INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Efficacy of Azithromycin in the Treatment of Community-acquired Pneumonia, Including Patients with Macrolide-Resistant *Streptococcus pneumoniae* Infection

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Abstract

Background and Objective The growing problem of drug resistance among respiratory pathogens in community-acquired pneumonia (CAP), particularly *Streptococcus pneumoniae*, (*S. pneumoniae*) has complicated initial empiric therapy of CAP. This study was undertaken to evaluate the efficacy and tolerability of a 3-day course of azithromycin in adults with mild to moderately severe CAP, and to determine whether *in vitro* macrolide resistance among strains of *S. pneumoniae* is related to clinical efficacy/failure.

Methods An open-label, non-comparative study was undertaken at 3 university-affiliated hospitals in Japan. Patients were eligible if they were 18 years or older and had mild or moderately severe CAP. All patients received azithromycin 500 mg/day for three days, and clinical and microbiological responses were evaluated 1 and 2 weeks after initiating therapy.

Results A total of 78 patients received the study medication, 59 of whom had sufficient data available for efficacy analysis. Overall, a good clinical response with azithromycin was achieved in 49 patients (83.1%) and a microbiological response was achieved in 78.3%. Azithromycin resistance, based on CLSI criteria, was demonstrated in 85.7% (12/14) of *S. pneumoniae* isolates, and the presence of *erm*B genes was found in 50.0% (7/14). However, among patients in whom *S. pneumoniae* was isolated (n=17), a good clinical response was achieved in 76.5% (13/17), and the microbiological response rate was 64.3% (9/14). Furthermore, 6 of 7 patients in whom high-level resistance was documented (MICs ＞256 μg/mL and carrying *erm*B genes) exhibited good clinical responses. Azithromycin was well tolerated; adverse events, mainly of a gastrointestinal nature, were recorded in 6 patients (7.7%).

Conclusion Most patients responed well to azithromycin, indicating that azithromycin might be clinically effective for the treatment of CAP with macrolide-resistant *S. pneumoniae*. However, a larger study is necessary to prove the efficacy against macrolide-resistant *S. pneumoniae*.

Key words: community-acquired pneumonia, azithromycin, macrolide resistance, *Streptococcus pneumoniae*

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Introduction

Community-acquired pneumonia (CAP) is a common and potentially life-threatening illness that continues to be a major medical problem (1-4). In Japan, it ranks as the fourth leading cause of death (1, 5), while in the US, it is the sixth leading cause and the most common cause of death from infectious disease (2, 6). The mainstay of treatment for most patients with CAP is timely and appropriate antimicrobial therapy, which should be guided by several considerations including the suspected pathogen, disease severity, the spectrum of activity, clinical pharmacological properties, efficacy and tolerability of the antimicrobial agent, the setting, the presence of co-morbidities (e.g. cardiopulmonary disease, diabetes, renal failure), and whether other antimicrobial therapy has been administered (1-4, 6, 7). The most commonly identified pathogen, both in Japan (8, 9) and the US and UK (2, 3), is *Streptococcus pneumoniae* (*S. pneumoniae*).

In recent years, there has been an increasing worldwide problem of drug resistance among respiratory pathogens, notably *S. pneumoniae* which has shown increasing levels of penicillin and macrolide resistance (10-13). This has complicated initial empiric therapy of CAP, particularly as macrolides are commonly recommended as first-line treatment for patients with no co-morbidities because of their activity against both *S. pneumoniae* and atypical pathogens (1, 6, 7). Resistance to macrolides among strains of *S. pneumoniae* is caused by two principal mechanisms: 1) methylation of a ribosomal binding site, which is encoded by the *erm*B gene; and 2) active drug efflux via a cell membrane protein transporters, which is encoded by the *mef*A gene (14). While the former mechanism appears to gives rise to high-level macrolide resistance (erythromycin MIC 128 μg/mL), the latter gives rise to lower-level resistance (erythromycin MIC 1 to 64 μg/mL) (7). In Japan, macrolide resistance among *S. pneumoniae* is now very common and is mediated predominantly by the *erm*B gene; in a recent study, 81.4% of *S. pneumoniae* isolates were resistant to erythromycin, and 50% possessed the *erm*B gene (12). However, the clinical relevance of macrolide resistance is uncertain. Although there have been reports of treatment failure with macrolides used as first-line treatment for *S. pneumoniae* infections, other observational data suggest that *in vitro* susceptibility may not correlate with clinical efficacy, and the true risk of treatment failure among patients with macrolide resistance remains unknown (15). Clinical efficacy of azithromycin against adults and children with pneumonia induced by macrolide resistant *S. pneumonia* is investigated. As a result, azithromycin may be clinically effective for the treatment of CAP with MRSP (16, 17).

AZM is a semisynthetic, acid-stable erythromycin derivative with an expanded spectrum of antimicrobial activity that includes the majority of commonly isolated pathogens in CAP. It generally achieves higher concentrations in tissues and tissue fluids than in serum, and has a pharmacokinetic profile that permits once-daily dosing (18, 19). In the treatment of pneumonia and other lower respiratory tract infections, a 3-day regimen of azithromycin given orally once daily has been shown to be as effective as traditional 5- to 10-day regimens of other antibacterial agents (18). The present study was undertaken to evaluate the efficacy and tolerability of a 3-day course of azithromycin administered at a dosage of 500 mg once daily in Japanese patients with mild to moderately severe CAP, and to determine whether *in vitro* macrolide resistance among isolated strains of *S. pneumoniae* is related to clinical efficacy.

Materials and Methods

Study design and conduct

The Azithromycin Adult Community-acquired Pneumonia Study was an open-label, non-controlled trial undertaken at 3 university-affiliated hospitals in Japan between October 2005 and June 2006. The study was approved by independent ethics committees at each site and all patients provided informed consent (written or verbal) to participate in the study before any procedures were performed.

Patients and medication

Patients eligible for enrollment in the study were required to be 18 years of age or older and to fulfil three diagnostic criteria for CAP: 1) the presence of infiltration on chest x-ray or computerized tomography, for which a diagnosis of pneumonia was the most likely explanation; 2) the appearance of sputum or coughing, or an increase of sputum volume or purulence; and 3) fever of 37°C or higher. Preferably, the following criteria were also required to be met: an increase in the serum C-reactive protein (CRP) concentration of $\geq$0.7 mg/dL (or higher than the upper limit of normal at the study centre); peripheral leukocytosis [white blood cell (WBC) count $\geq$8,000 cells/mL]; and a good quality sputum specimen for isolation of causative pathogens. The severity of the infection was graded as 'mild' or 'moderate' according to the Japanese Respiratory Society's (JRS) pneumonia severity classification system (20), whereby 'mild' was defined as the absence of any of the 5 following conditions and 'moderate' was defined as the presence of one or two: 1) systolic blood pressure $\leq$90 mmHg; (2) SpO_2 $\leq$90% (PaO_2 $\leq$60 Torr); 3) blood urea nitrogen (BUN) $\geq$21 mg/dL or dehydration; 4) confusion; 5) age $\geq$70 years (males) or $\geq$75 years (females). The indication of oral antibiotics such as macrolides is 'mild' or 'moderate' pneumonia. Thus, these patients were enrolled in this study.

Exclusion criteria included severe renal or hepatic dysfunction or other serious underlying illnesses, concomitant administration of any antimicrobial agent (except anti-influenza drugs), achievement of a clinical response to any antimicrobial drug in the previous 7 days, hospitalization in the previous 14 days, pregnancy or lactation, and a history of hypersensitivity to azithromycin or any macrolide antibi-

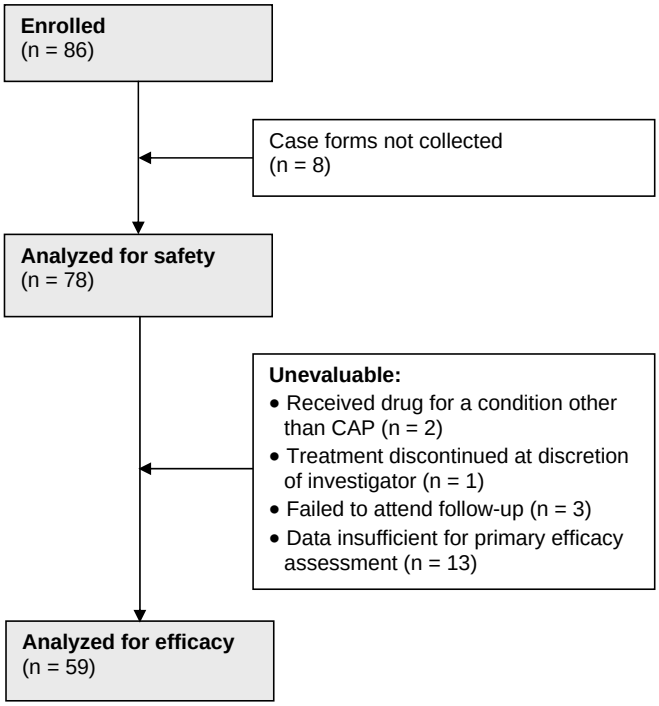


Figure 1. **Patient population.**

Table 1. **Demographic Characteristics of the Patients Analyzed for Efficacy (n=59)**

Mean age, years (range)	53.4 (20-82)
Gender (male/female), n (%)	29/30 (49.2%/50.8%)
Outpatients/inpatients, n (%)	47/12 (79.7%/20.3%)
Severity of pneumonia, n (%):	
Mild[a]	38 (64.4%)
Moderate	15 (25.4%)
Unknown	6 (10.2%)
Concomitant illnesses, n (%):	
Pulmonary emphysema	1 (1.7%)
Chronic pharyngitis	1 (1.7%)
Acute sinusitis	1 (1.7%)
Allergic rhinitis	1 (1.7%)
Others	12 (20.3%)

[a] The majority of patients with mild community-acquired pneumonia were outpatients (97.4%).

otic.

Patients who met the criteria for enrollment in the study received azithromycin 500 mg (2 tablets of Zithromac®; Pfizer Japan, Inc.) once daily for 3 days. All patients were instructed to record their symptoms and compliance with the medication instruction in a diary on a daily basis.

Assessments

Patients were evaluated on the first day of therapy (day 1), at the end of therapy (day 4), and at 1 and 2 weeks after initiating therapy (days 8 and 15, respectively). Clinical and microbiological responses were assessed via data review by 9 delegates from each of the participating centres, based on the attending physician's evaluation.

Assessments of each patient included clinical symptoms (fever, cough, amount and nature of sputum, dyspnea, consciousness, chest pain/rales, dehydration), chest x-rays, vital signs, arterial oxygen saturation, laboratory tests (WBC, CRP, BUN), sputum Gram's stain, sputum culture and determination of minimum inhibitory concentrations (MICs) of azithromycin (and other antibacterial agents), urine antigen tests (*S. pneumoniae* and *L. pneumophila* antigens), blood cultures, and serological assays (*M. pneumoniae* and *C. pneumoniae* antibodies). Strains of *S. pneumoniae* isolated were also subjected to genetic analysis.

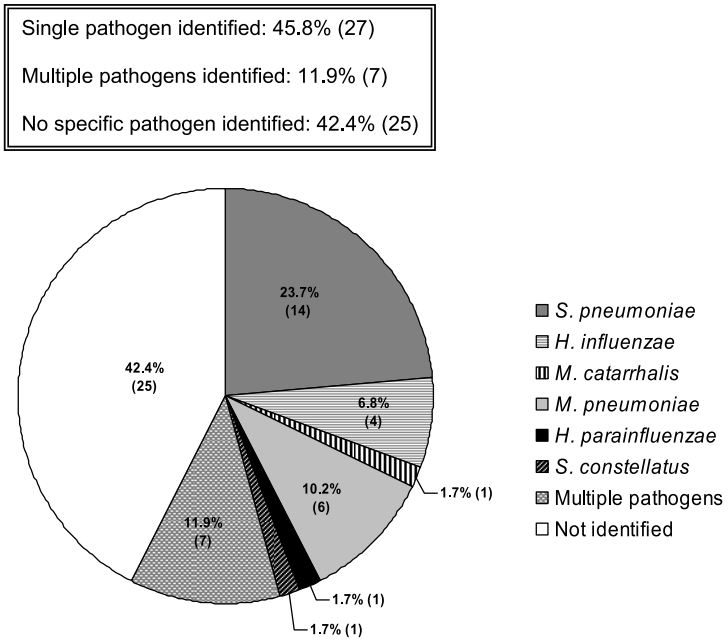
The primary endpoint was the clinical response on day 8, which was assessed using the JRS clinical response criteria (20). The clinical response was rated as 'good' if 3 of the following 4 outcomes were achieved: 1) resolution of fever (temperature $\leq$37°C); 2) resolution of leukocytosis (normalization of WBC count); 3) improvement of serum CRP (decreased to $\leq$30% of the highest value); and 4) significant improvement of chest x-ray findings. Secondary endpoints included the microbiological response (assessed by the presence/absence of the infecting micro-organism in the sputum on days 4 and 8), and safety variables assessed via the occurrence of adverse events and laboratory abnormalities.

Patients were withdrawn from the study if infection with Gram-negative bacilli for which azithromycin is not indicated (e.g. *Klebsiella pneumoniae*) was demonstrated, any serious adverse event occurred, or any concomitant condition was aggravated.

Results

A total of 86 patients were enrolled, 78 of whom received the study medication and had safety data available. Of these, 59 patients had sufficient data available for the primary efficacy analysis (Fig. 1). The demographic characteristics of the efficacy analysis population, including their mean age, severity of pneumonia, outpatient/inpatient ratio, and concomitant illnesses are shown in Table 1. Single causative pathogens were identified in 27 patients (45.8%) and multiple pathogens in 7 (11.9%), but no pathogens were identified in 25 (42.4%) (Fig. 2). The most common pathogen isolated was *S. pneumoniae*, which was isolated in a total of 17 patients (28.8%), followed by *H. influenzae* (10 patients; 16.9%) and *M. pneumoniae* (7 patients; 11.9%). These three micro-organisms were identified as single pathogens in 40.7% of our patient samples and in combination with other pathogens in a further 11.9% (Fig. 2).

Data from microbiological testing undertaken during the study indicated that the azithromycin MIC for strains of *S. pneumoniae* isolated (n=14) was 1 μg/mL for 2 strains, 16 μg/mL for 4 strains, and 128 μg/mL for 1 strain, while 7



S. pneumoniae + *H. influenzae*	3.4% (2)
S. pneumoniae + *M. pneumoniae*	1.7% (1)
H. influenzae + *M. catarrhalis*	1.7% (1)
H. influenzae + *S. aureus*	3.4% (2)
H. influenzae + *C. pneumoniae*	1.7% (1)

Figure 2. **Pathogens identified in individual patients.**

strains demonstrated high-level resistance (MICs >256 μg/mL); all of the latter carried the *erm*B gene, while 5 of the 12 more susceptible strains carried the *mef*A gene (Fig. 3). Azithromycin resistance, based on CLSI criteria (MICs >2 μg/mL), was demonstrated in 85.7% (12/14) of *S. pneumoniae* strains, and the presence of *erm*B genes was found in 50.0% (7/14). In the case of *H. influenzae* (n=8), the azithromycin MIC was 1 μg/mL for 1 strain, 2 μg/mL for 4 strains, and 4 μg/mL for 3 strains (Fig. 4).

Clinical and microbiological responses

Overall, a good clinical response with azithromycin was achieved in 49 patients (83.1%), while 10 (16.9%) had a poor clinical response. In 23 patients in whom it was possible to judge the microbiological response, eradication or presumed eradication of the infecting micro-organism from the sputum was achieved in 78.3%, while 21.7% exhibited persistence.

Among patients in whom either *S. pneumoniae* (n=17) or *H. influenzae* (n=8) were isolated, good clinical responses were achieved in 76.5% and 100%, respectively, while microbiological responses (eradication or presumed eradication) were achieved in 64.3% and 100%, respectively (Fig. 5).

An analysis of the clinical and microbiological response rates in patients in whom *S. pneumoniae* was isolated in relation to the azithromycin MIC (and that of erythromycin and other antibacterials), and the presence of *mef*A or *erm*B genes is shown in Table 2. While there was a tendency for *S. pneumoniae* to persist in those with strains with a high azithromycin MIC carrying the *erm*B gene, 3 of 5 patients in whom bacterial persistence occurred showed good clinical responses (all of whom had MICs >256 μg/mL). Overall, 6 of 7 patients in whom MICs >256 μg/mL and the presence of *erm*B genes were recorded had good clinical responses, while 3 of 6 with intermediate or low MICs (≤16 μg/mL) had poor clinical responses (Fig. 3).

Tolerability

The safety analysis population comprised 78 patients. Adverse events, mainly of a gastrointestinal nature, were recorded in 6 patients (7.7%). They included diarrhea (mild and resolved on the same or following day) in 2, abdominal pain/discomfort (mild and resolved on the same day) in 1, an elevation of γ-glutamyltranspeptidase (GGT) from 46 to 51 U/L in 1, and unspecified events in 2.

Discussion

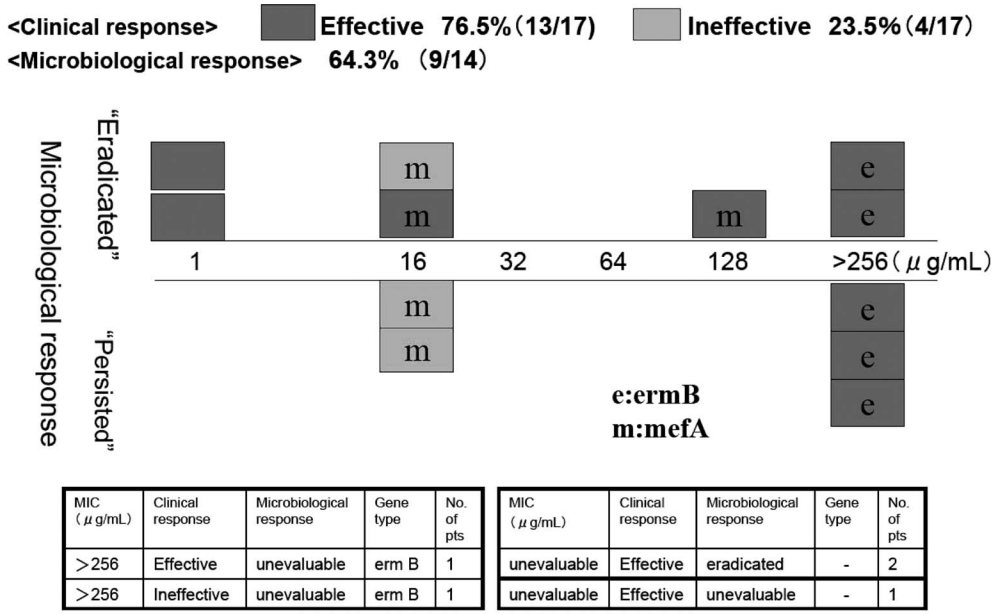
Although this study was an open-label, non-comparative investigation, its principal finding that a 3-day azithromycin regimen is an effective and well tolerated treatment in adults with CAP confirmed those reported in earlier comparative studies evaluating the efficacy and safety of azithromycin

Table 2. Clinical and Microbiological Responses in 17 Patients in Whom *S. pneumoniae* was Isolated (Susceptibility Data were Obtained in 14 Patients but Unobtainable in 3).

Patient No.	Strain	Antibacterial drug susceptibility (MICs; μg/mL)								Gene	Response	
			Other antibacterials:								Microbiological	Clinical
		AZM	EM	CAM	PCG	ABPC	CDTR	GFLX	LVFX			
1	*S. pneumoniae*	1	0.25	0.12	≤0.03	0.06	0.06	0.12	1	-	Eradicated	Good
2	*S. pneumoniae*	1	0.25	0.12	≤0.03	≤0.03	≤0.03	2	0.25	-	Presumed eradicated	Good
3	*S. pneumoniae*	16	8	8	≤0.03	0.06	0.06	1	0.25	*mef*A	Presumed eradicated	Good
4	*S. pneumoniae*	16	8	4	≤0.03	≤0.03	0.06	0.25	2	*mef*A	Eradicated	Poor
5	*S. pneumoniae*	128	16	16	≤0.03	0.06	0.25	2	0.25	*mef*A	Presumed eradicated	Good
6	*S. pneumoniae*	>256	0.25	≤0.03	≤0.03	≤0.03	≤0.03	0.12	0.12	*erm*B	Eradicated	Good
7	*S. pneumoniae*	>256	>64	>64	1	2	0.5	2	0.25	*erm*B	Presumed eradicated	Good
8	*S. pneumoniae*	>256	8	8	0.5	1	0.5	0.5	2	*erm*B	Persisted	Good
9	*S. pneumoniae*	>256	>64	>64	≤0.03	0.06	0.06	2	0.5	*erm*B	Persisted	Good
10	*S. pneumoniae*	>256	>64	>64	1	1	0.25	0.25	2	*erm*B	Persisted	Good
11	*S. pneumoniae*	16	8	8	0.25	0.25	0.25	8	2	*mef*A	Persisted	Poor
12	*S. pneumoniae*	16	>64	>64	≤0.03	0.06	0.12	2	0.5	*mef*A	Persisted	Poor
13	*S. pneumoniae*	>256	>64	>64	0.06	0.06	0.5	1	0.25	*erm*B	Unevaluable	Good
14	*S. pneumoniae*	>256	>64	>64	≤0.03	0.12	0.06	32	2	*erm*B	Unevaluable	Poor
15	*S. pneumoniae*	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]		Eradicated	Good
16	*S. pneumoniae*	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]		Eradicated	Good
17	*S. pneumoniae*	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]		Unevaluable	Good

[a] Susceptibility data not obtainable.

ABPC = ampicillin; **AZM** = azithromycin; **EM** = erythromycin; **CAM** = clarithromycin; **CDTR** = cefditoren; **GFLX** = gatifloxacin; **LVFX** = levofloxacin; **MIC** = minimum inhibitory concentration; **PCG** = penicillin G (benzylpenicillin).



MIC (μg/mL)	Clinical response	Microbiological response	Gene type	No. of pts
>256	Effective	unevaluable	erm B	1
>256	Ineffective	unevaluable	erm B	1

MIC (μg/mL)	Clinical response	Microbiological response	Gene type	No. of pts
unevaluable	Effective	eradicated	-	2
unevaluable	Effective	unevaluable	-	1

Figure 3. Summary of clinical and microbiological responses to azithromycin in subjects with *S. pneumoniae*.

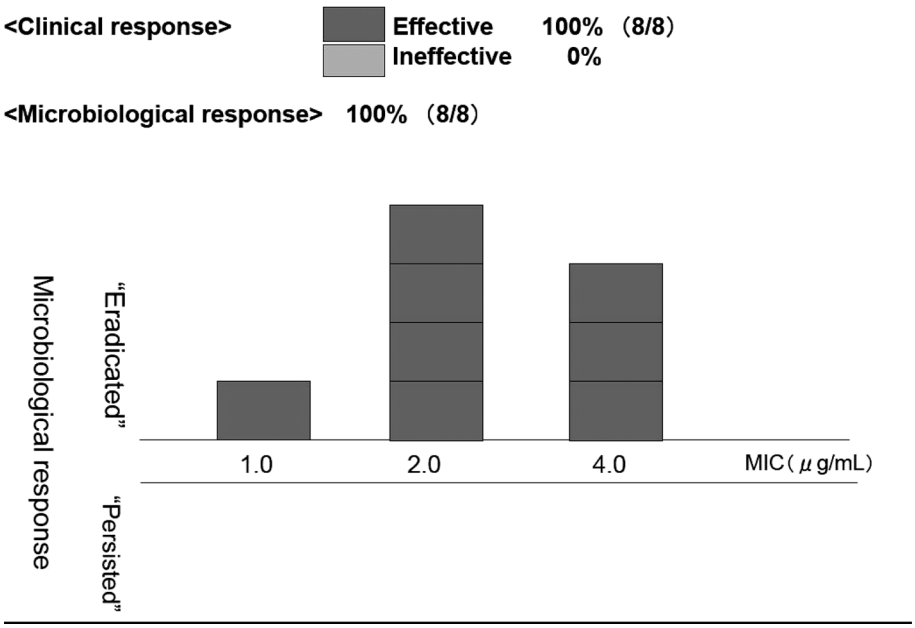


Figure 4. **Summary of clinical and microbiological responses to azithromycin in subjects with *H. influenzae*.**

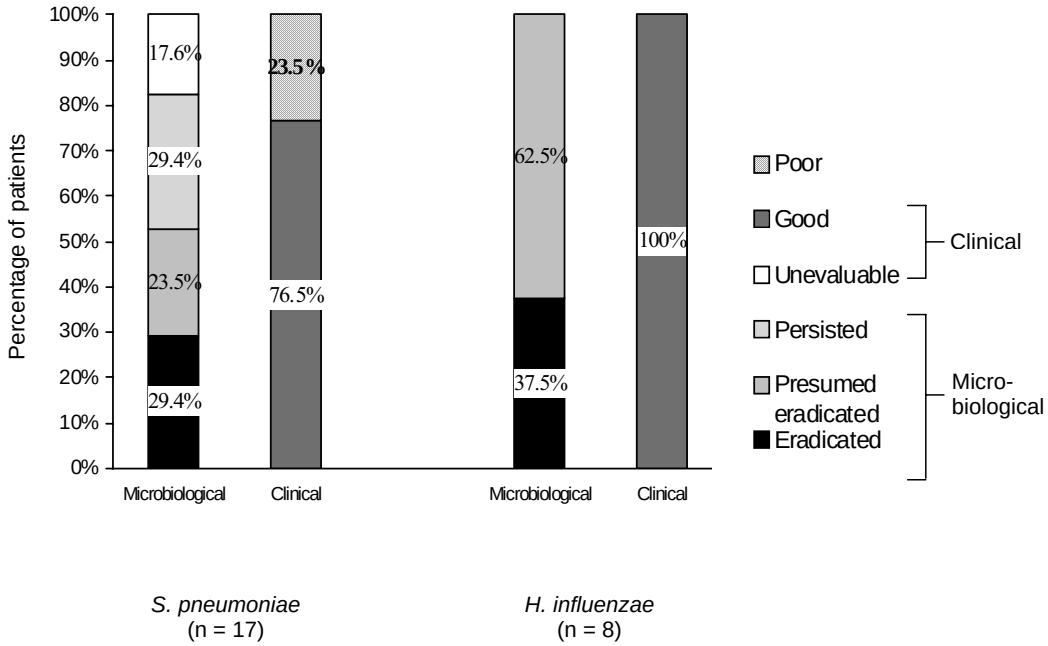


Figure 5. **Clinical and microbiological responses to azithromycin treatment in patients in whom either *S. pneumonia* or *H. influenzae* were isolated (either as single or multiple pathogens).**

monotherapy versus other antimicrobial agents (21-24). In 59 patients with mild or moderately severe CAP in whom sufficient data were available for efficacy analysis, we observed a good clinical response with azithromycin in 49 (83.1%), while 10 (16.9%) had a poor clinical response. No clear association of clinical responsiveness with fever, laboratory data (WBC, CRP), and chest x-rays at first presentation was evident. Although poor responders mostly had a tendency towards improved clinical responses at day 4 or day 8, this was due to outpatients being changed to other antimicrobial agents. The causative micro-organisms isolated in our patients reflected recent studies of the aetiology of CAP in Japan (8, 9), in that the most commonly isolated pathogens were *S. pneumoniae*, *H. influenzae* and *M. pneumoniae* (Fig. 2). A microbiological response to azithromycin treatment (eradication or presumed eradication of the infecting micro-organism from the sputum) was achieved in 18 of 23 patients in whom it was possible to judge the bacteriological effect (78.3%), while 5 (21.7%) exhibited microbiological persistence.

When the clinical and microbiological results were examined in patients in whom strains of *S. pneumoniae* had been

identified (around half of which had azithromycin MICs ≥ 128 μg/mL), the clinical response was judged as good in 76.5%, but bacteriological persistence was evident in 35.7% and eradication or presumed eradication of the infecting micro-organism was recorded in only 64.3% of patients. In comparison, all patients in whom *H. influenzae* was isolated showed good clinical responses, and all exhibited eradication or presumed eradication of the pathogen, reflecting the good activity of azithromycin against this micro-organism (25). Azithromycin has shown greater activity than other macrolides against *H. influenzae*, which may be related to its ability to penetrate the outer bacterial membrane and to more efficiently inhibit 50S ribosomal subunit assembly in *H. influenzae* cells than other macrolides (25-27).

Further analysis of the clinical and microbiological response rates in patients in whom *S. pneumoniae* was isolated indicated that while bacteriological persistence was more likely to occur in those with strains exhibiting high-level resistance (MIC >256 μg/mL) and carrying *erm*B genes, 6 of 7 patients in this category achieved good clinical responses. Conversely, 3 of 6 patients with intermediate or low MICs (≤16 μg/mL) had poor clinical responses. Additional antibiotics were not necessary for even the patients with high-level resistant *S. pneumoniae*. The reccurence of pneumonia was not observed. This finding supports Nuermberger and Bishai's (15) contention that *in vitro* macrolide resistance among strains of *S. pneumoniae* may not be correlated with treatment failure. A possible reason for this may relate to the good tissue penetration of azithromycin such that it may attain sufficiently high drug concentrations to inhibit resistant strains of *S. pneumoniae* in infected tissue (which may be more likely for lower-level, *mef*A-mediated resistance) (15). In this regard, a study of the intrapulmonary pharmacokinetics of azithromycin showed that the drug is extensively concentrated in alveolar macrophages and epithelial lining fluid (28), which suggests that tissue and intracellular concentrations may be more useful for assessing the antibacterial activity of azithromycin than serum concentrations.

Another potential reason for the apparent clinical effectiveness of azithromycin in patients with macrolide-resistant *S. pneumoniae* may relate to the effects of sub-minimum inhibitory concentrations (sub-MICs) on bacterial virulence factors. For example, sub-MICs of azithromycin and clarithromycin have been found to inhibit production of the cholesterol-dependent virulence factor pneumolysin (PLY) by high-level macrolide-resistant *S. pneumoniae* in an experimental murine model (29). As PLY is a multifunctional virulence factor that appears to augment intrapulmonary growth and dissemination during the early pathogenesis of *S. pneumoniae* infection, this mechanism may be a factor in the apparent effectiveness of azithromycin against CAP caused by strains of *S. pneumoniae* exhibiting high-level resistance *in vitro* (29). The reason why the better clinical responses were observed in patients with strains exhibiting high-level resistance (MIC >256 μg/mL) is unclear. *S. pneumoniae* carrying *mef*A (lower-level resistant) may diminish the immunological effect of azithromycin.

Azithromycin has been proved to be well tolerated in patients with CAP, and the majority of adverse events, which are mainly gastrointestinal in nature, are of mild-to-moderate severity (18, 30). In the present study, the only specific adverse events noted were mild diarrhea or abdominal pain/discomfort in 3 patients (3.8%) and a mild elevation of GGT in 1 (1.3%).

Conclusions

A 3-day course of azithromycin is an effective first-line treatment for adults with mild to moderately severe CAP, and one that provides advantages for patients in terms of convenience, encouragement of medication compliance, and clearance of symptoms. In this study, 83.1% of adult patients showed a good clinical response with azithromycin monotherapy (500 mg once daily for 3 days, orally), and 78.3% of those with adequate microbiological data achieved a microbiological response. In those in whom strains of *S. pneumoniae* were identified (about half of which showed *in vitro* macrolide resistance), clinical and bacteriological responses were lower (76.5% and 64.3%, respectively), but 6 of 7 patients with high-level resistant strains (MICs >256 μg/mL) and carrying *erm*B genes had good clinical responses to azithromycin. Although the JRS currently advocates macrolides as first-line therapy for mild to moderately severe CAP apparently caused by atypical pathogens (1), these findings suggest that empirical therapy with azithromycin may also be appropriate in situations where rapid urine antigen assays have failed to provide an indication of the causative pathogen but where a macrolide-resistant strain of *S. pneumoniae* could be present. However, further investigation is needed to define the efficacy of azithromyicn against MRSP.

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