer websites to identify other relevant studies. No language restrictions were applied during the search process.

Study Selection

Our inclusion criteria required studies to be randomized controlled trials in adults (age ≥12 years) that compared the clinical efficacy of a short-course (7 days or less) antibiotic monotherapy regimen versus an extended course (>7 days) regimen. All patients had radiographically confirmed pneumonia. Noncomparative and nonrandomized studies were excluded, as were trials with a large proportion of patients with bronchitis, chronic obstructive pulmonary disease exacerbations, or health-care-associated pneumonias. Two reviewers (JL and LW) independently evaluated full text articles to determine eligibility for inclusion into the study and independently extracted data from relevant trials. Discrepancies between the reviewers were resolved through discussion.

Outcomes

The primary outcome measure was failure to achieve clinical improvement or cure. Secondary outcomes were mortality, bacteriologic failure, and adverse events. The outcome measures and time to outcome assessment were defined by each individual study. Clinical failure was determined by the investigators of each study generally based on clinical symptoms and the need for additional antibiotics. The time to outcome assessment was generally between 10 and 42 days. The quality of each study was evaluated using the Jadad scoring system as previously described, which takes into account allocation generation, concealment, and dropouts.[21]

Statistical Analysis

For the primary data analysis, we used the intention-to-treat or modified intention-to-treat (participants who were randomized and received at least one dose of study medication) principle. In studies that only reported a per-protocol analysis, we conservatively assumed that all dropouts were treatment failures for inclusion in the intention-to-treat analysis. Clinical success using the per-protocol patient population also was evaluated. Stata version 9.0 (StataCorp LP, College Station, Tex) was employed to calculate the relative risks (RR) and 95% confidence intervals (CI) using the fixed-effects model (a random-effects model also was used and was found to not significantly alter the results). To test for publication bias, we used the Stata program *metabias*, which performs the Begg's and Egger's regression asymmetry test for publication bias. To test for heterogeneity, we calculated a chi-squared statistic that is the sum of the squared differences between each study and the summary mean divided by the variance (StataCorp LP).

RESULTS

Description of Studies

Our search strategy identified more than 3700 potential references (Figure 1). Most studies were excluded due to the fact that they were not randomized controlled trials or did not compare a short-course versus an extended-course antibiotic regimen. Fifteen studies met our inclusion and exclusion criteria and were included in this meta-analysis

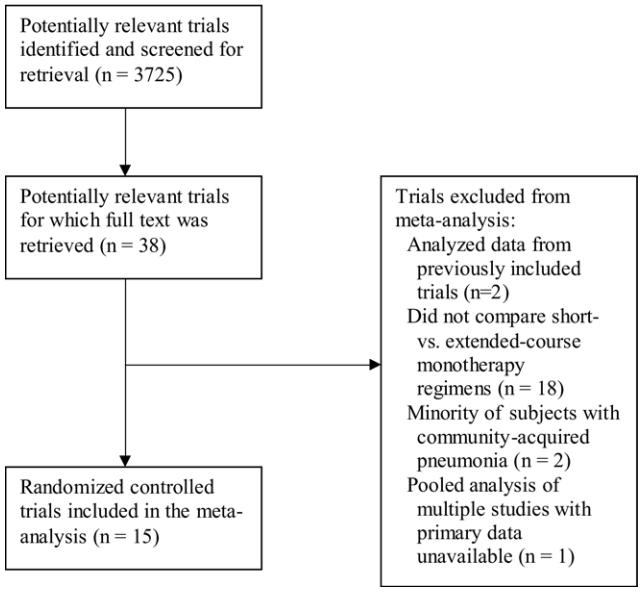

Figure 1 Study flow diagram.

(Table 1). These studies were published between 1990 and 2004 and comprised a total of 2796 subjects. Ten studies enrolled more than 100 participants (range, 42-528 subjects). The mean age of the participants ranged from 40 to 64 years. All of the trials included only patients with mild-moderate community-acquired pneumonia. Eight of the studies exclusively used oral antibiotics and excluded those with more severe disease requiring intravenous antibiotics. The other trials excluded patients with signs of clinical decompensation (eg, patients requiring intensive care unit stay, Pneumonia Severity Index >130).[22] In the 10 studies examining the efficacy of short-course azithromycin,[23-32] 6 trials used 3-day regimens,[26-30,32] whereas 4 trials used 5-day regimens.[23-25,31] Most compared it with another macrolide, although the comparative drug was Cefaclor in one study[25] and in another, multiple comparative antibiotics were used.[28] Other short-course regimens studied included fluoroquinolones (n = 2),[33,34] beta-lactams (n = 2),[35,36] and a ketolide (n = 1).[37] The majority of extended-course antibiotic regimens involved macrolide antibiotics (n = 9), but also examined the beta-lactam (n = 4) and fluoroquinolone (n = 1) antibiotic classes.

Although the majority of studies examined short-course macrolide antibiotics, the distribution of subjects was more evenly distributed among the different antibiotic classes. Of the 2796 total participants, 39% were in studies examining short courses of macrolide antibiotics, 30% in the fluoroquinolone trials, 20% in the ketolide study, and 11% in the studies examining short-course beta-lactam antibiotics. Both inpatients and outpatients were represented, with 2 studies performed exclusively in outpatients,[27,28] 4 studies with only inpatients,[23,29,30,35] and 6 studies evaluating both inpatients and outpatients[26,31-34,37] (2 studies did not specify).[24,25]

All studies identified participants by a combination of clinical symptoms and radiographic features. Several studies had more targeted inclusion criteria. Bohte et al divided their cohort into patients suspected to have pneumococcal and nonpneumococcal pneumonia based on clinical and microbiological criteria.[23] The pneumococcal subgroup was not included in this analysis, as the duration of antibiotic use was not specified for the comparison medication. In 2 studies, both involving azithromycin compared with another macrolide, the patient population was restricted to those deemed to have "atypical pneumonia" by either clinical/radiographic criteria or through serologic antibody titers.[30,31] Finally, in the study by Leophonte et al comparing gemifloxacin and amoxicillin/clavulanic acid, the participants were limited to those who were thought to have likely

Table 1 Characteristics of Included Studies

Study	Short-Course	Extended-Course	n	Mean Age*	Time to Outcome Assessment
Bohte et al, 1995[23]	Azithromycin, 5 d	Erythromycin, 10 d	42	61	Within 21 days of discharge
Brion et al, 1990[24]	Azithromycin, 5 d	Josamycin, 10 d	97	53	30 days
Dunbar et al, 2003[33]	Levofloxacin, 5 d	Levofloxacin, 10 d	528	54	7-14 days after last dose of antibiotic
Kinasewitz & Wood, 1991[25]	Azithromycin, 5 d	Cefaclor, 10 d	119	42	10-13 days
Kobayashi et al, 1995[26]	Azithromycin, 3 d	Clarithromycin, 14 d	163	Not reported	14 days
Leophonte et al, 2004[34]	Gemifloxacin, 7 d	Amoxicillin/clav, 10 d	320	54	24-30 days
Leophonte et al, 2002[35]	Ceftriaxone, 5 d	Ceftriaxone, 10 d	244	64	10 days
O'Doherty & Muller, 1998[27]	Azithromycin, 3 d	Clarithromycin, 10 d	203	51	12-16 days
Rahav et al, 2004[28]	Azithromycin, 3 d	Multiple abx, 10 d	108	50	10-14 days
Rizzato et al, 1995[29]	Azithromycin, 3 d	Clarithromycin, 10 d	40	46	30 days
Schonwald et al, 1994[30]	Azithromycin, 3 d	Roxithromycin, 10 d	150	40	14 days
Schonwald et al, 1990[31]	Azithromycin, 5 d	Erythromycin, 10 d	101	Not reported	15-21 days
Siegel et al, 1999[36]	Cefuroxime, 7 d	Cefuroxime, 10 d	52	61	42 days
Sopena et al, 2004[32]	Azithromycin, 3 d	Clarithromycin, 10 d	70	43	25-30 days
Tellier et al, 2004[37]	Telithromycin, 5 or 7 d	Clarithromycin, 10 d	559	42	17-21 days

*Mean age (years) is estimated to be the average age of the 2 arms if reported separately.

Table 2 Number of Patients with Community-Acquired Pneumonia Failing to Improve Clinically by Intention-to-Treat (ITT) and Per-Protocol (PP) Analysis

	ITT Analysis n/N		PP Analysis n/N		Risk Ratios	
Study	Short-Course	Extended-Course	Short-Course	Extended-Course	ITT (95% CI)	PP (95% CI)
Bohte et al, 1995[23]	5/20	6/22	4/19	5/21	0.92 (0.33-2.54)	0.88 (0.28-2.82)
Brion et al, 1990[24]	13/50	9/47	9/46	5/43	1.36 (0.64-2.88)	1.68 (0.61-4.62)
Dunbar et al, 2003[33]	73/256	97/272	15/198	17/192	0.80 (0.62-1.03)	0.86 (0.44-1.66)
Kinasewitz & Wood, 1991[25]	23/53	27/66	2/32	0/39	1.06 (0.70-1.62)	6.06 (0.30-121.9)
Kobayashi et al, 1995[26]	23/81	25/82	1/59	6/63	0.93 (0.58-1.50)	0.18 (0.02-1.43)
Leophonte et al, 2004[34]	38/167	32/153	13/115	14/113	1.09 (0.72-1.65)	0.91 (0.45-1.85)
Leophonte et al, 2002[35]	32/125	34/119	17/94	16/92	0.90 (0.59-1.35)	1.04 (0.56-1.93)
O'Doherty & Muller, 1998[27]	18/101	18/102	5/88	4/88	1.01 (0.56-1.83)	1.25 (0.35-4.50)
Rahav et al, 2004[28]	1/62	6/46	1/62	6/46	0.12 (0.02-0.99)	0.12 (0.02-0.99)
Rizzato et al, 1995[29]	1/20	3/20	1/20	2/19	0.33 (0.04-2.94)	0.47 (0.05-4.82)
Schonwald et al, 1994[30]	2/90	10/60	1/89	3/53	0.13 (0.03-0.59)	0.20 (0.02-1.86)
Schonwald et al, 1990[31]	18/57	12/44	0/39	0/32	1.16 (0.63-2.14)	
Siegel et al, 1999[36]	6/27	5/25	3/24	2/22	1.11 (0.39-3.19)	1.37 (0.25-7.47)
Sopena et al, 2004[32]	6/34	8/36	3/31	4/32	0.79 (0.31-2.05)	0.77 (0.19-3.18)
Tellier et al, 2004[37]	67/378	34/181	35/320	12/146	0.94 (0.65-1.37)	1.33 (0.71-2.49)
Summary RR					0.89 (0.78-1.02)	0.94 (0.72-1.22)

*Relative risk unable to be calculated for the PP population for Schonwald et al. due to the lack of patients who failed to improve in both arms of the study.

pneumococcal pneumonia based on clinical findings or examination of a respiratory sample.[34]

Risk of Clinical Failure

The risk of clinical failure was the primary outcome measure for all studies. No significant differences were found between the risk of clinical failure in the short-course and extended-course arms (Table 2, Figure 2) either by intention-to-treat (RR 0.89, 95% CI, 0.78-1.02) or by per-protocol analysis (RR 0.94, 95% CI, 0.72-1.22). No significant differences in outcome were found in those participants taking short-course macrolides (10 studies: RR 0.88, 95% CI, 0.71-1.09), fluoroquinolones (2 studies: RR 0.88, 95% CI, 0.71-1.08), or beta-lactam antibiotics (2 studies: RR 0.92, 95% CI, 0.63-1.36). A subgroup analysis of studies using 3-day regimens of azithromycin showed a significant reduction in clinical failures with the fixed-effects model (6 studies: RR 0.70, 95% CI, 0.51-0.96), but not the random-effects model (6 studies: RR0.61, 95% CI, 0.34-1.10). The reported rate of clinical failure by per-protocol analysis was

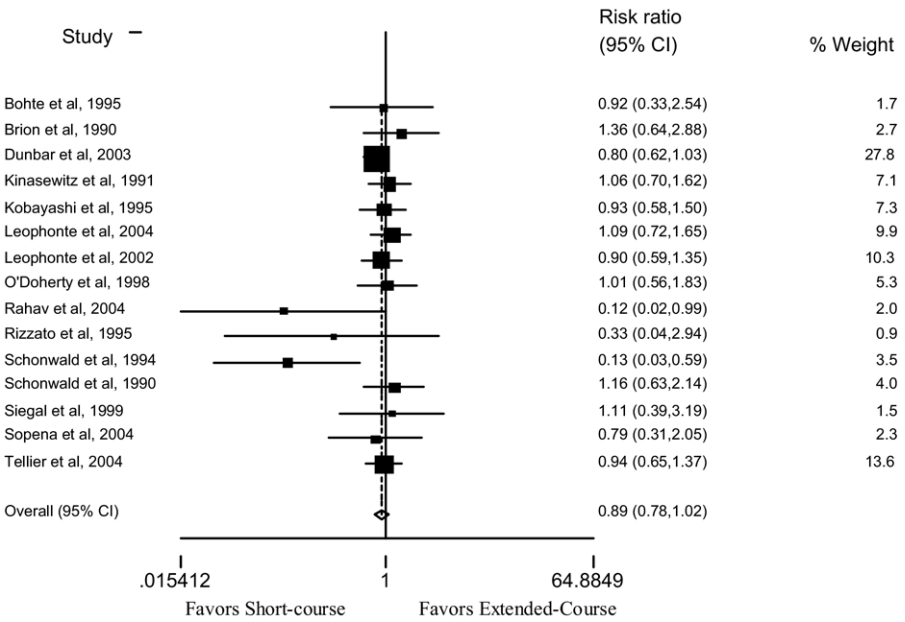

Figure 2 Relative risk of clinical failure with short-course versus extended course antibiotic regimens.

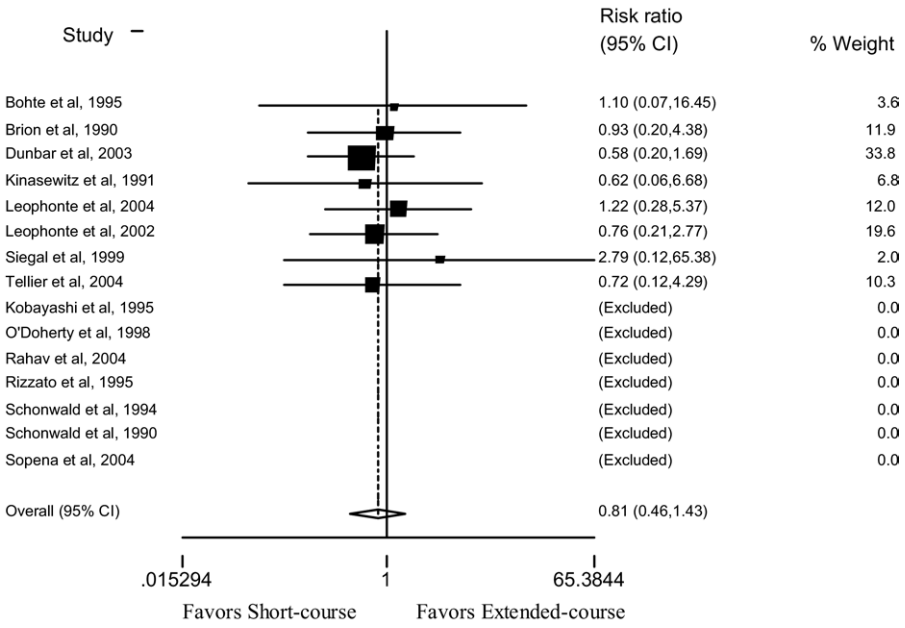

Figure 3 Relative risk of mortality with short-course versus extended-course antibiotic regimens. (The relative risk of mortality could not be calculated in 7 studies due to the lack of deaths in both arms).

8.9% for participants in the short-course antibiotic arm and 9.6% in the extended-course antibiotic arm.

Secondary Outcome Measures

The overall mortality rate was 1.7%, with 7 studies reporting no deaths. Among those studies with at least one death, the mortality rates ranged from 0.9% to 6.7%. Among the analyzable studies, no significant differences were found in the risk of mortality between the 2 arms (Figure 3; RR 0.81, 95% CI, 0.46-1.43). Bacteriologic failure was reported in 7 studies and was generally defined as persistently positive cultures or an absence of culture/serologic testing results in those who had clinical failure. Prolonged antibiotic course was not associated with significantly improved bacteriologic response (RR 1.09, 95% CI, 0.75-1.58). Adverse events were defined as clinical symptoms or laboratory abnormalities deemed likely to be related to medication use by the investigators. There was a wide range in the reported rates of adverse events (2.3%-22.4%), with a mean of 14.1%. No significant differences in the risk of adverse events were found between the arms (RR 0.86, 95% CI, 0.71-1.04). No heterogeneity was found for the intention-to-treat analysis of clinical failure ($P = .36$), mortality ($P = 1.0$), bacteriologic eradication ($P = .60$), or for any subgroup analysis ($P > .1$ for all comparisons). Tests for publication bias found no evidence of publication bias for any of the summary measures ($P > .1$ for all comparisons). Unless noted above, analysis by the random effects model resulted in no significant differences among the results.

Methodologic Quality of Studies

The quality of the studies was evaluated on the basis of adequate allocation randomization, concealment, and the reporting of dropouts. This was done through the Jadad score as previously described.[21] Eight studies were found to be of relatively high quality (Jadad score ≥3). A subgroup analysis including only the high quality studies found no significant differences in the risk of clinical failure with the use of short-course antibiotic regimens (RR 0.92, 95% CI, 0.80-1.07).

DISCUSSION

In this meta-analysis, we found no significant differences between short-course and extended-course antibiotic regimens for the treatment of mild to moderate community-acquired pneumonia with respect to clinical success, mortality, bacteriologic success, and adverse events. The results were consistent across a wide range of analyses, including both the intention-to-treat and per-protocol patient populations, high-quality studies, and individual antibiotic classes. Both outpatients and inpatients were included, and 4 of the antibiotic classes most commonly used for community-acquired pneumonia (macrolide, fluoroquinolone, beta-lactam, and ketolide) were represented in this meta-analysis. In addition, the studies taken together included subjects with a wide mean age range.

The optimal length of treatment for community-acquired pneumonia has been unclear, with current guidelines suggesting a regimen that varies from 5 to 14 days.[5,7,8,14,38,39] In addition, the most recent Infectious Diseases Society of America and American Thoracic Society guidelines specifically recommend treatment until 72 hours after the patient becomes afebrile and until clinically stable.[1,8,9] Several arguments have already been put forth for the use of shorter duration of treatment for pneumonia. Studies in children have demonstrated the equivalent efficacy of 3 days versus

5 days of antibiotic treatment for pneumonia.[40,41] An older study of community-acquired pneumonia patients in Nigeria suggested that patients could be successfully treated with as little as 2.5 days of antibiotic therapy.[42] In the treatment of ventilator-associated pneumonia, 8 days of antibiotic treatment was found to be as efficacious as 15 days of treatment in most cases.[43] In addition, a study of patients with nosocomial pneumonia found, using serial bronchoscopy, that in only 6% of cases were initially isolated microbes not eradicated within just 3 days of treatment.[44] One reason that azithromycin has been so frequently studied in short-course regimens is its pharmacokinetic properties that allow the drug to have high tissue concentrations for 3-4 days after completion of therapy.[15,45] It is interesting to note that in 6 of 10 azithromycin trials included here, azithromycin was given for only 3 days, which would suggest that 1 week of an antibiotic without this type of prolonged activity should be sufficient. Finally, a recent multi-centered clinical trial in the Netherlands found that two thirds of patients with community-acquired pneumonia had improved clinically after just 3 days of treatment with amoxicillin. In those patients who had substantially improved, there was no benefit in taking additional antibiotics.[46]

The avoidance of extended-course antibiotic regimens may have many important benefits. Increasing rates of antimicrobial resistance has become a major concern for *S. pneumoniae* and other organisms causing community-acquired pneumonia.[4,38,47,48] It is clear that one of the major causes is the frequency and length of antibiotic use, and subsequent selective pressures for resistance.[16,43,49,50] The use of shorter course antibiotic regimens may help limit the spread of drug-resistant bacteria. Patient compliance is another factor to consider, as several studies have shown improved patient adherence with regimens of $<$7 days compared with longer courses.[50-52] Finally, shorter courses of antibiotics can potentially reduce the risk of medication side effects. In this study, there was a trend toward lower adverse events with the short-course regimen.

The issue of antibiotic resistance has become a grave concern, especially with the well-documented increase in macrolide-resistant *S. pneumoniae*.[8,53] *S. pneumoniae* resistance to fluoroquinolones also has been documented worldwide, but resistance to respiratory fluoroquinolones (levofloxacin, moxifloxacin, and gemifloxacin) is still relatively rare in the United States.[53-57] Although there was a trend toward favorable clinical efficacy for the short-course regimen in all antibiotic classes, many of the included studies are of relatively small size and little information can be extrapolated as to the effect of antimicrobial resistance. This study is intended to address whether a short duration of antibiotic therapy is adequate using the antimicrobial classes that have been studied, but the appropriate selection of the type of antibiotic for community-acquired pneumonia may evolve as resistance patterns change. At this time, macrolides are still recommended as first-line therapy for the outpatient treatment of community-acquired pneumonia in patients who are previously healthy and have no risk factors for drug-resistant *S. pneumoniae*.[8] It also is important to note that telithromycin has been linked to a number of cases of hepatotoxicity and caution should be advised when prescribing this antibiotic.[58,59]

One important limitation of this study is the underrepresentation of some classes of antibiotics. For example, no study of doxycycline was found that matched the inclusion criteria. In addition, only 1 ketolide, 2 beta-lactam, and 2 fluoroquinolone studies were found. However, because these studies were larger, the overall number of subjects receiving each class of antibiotic was more evenly distributed. Although 10 of 15 studies examined the efficacy of azithromycin, these studies involved only 39% of the total number of participants. The 2 fluoroquinolone trials enrolled 848 participants, or 30% of the total number, whereas the one ketolide study alone had 559 participants. Another limitation is that most trials included only mild-moderate pneumonia, with elderly patients generally under-represented in the study populations. Even in the inpatient studies, respiratory failure and septic shock were common exclusion criteria. Therefore, although the results of this meta-analysis should be generalizable to most adults, they cannot be extrapolated to those with severe community-acquired pneumonia. Finally, as with all recommendations, individual response to treatment should be taken into account. As discussed in the recent study by el Moussaoui et al,[46] short courses of treatment are probably most appropriate in patients who have significantly improved with initial therapy.

In summary, the available data suggest that adults with mild-moderate community-acquired pneumonia can be safely and effectively treated with an antibiotic regimen of 7 days or less. Given the potential cost savings and implications in reducing antimicrobial drug resistance, larger studies should be performed confirming these results across antibiotic classes.

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