Azithromycin vs Cefuroxime Plus Erythromycin for Empirical Treatment of Community-Acquired Pneumonia in Hospitalized Patients

A Prospective, Randomized, Multicenter Trial

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Objective: To compare the efficacy and safety of azithromycin dihydrate monotherapy with those of a combination of cefuroxime axetil plus erythromycin as empirical therapy for community-acquired pneumonia in hospitalized patients.

Methods: Patients were enrolled in a prospective, randomized, multicenter study. The standard therapy of cefuroxime plus erythromycin was consistent with the American Thoracic Society, Canadian Community-Acquired Pneumonia Consensus Group, and Infectious Disease Society of America consensus guidelines. The doses were intravenous azithromycin (500 mg once daily) followed by oral azithromycin (500 mg once daily), intravenous cefuroxime (750 mg every 8 hours), followed by oral cefuroxime axetil (500 mg twice daily), and erythromycin (500-1000 mg) intravenously or orally every 6 hours. Randomization was stratified by severity of illness and age. Patients who were immunosuppressed or residing in nursing homes were excluded.

Results: Data from 145 patients (67 received azithromycin and 78 received cefuroxime plus erythromycin) were evaluable. *Streptococcus pneumoniae* and *Haemophilus influenzae* were isolated in 19% (28/145) and 13% (19/145), respectively. The atypical pathogens accounted for 33% (48/145) of the etiologic diagnoses; *Legionella pneumophila*, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae* were identified in 14% (20/145), 10% (15/145), and 9% (13/145), respectively. Clinical cure was achieved in 91% (61/67) of the patients in the azithromycin group and 91% (71/78) in the cefuroxime plus erythromycin group. Adverse events (intravenous catheter site reactions, gastrointestinal tract disturbances) were significantly more common in patients who received cefuroxime plus erythromycin (49% [30/78]) than in patients who received azithromycin (12% [8/67]) ($P<.001$).

Conclusions: Treatment with azithromycin was as effective as cefuroxime plus erythromycin in the empirical management of community-acquired pneumonia in immunocompetent patients who were hospitalized. Azithromycin was well tolerated.

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COMMUNITY-acquired pneumonia is the most frequent general medicine discharge diagnosis and is the sixth leading cause of death in the United States.[1,2] The initial antibiotic regimen for community-acquired pneumonia is generally empirical, since precise knowledge of the causative agent is not known at the time of admission. Guidelines for initial therapy in adults with community-acquired pneumonia have been published by the American Thoracic Society, Canadian Community-Acquired Pneumonia Consensus Group, and the Infectious Disease Society of America.[3-5] For hospitalized patients, the use of one drug that has in vitro activity against "typical" bacterial pathogens (*Streptococcus pneumoniae* and *Haemophilus influenzae*) and a second drug that has in vitro activity against "atypical" pathogens (*Legionella pneumophila*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*) was recommended for initial empirical use. These regimens included second- or third-generation cephalosporins or the β-lactam and β-lactamase inhibitors plus a macrolide.

Since the publication of the 1993 American Thoracic Society guidelines, the parenteral form of the new macrolide azithromycin has become available for commercial use. The Infectious Disease Society of America guidelines recommended empirical therapy with a β-lactam with or without the addition of a macrolide for patients hospitalized on a general medical ward.[5] Azithromycin exhibits in vitro activity against both typical and atypical bacterial pathogens.[6-8] Furthermore, azithromycin has improved pharmacokinetics and excellent lung tissue penetration, allowing for once-daily administration and a shorter course of therapy. Monotherapy has the advantages of sim-

PATIENTS AND METHODS

STUDY POPULATION

Patients were eligible for participation in the study if they were adults (aged ≥18 years) hospitalized with a primary diagnosis of community-acquired pneumonia. Community-acquired pneumonia was defined as (1) a new pulmonary infiltrate compatible with pneumonia by chest radiograph and confirmed by a radiologist; and (2) 1 or more signs and symptoms consistent with a lower respiratory tract infection, including temperature greater than 38°C, new or increased cough, production of purulent sputum, crackles, rhonchi, or pleuritic chest pain or dyspnea; or (3) an elevated white blood cell count ($>10 \times 10^9$/L) or greater than 0.15 band forms.

Patients were excluded from the study for the following reasons: known hypersensitivity to β-lactam or macrolide antibiotics, presence of gastrectomy or other condition affecting drug absorption, receipt of chemotherapy or other immunosuppressive therapy at time of pneumonia onset, known acquired immunodeficiency syndrome, severe renal impairment (creatinine clearance <0.42 mL/s [<25 mL/min]), neutropenia ($<0.5 \times 10^9$/L), hospitalization within the preceding 14 days, or nursing home residence. Patients who received treatment with an antibiotic other than the study drugs within 24 hours before enrollment were excluded. The study was approved by each center's institutional review board, and written informed consent was obtained from all patients.

STUDY DESIGN

This prospective randomized, comparative, multicenter study was conducted from 1994 to 1996 at 4 medical centers: the Veterans Affairs Healthcare Systems in Little Rock, Ark, and Pittsburgh, Pa; Summa Health System, Akron, Ohio; and Santa Clara Valley Medical Center, San Jose, Calif.

STUDY REGIMENS

The experimental regimen was azithromycin dihydrate administered intravenously as a 1-hour infusion at a dosage of 500 mg once daily for 2 to 5 days, followed by 500 mg orally to complete a total of 7 to 10 days of therapy. The control regimen was cefuroxime combined with erythromycin. Cefuroxime was administered intravenously at a dosage of 750 mg every 8 hours for 2 to 7 days, followed by cefuroxime axetil at a dosage of 500 mg orally twice daily to complete a total of 7 to 10 days of therapy. In addition, erythromycin lactobionate or erythromycin base at a dosage of 500 to 1000 mg was given intravenously or orally every 6 hours and continued for up to 21 days. This study was nonblinded because of differences in drug dosing frequency between azithromycin and cefuroxime combined with erythromycin.

Patients were allocated to the regimens by computer-generated random number method. Patients were first stratified by severity of illness as defined by vital signs at onset and age; these factors have been reported to be prognostic of outcome in patients with community-acquired pneumonia.[9] The prognostic factors were as follows: (1) abnormal vital signs as defined by systolic blood pressure less than 90 mm Hg, pulse greater than 120 beats/min, or respiratory rate greater than 30/min and (2) age of 65 years or greater. Randomization was then performed for patients within each of 4 subgroups, eg, age of 65 years or greater and abnormal vital signs. This minimized disproportional allocation of high-risk patients into one treatment regimen.

The study patients were monitored daily by the clinical investigators at each participating site, and the decision to switch to oral therapy was made on the basis of improvement in cough, diminution in purulent sputum production, defervescence, and reduction in leukocytosis.

MICROBIOLOGICAL INVESTIGATIONS

The following were routinely ordered for each study patient: a sputum specimen for culture and Gram stain; 2 sets of blood cultures; specialized testing for *Legionella* species, including culture of sputum on selective media,[10] direct fluorescent antibody stains (monoclonal and polyclonal), urinary antigen, serological studies (IgG and IgM) for *L pneumophila* serogroups 1 through 6 and *Legionella micdadei* at baseline (acute), at time of hospital discharge, and again at 4- to 6-week posttreatment follow-up visits; serological studies for antibody against *C pneumoniae* and *M pneumoniae* at baseline, at time of hospital discharge, and again at 4- to 6-week posttreatment follow-up visits by microimmunofluorescence and complement-fixation methods; polymerase chain reaction assays of oropharyngeal swab specimens for detection of *L pneumophila*, *C pneumoniae*, and *M pneumoniae*[11]; and culture of pleural fluid or bronchoalveolar lavage when

Continued on next page

plicity in administration and lower costs than those of combination therapy. We therefore conducted a prospective, randomized, multicenter study to compare azithromycin as monotherapy vs cefuroxime plus erythromycin for the treatment of hospitalized patients with community-acquired pneumonia. The latter combination is a commonly prescribed regimen consistent with American Thoracic Society, Canadian Community-Acquired Pneumonia Consensus Group, and Infectious Disease Society of America guidelines.[3-5]

RESULTS

One hundred sixty-nine patients were enrolled. Sixteen patients (10 from the azithromycin group and 6 from the cefuroxime-erythromycin group) were excluded because (1) the diagnosis of pneumonia was not confirmed, including questionable evidence of pulmonary infiltrate on chest radiograph in 5 patients, pulmonary edema in 3 patients, and acute pericarditis in 1 patient, and (2) protocol violations occurred, including unauthorized enrollment in 1 patient, improper informed consent or withdrawal of consent in 3 patients, concurrent antibiotic treatment at enrollment in 2 patients, and erroneous administration of both study regimens in 1 patient. An additional 8 patients (6 from the azithromycin group and 2 from the cefuroxime-erythromycin group) were excluded on the basis of clinical nonevaluability; specifically, 7 patients received 48 hours or less of study drug and 1 patient had infective endocarditis.

available. Sputum samples were considered suitable for culture if there were more than 25 polymorphonuclear leukocytes and fewer than 10 squamous epithelial cells per low-power field on a Gram stain. The DNA banding patterns of *Haemophilus influenzae* were analyzed by means of pulsed-field gel electrophoresis of *Sma*I digests.

Microbiological classification of pneumonia as definitive or presumptive and identification of atypical pathogens were defined as follows: Definitive identification: (1) blood or pleural fluid cultures yielding a pathogen; (2) isolation of *Legionella* species from respiratory tract samples or a 4-fold rise in *Legionella* antibody titer to 1:256 or greater; (3) positive urinary antigen for *L pneumophila* serogroup 1; (4) positive polymerase chain reaction result with another positive test result fulfilling the criteria for a presumptive diagnosis for *L pneumophila*, *C pneumoniae*, or *M pneumoniae*; (5) 4-fold rise in IgG antibody titer for *C pneumoniae* to 1:32 or greater; or (6) 4-fold rise in IgG antibody titer for *M pneumoniae* to 1:32 or greater.

Presumptive identification was defined as follows: (1) heavy or moderate growth of a predominant bacterial pathogen on sputum culture; (2) light growth of a pathogen in which the sputum Gram stain showed a bacterium compatible with the culture results; (3) in the case of multiple potential bacterial pathogens, if the Gram stain demonstrated the presence of multiple organisms consistent with those isolated on culture, then multiple pathogens were considered to be the cause; (4) *L pneumophila:* a single IgM antibody titer to 1:512 or greater or positive direct fluorescent antibody stain only; (5) *C pneumoniae:* a single IgM antibody titer of 1:32 or more or a single IgG antibody titer of 1:1024 or more; (6) *M pneumoniae:* a single IgM antibody titer of 1:64 or more; and (7) positive polymerase chain reaction assay results alone were considered presumptive evidence of infection with the atypical pathogens.

Unknown etiology was defined as follows: (1) "normal flora" on sputum culture, (2) light growth of multiple organisms on culture, and (3) cases not fulfilling any of the above conditions.

It should be noted that we applied stricter serological criteria for the establishment of an etiologic diagnosis of an atypical pathogen than were used in previous studies.[12,13]

IN VITRO SUSCEPTIBILITY TESTING

Susceptibility testing was performed using agar-based quantitative minimum inhibitory concentration (MIC) determinations (E-test; AB BIODISK, Piscataway, NJ) for *S pneumoniae* and broth microdilution (Clinical Microbiology Institute, Tualain, Ore) for *H influenzae*. Susceptibility to azithromycin was defined according to the 1997 National Committee for Clinical Laboratory Standards (NCCLS) as an MIC of 2 µg/mL or less for *S pneumoniae* and 4 µg/mL or less for *H influenzae*. Susceptibility to cefuroxime was defined according to the 1998 NCCLS as an MIC of 0.5 µg/mL or less for *S pneumoniae* and 4 µg/mL or less for *H influenzae*. Susceptibility to penicillin G was defined according to the 1997 NCCLS as an MIC of 0.06 µg/mL or less for *S pneumoniae* and 0.75 µg/mL or less for *H influenzae*.

END POINT ASSESSMENTS

Clinical response was the primary efficacy end point. Patients were assessed for symptoms and signs (cough, dyspnea, crackles, rhonchi, pleuritic chest pain) of infection at baseline, day 3, and every 5 to 7 days during therapy, and within 10 to 14 days and 4 to 6 weeks after treatment.

Clinical cure was defined as the receipt of a minimum of 3 days of therapy with resolution of symptoms and signs at conclusion of therapy. *Clinical failure* was defined as failure of symptoms and signs of pneumonia to resolve. Patients were considered to have nonevaluable data for clinical efficacy if (1) they received 2 days or less of antibiotic therapy, (2) they received concomitant antibiotics for treatment of different infections, or (3) pneumonia was not confirmed radiographically after entry into the study. Secondary end points included adverse events and in-hospital mortality.

STATISTICAL ANALYSIS

A sample size estimate of 140 was chosen to detect a difference in clinical response rates between azithromycin and cefuroxime plus erythromycin of 14% with a power of 80%. The calculations assumed an 85% cure rate in the cefuroxime therapy group and 2-sided significance level of 5%.

Clinical cure rates were compared between treatment groups by the 2-sided Fisher exact test. Two-sided 95% confidence intervals (CIs) for the overall clinical cure rates and mortality rates were computed by the normal approximation to the binomial. A P value of .05 or less was considered to be statistically significant.

One hundred forty-five patients were assessed for clinical response. Sixty-seven patients were assigned to receive azithromycin and 78 patients were assigned to receive cefuroxime-erythromycin. Patients randomized to receive azithromycin received an average of 8 days of intravenous and oral therapy, whereas patients randomized to receive cefuroxime plus erythromycin received an average of 10 days of intravenous and oral therapy. Thirteen patients (5 from the azithromycin group and 8 from the cefuroxime-erythromycin group) were admitted to the intensive care unit during the course of the study. Stratification variables of age and vital signs were comparable among both groups, as expected. Initial physical symptoms, including chills, cough, shortness of breath, and pleuritic chest pain, were comparable among both groups (data not shown). The most common comorbid illnesses and risk factors among patients in the azithromycin group included cigarette smoking in 51% (34/67), chronic obstructive lung disease in 37% (25/67), coronary artery disease in 22% (15/67), type 2 diabetes mellitus in 18% (12/67), chronic alcoholism in 16% (11/67), and ulcer disease in 15% (10/67). The most common comorbid illnesses and risk factors in the cefuroxime-erythromycin group included cigarette smoking in 56% (44/78), chronic obstructive lung disease in 35% (27/78), coronary artery disease in 36% (28/78), type 2 diabetes mellitus in 15% (12/78), chronic alcoholism in 14% (11/78), and ulcer disease in 17% (13/78). The allocation of comorbid illnesses and risk factors was similar for each treatment arm.

Table 1. Etiologic Diagnoses in 145 Patients With Community-Acquired Pneumonia*

Pathogen	Definitive	Presumptive	Total
Streptococcus pneumoniae	7	21	**28**
Legionella pneumophila	7	13	**20**
Haemophilus influenza a	1	18	**19**
Chlamydia pneumoniae	2	13	**15**
Mycoplasma pneumoniae	12	1	**13**
Haemophilus species	0	6	**6**
Branhamella catarrhalis	0	6	**6**
Staphylococcus aureus	0	6	**6**
Unknown	. . .†	. . .†	60
Total	**29**	**84**	**173**

**Includes multiple etiologies in 24 patients. Data are given as number of diagnoses.*
†Not applicable.

CAUSATIVE AGENT

The most common causative agents were *S pneumoniae*, *L pneumophila*, *H influenzae*, and *C pneumoniae* (**Table 1**). The most common agents that fulfilled the criteria for definitive etiology were *M pneumoniae*, *S pneumoniae*, and *L pneumophila*. Mixed etiologies were seen in 24 patients. There were 2 instances of concurrent infection with 2 definitive etiologies (*S pneumoniae* and *M pneumoniae*; *S pneumoniae* and *C pneumoniae*); 5 instances of concurrent infection with a definitive etiology and a presumptive etiology, including *M pneumoniae* and *L pneumophila* in 2 cases and *M pneumoniae* and *Haemophilus* species in 3 cases; and 3 instances of concurrent infection with 1 definitive etiology and 2 presumptive etiologies (*M pneumoniae* with *C pneumoniae* and *L pneumophila*; *L pneumophila* with *S pneumoniae* and *H influenzae*; and *L pneumophila* with *Branhamella catarrhalis* and *H influenzae*). The remaining 14 multiple infections consisted of presumptive etiologies. No pathogens were identified in 41% of patients (60/145).

SUSCEPTIBILITY TESTING

Nineteen isolates of *S pneumoniae* (5 from bloodstream in 4 patients and 14 from sputum culture in 14 patients) and 18 isolates of *H influenzae* (1 from bloodstream in 1 patient and 17 from sputum culture in 15 patients) were available for in vitro susceptibility testing (**Table 2**).

S pneumoniae Susceptibility

Twenty-eight patients had *S pneumoniae* pneumonia (21 presumptive, 7 definitive). In 18 patients, the isolate was available for testing, with 1 patient having 2 isolates. Seventeen were susceptible to azithromycin (MIC, ≤2.0 µg/mL), 2 were resistant to azithromycin (MIC, ≥8.0 µg/mL), 16 isolates were susceptible to erythromycin (MIC, ≤0.25 µg/mL), 1 was intermediately susceptible to erythromycin (MIC, 0.38 µg/mL), and 2 were resistant to erythromycin (MIC, ≥3.0 µg/mL). Seventeen isolates were susceptible to cefuroxime (MIC, ≤0.19 µg/mL), and 2 isolates were resistant to cefuroxime (MIC, 6.0-8.0 µg/mL). Fifteen isolates were susceptible to penicillin G (MIC, ≤0.02 µg/mL), 3 were intermediately susceptible to penicillin G (MIC, 0.064-0.75 µg/mL), and 1 was resistant to penicillin (MIC, 2.0 µg/mL). The 4 bacteremic isolates of *S pneumoniae* that were available for testing were uniformly susceptible to azithromycin (MIC, ≤1.5 µg/mL), erythromycin (MIC, 0.19 µg/mL), penicillin G (MIC, ≤0.12 µg/mL), and cefuroxime (MIC, ≤0.19 µg/mL) (Table 2). Three bacteremic isolates of *S pneumoniae* were not available for in vitro susceptibility testing.

Table 2. Clinical Efficacy for Isolates of *Streptococcus pneumoniae* and *Haemophilus influenzae* Subclassified by In Vitro Susceptibility*

	Azithromycin		Cefuroxime/ Erythromycin	
Pathogen	Cure	Failure	Cure	Failure
S pneumoniae†				
Penicillin sensitive (n = 14)	80 (4/5)	20 (1/5)	100 (9/9)	0 (0/9)
Penicillin resistant (n = 4)‡	100 (1/1)	0 (0/1)	67 (2/3)	33 (1/3)
Azithromycin sensitive (n = 16)	80 (4/5)	20 (1/5)	91 (10/11)	9 (1/11)
Azithromycin resistant (n = 2)§	100 (1/1)	0 (0/1)	100 (1/1)	0 (0/1)
H influenzae‖				
Penicillin sensitive (n = 12)	89 (8/9)	11 (1/9)	100 (3/3)	0 (0/3)
Penicillin resistant (n = 4)¶	50 (1/2)	50 (1/2)	100 (2/2)	0 (0/2)
Azithromycin sensitive (n = 16)	82 (9/11)	18 (2/11)	100 (5/5)	0 (0/5)

**Data are given as percentage (number/total number).*
†Isolates from 18 of 28 patients were available for in vitro testing. Fourteen isolates were susceptible to both azithromycin and penicillin, 2 isolates were resistant to both azithromycin and penicillin, and 2 isolates were susceptible to azithromycin but resistant to penicillin.
‡Minimum inhibitory concentration range, 0.064 to 2 µg/mL.
§Minimum inhibitory concentration range, 8 to greater than 256 µg/mL.
‖Isolates from 16 of 19 patients were available for in vitro testing. Twelve isolates were susceptible to both azithromycin and penicillin, and 4 isolates were susceptible to azithromycin but resistant to penicillin.
¶Minimum inhibitory concentration range, 6 to greater than 32 µg/mL.

H influenzae Susceptibility

Nineteen patients had *H influenzae* pneumonia (18 presumptive, 1 definitive). In 16 patients, the isolate was available for testing, with 1 patient having 3 isolates. Sixteen were susceptible to azithromycin (MIC, ≤2.0 µg/mL) and 2 were resistant (MIC, ≥4.0 µg/mL). Thirteen isolates were susceptible to erythromycin (MIC, ≤4.0 µg/mL) and 5 were resistant (MIC, ≥8.0 µg/mL). Seventeen isolates were susceptible to cefuroxime (MIC, ≤3.0 µg/mL) and 1 was resistant (MIC, 12.0 µg/mL). Twelve isolates were susceptible to penicillin G (MIC, ≤0.75 µg/mL) and 6 were resistant to penicillin G (MIC, ≥6.0 µg/mL). The 1 bacteremic isolate was uniformly susceptible to azithromycin (MIC, 0.75 µg/mL), erythromycin (MIC, 0.25 µg/mL), penicillin G (MIC, 0.25 µg/mL), and cefuroxime (MIC, 1.0 µg/mL) (Table 2). β-Lactamase production was documented in 5 isolates of *H influenzae*.

Table 3. Clinical Response Rate in 145 Hospitalized Patients*

Pathogen (N = 173)	Azithromycin		Cefuroxime/Erythromycin	
	Cure	Failure	Cure	Failure
Definitive and presumptive etiologies				
Streptococcus pneumoniae (n = 28)	88 (7/8)	12 (1/8)	95 (19/20)	5 (1/20)
Haemophilus influenzae (n = 19)	83 (10/12)	17 (2/12)	100 (7/7)	0 (0/7)
Branhamella catarrhalis (n = 6)	100 (2/2)	0 (0/2)	100 (4/4)	0 (0/4)
Staphylococcus aureus (n = 6)	100 (4/4)	0 (0/4)	100 (2/2)	0 (0/2)
Legionella pneumophila (n = 20)	92 (11/12)	8 (1/12)	88 (7/8)	13 (1/8)
Chlamydia pneumoniae (n = 15)	86 (6/7)	14 (1/7)	88 (7/8)	13 (1/8)
Mycoplasma pneumoniae (n = 13)	100 (9/9)	0 (0/9)	100 (4/4)	0 (0/4)
Definitive etiologies only				
S pneumoniae (n = 7)	100 (2/2)	0 (0/2)	100 (5/5)	0 (0/5)
H influenzae (n = 1)	0 (0/0)	0 (0/0)	100 (1/1)	0 (0/1)
L pneumophila (n = 7)	100 (4/4)	0 (0/4)	67 (2/3)	33 (1/3)
C pneumoniae (n = 2)	100 (2/2)	0 (0/2)	0 (0/0)	0 (0/0)
M pneumoniae (n = 12)	100 (8/8)	0 (0/8)	100 (4/4)	0 (0/4)
Unknown (n = 60)	93 (25/27)	7 (2/27)	88 (29/33)	12 (4/33)

*Data are given as percentage (number/total number). Multiple etiologies were identified in 24 patients.

STUDY END POINTS

The clinical cure rate was 91% (61/67) (95% CI, 82%-97%) in the azithromycin group and 91% (71/78) (95% CI, 92%-96%) in the cefuroxime-erythromycin group ($P = .95$). For the intention-to-treat analysis of all 169 patients, the clinical cure rates were 75% (62/83) (95% CI, 64%-84%) for the azithromycin treatment group and 83% (71/86) (95% CI, 73%-90%) for the cefuroxime-erythromycin treatment group ($P = .26$). The overall mortality rate was 2% (3/145); the mortality subclassified by treatment group (azithromycin vs cefuroxime combined with erythromycin) was 3% (2/67) (95% CI, 0.4%-10%) and 1% (1/78) (95% CI, 0%-7%), respectively. The overall mortality in the intention-to-treat group was 2% (4/169); the mortality subclassified by treatment group (azithromycin vs cefuroxime combined with erythromycin) was 4% (3/83) and 1% (1/86), respectively. The cause of death in the 3 patients included cerebrovascular accident, pulmonary embolus, and respiratory failure resulting from chronic obstructive lung disease. Two patients did not have an etiologic diagnosis, and 1 patient had sputum culture evidence of pneumonia caused by *H influenzae* and serological evidence of pneumonia caused by *C pneumoniae* (presumptive). The isolate of *H influenzae* was not available for susceptibility testing. Two of these patients (one with an unknown etiology and one with presumptive evidence of mixed infection with *H influenzae* and *C pneumoniae*) received azithromycin, and the remaining patient (unknown etiology) received cefuroxime plus erythromycin.

CLINICAL RESPONSE BY SPECIFIC PATHOGENS

Clinical cure and failure rates by subclassified pathogen for both antibiotic regimens are presented in **Table 3**. There were no clinical failures among cases with bacteremic pneumonia (definitive etiology) caused by *S pneumoniae* treated with azithromycin (2 patients) or cefuroxime-erythromycin (5 patients). In 21 patients with sputum culture evidence of pneumonia caused by *S pneumoniae* (presumptive etiology), there was 1 clinical failure for both azithromycin and cefuroxime-erythromycin. The 1 case of bacteremic pneumonia (definitive etiology) from *H influenzae* was cured with cefuroxime-erythromycin. In 18 patients with sputum culture evidence (presumptive etiology) of pneumonia from *H influenzae*, there were 2 clinical failures of azithromycin. There were no clinical failures of azithromycin among the 4 cases of *L pneumophila* pneumonia classified as definitive etiology and 1 clinical failure of cefuroxime-erythromycin in the case of *L pneumophila* classified as definitive etiology. In 13 patients with serological or polymerase chain reaction evidence of pneumonia caused by *L pneumophila* (presumptive etiology), there was 1 clinical failure of azithromycin.

ADVERSE EVENTS

Overall, there were 46 treatment-related adverse events (8 among patients treated with azithromycin and 38 among patients treated with cefuroxime-erythromycin) (**Table 4**). Intravenous catheter site reactions (pain, swelling, and redness) and gastrointestinal tract disturbances (nausea, vomiting, abdominal pain, and diarrhea) were more commonly seen with cefuroxime-erythromycin than with azithromycin ($P<.001$).

DRUG COSTS

The antibiotic acquisition costs for azithromycin, cefuroxime, and erythromycin were obtained from each of the 4 participating sites. The average drug cost per day of hospitalization for 500 mg of azithromycin administered intravenously once daily was $15.84 (range, $13.50-$18.49). The average drug cost per day for 750 mg of cefuroxime administered intravenously every 8 hours was $10.45 (range, $8.10-$15.39), and for erythromycin, 500 to 1000 mg administered intravenously every 6 hours was $17.02 (range, $0.52-$29.12). The average drug cost per day after switchover to oral drug for

Table 4. Incidence of Adverse Events by Antibiotic Regimen*

Adverse Event	Azithromycin	Cefuroxime/ Erythromycin	*P*
All adverse events	12 (8/67)	49 (38/78)	<.001
Intravenous catheter site reaction†	6 (4/67)	36 (28/78)	<.001
Gastrointestinal tract‡	1 (1/67)	23 (18/78)	.002
Abnormal liver injury markers§	7 (5/67)	3 (2/78)	NS‖
Ototoxic effects	0 (6/7)	1 (1/78)	NS

**Except for* P*, data are given as percentage (number/total number). Includes multiple adverse events in 14 patients.*

†Includes pain, swelling, and redness.

‡Includes nausea, vomiting, abdominal pain, and diarrhea.

§Includes elevated levels of alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, alkaline phosphatase, and lactate dehydrogenase.

*‖NS indicates not significant (*P*>.02).*

500 mg of azithromycin once daily was $8.69 (range, $7.26-$10.22). The average drug cost per day for 500 mg of cefuroxime axetil twice daily was $8.10 (range, $6.10-$10.38), and for erythromycin, 500 to 1000 mg taken every 6 hours was $0.48 (range, $0.32-$0.88). Costs related to preparation and administration and adverse events were not calculated, such that the pharmacoeconomic superiority of monotherapy with azithromycin was underestimated when compared with standard combination therapy given 3 to 4 times daily.

COMMENT

Antibiotic studies in community-acquired pneumonia have been difficult to evaluate for a number of reasons: (1) inclusion of patients with chronic bronchitis, (2) comparison with an antibiotic that is not an acceptable standard for community-acquired pneumonia, (3) disproportionate inclusion of sicker patients to one arm of the study more than another, and (4) failure to classify microbial etiologies as definitive or presumptive.[14]

Our study incorporated a number of features designed to overcome these weaknesses: (1) explicit clinical and radiographic definitions for pneumonia were given to ensure that patients with exacerbations of chronic bronchitis were excluded; (2) randomization was stratified by age and severity of illness to minimize disproportionate allocation of patients with poor prognostic factors; (3) the study drug was compared with a standard antibiotic regimen consistent with the American Thoracic Society,[3] Canadian Community-Acquired Pneumonia Consensus Group,[4] and Infectious Disease Society of America[5] guidelines; (4) etiologic diagnoses were classified as either presumptive or definitive; and (5) extensive diagnostic modalities for the "atypical" pathogens were applied. The end points in our study were (1) clinical cure as defined by the resolution of initial symptoms and signs by 3 days after the initiation of antibiotic therapy and (2) mortality.

Azithromycin treatment resulted in a 91% (61/67) clinical cure, which was identical to the 91% (71/78) clinical cure obtained with cefuroxime-erythromycin. The mortality rate subclassified by treatment with azithromycin vs cefuroxime-erythromycin was only 3% (2/67) and 1.3% (1/78), respectively, despite the fact that 9% of the patients were admitted to the intensive care unit. None of the deaths were attributed to antibiotic failure.

The rank order of etiologic diagnoses was comparable with that in many previous studies,[12,15-21] with *S pneumoniae* being the most common etiologic agent, followed by either *H influenzae* or *L pneumophila*. This study also confirmed the rarity of aerobic gram-negative bacilli or *Pseudomonas aeruginosa* as etiologic agents in immunocompetent patients with community-acquired pneumonia. Although gram-negative bacilli were isolated from sputum culture in 5 patients, Gram stain confirmation was lacking, and these were not considered pathogenic. Two of these 5 patients were randomized to the azithromycin group, and all experienced clinical cure, providing circumstantial evidence that these gram-negative bacilli were colonizing rather than pathogenic microorganisms. It should be noted that, despite the uncertainty of precisely delineating a cause with current laboratory methods, both regimens were effective therapy for virtually all patients.

The serum concentrations of azithromycin are relatively low compared with those of β-lactam agents, such that concern has been raised about its efficacy for pneumococcal bacteremia. In our study, clinical cures were documented in the 2 patients with bacteremic pneumonia caused by *S pneumoniae* treated with azithromycin. Similar clinical cure rates were found for both regimens in our 28 patients with pneumonia caused by *S pneumoniae*. The efficacy of azithromycin for patients with pneumococcal bacteremia has been confirmed in other studies.[22-24] The *S pneumoniae* sputum isolates from 2 patients in whom treatment with azithromycin or cefuroxime-erythromycin failed were both susceptible to azithromycin (MIC range, 1.5-2.0 µg/mL) and to cefuroxime (MIC range, 0.047-0.19 µg/mL), respectively (Table 2). The sputum isolate obtained from the patient in whom cefuroxime-erythromycin treatment failed was intermediately susceptible to both erythromycin (MIC, 0.38 µg/mL) and penicillin G (MIC, 0.064 µg/mL). Azithromycin resistance in vitro has been reported to be as high as 71% in penicillin-resistant pneumococci.[25-27] It should be noted that azithromycin concentrations and half-life in alveolar macrophages, lung tissue, and respiratory secretions are high compared with those of other antimicrobial agents,[28-30] so correlation between in vitro azithromycin resistance of pneumococci and subsequent outcome is important. In one study of patients who received erythromycin for pneumococcal pneumonia, the presence of erythromycin resistance in vitro did not correlate with subsequent outcome.[31] In our study, despite in vitro resistance to azithromycin (MIC, 8.0 µg/mL) in *S pneumoniae* isolated from sputum, this patient was cured with azithromycin (Table 2).

A clinical failure rate of 17% (2/12) was observed with azithromycin in patients with pneumonia caused by *H influenzae*. The sputum isolates from these 2 patients were susceptible in vitro to azithromycin (MIC, 2.0 µg/mL). An increase in resistance to both azithromycin (MIC range, 8.0-16.0 µg/mL) and erythromycin (MIC, ≥16 µg/mL) was observed in 3 distinct sputum isolates of *H influenzae* from the same patient obtained during azithromycin therapy. In 2 comparative studies of community-acquired pneumonia, the bacteriological efficacy of azithromycin for pa-

tients infected with *H influenzae* ranged from 94% (15/16)[22] to 100% (30/30)[24]; interestingly, the comparative regimens used had lower success rates (73% [8/11] and 85% [29/34], respectively) than azithromycin, but the differences were not statistically significant. Oral azithromycin (95%) was significantly superior to cefaclor (61%) for *H influenzae* in a blinded study of 272 patients with acute lower respiratory tract infection.[32]

Clinical failures of azithromycin and cefuroxime-erythromycin were seen in 8% (1/12) and 13% (1/8), respectively, of patients with pneumonia caused by *L pneumophila*. Similarly, clinical failures of azithromycin and cefuroxime-erythromycin were seen in 14% (1/7) and 13% (1/8), respectively, among patients with pneumonia caused by *C pneumoniae*. There were no clinical failures of either regimen in patients with pneumonia caused by *M pneumoniae*.

Azithromycin was well tolerated. The incidence of drug-related intravenous site reactions and gastrointestinal intolerance was significantly less than with the cefuroxime-erythromycin regimen ($P<.001$) (Table 4).

We conclude that, for the initial, empirical treatment of patients hospitalized for community-acquired pneumonia, azithromycin as monotherapy was comparable with cefuroxime-erythromycin with respect to clinical cure. Azithromycin was significantly better tolerated than cefuroxime-erythromycin, with fewer adverse events. Finally, azithromycin was less expensive than the combination of cefuroxime plus erythromycin. The once-daily dose of azithromycin may also result in better patient acceptance and in compliance with the oral form once the switch is made from intravenous therapy. (Appendices containing information about the clinical failures with *S pneumoniae* and *H influenzae* and information on aerobic gram-negative bacilli are available on request.)

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