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Original Article

An open, randomized, comparative study of clarithromycin and erythromycin in the treatment of children with community-acquired pneumonia

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Background and Purpose: This study aimed to evaluate the efficacy and safety of clarithromycin and erythromycin in the treatment of community-acquired pneumonia in children.

Methods: Children with community-acquired pneumonia were randomly assigned to receive 10-day regimens of either clarithromycin 15 mg/kg/day, twice a day, or erythromycin 30-50 mg/kg/day, four times daily.

Results: A total of 97 children entered this study, including 26 with *Mycoplasma pneumoniae* infection, 15 with *Chlamydia pneumoniae* infection, and 6 with mixed mycoplasma and chlamydia infections. Fifty and 47 children received clarithromycin and erythromycin treatment, respectively. Three children withdrew from the study because the identified pathogens were resistant to the study drugs. All 47 children with mycoplasma or chlamydia infection were cured clinically. Delayed defervescence, defined as a fever lasting for more than 72 h after treatment, was observed in 4 of 22 clarithromycin-treated children (18%) and in 3 of 15 erythromycin-treated children (20%) [$p>0.05$]. Gastrointestinal side effects, including vomiting, abdominal pain and diarrhea, were observed in 3 of 50 children (6%) receiving clarithromycin and in 11 of 49 children (22%) receiving erythromycin ($p=0.039$). Excluding children with abnormal pretreatment liver function, abnormal liver function after treatment was observed in only one child, treated with erythromycin. Post-treatment eosinophil and platelet counts were significantly elevated after treatment in both groups.

Conclusions: Clarithromycin showed efficacy equivalent to erythromycin for the treatment of mycoplasma or chlamydia pneumonia in children. However, the tolerability of clarithromycin was superior to that of erythromycin.

Key words: *Chlamydia pneumoniae*; Community-acquired infections; Macrolides; *Mycoplasma pneumoniae*; Pneumonia; Randomized controlled trial

Introduction

Clarithromycin is a new macrolide antibiotic with in vitro activity similar to erythromycin [1-3]. Clarithromycin is effective against a wide range of microorganisms, including Gram-positive cocci, *Haemophilus influenzae*, *Moraxella catarrhalis*, mycoplasma, chlamydia, selected mycobacteria, *Legionella* spp. and protozoan organisms [4]. Pharmacokinetic studies showed that clarithromycin, in combination with its active 14-hydroxy metabolite, has a longer half-life and higher plasma level than erythromycin, thus allowing twice-a-day dosing [5].

Clarithromycin is concentrated in cells and tissues, including tonsil, nasal mucosa, middle ear fluid and lung. Higher concentrations of drug are achieved in lung tissue than in concurrent samples of plasma [4,6]. Clarithromycin appears to be safe and generally very well tolerated. In comparative clinical trials, overall adverse event rates associated with clarithromycin were similar to those with amoxicillin, penicillin, cefaclor and cefadroxil [4]. Clarithromycin-related gastrointestinal side effects were shown to occur at a lower frequency than those associated with erythromycin [7].

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Clinical efficacy has been demonstrated in randomized trials of children with acute otitis media, streptococcal pharyngitis, infections of skin and skin structures, and community-acquired pneumonia [4,8, 9]. It was shown that *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* may be detected in one-half of ambulatory children with radiographically proven pneumonia [8]. Therefore, macrolide antibiotics should be considered the empiric oral antibiotic choice for community-acquired pneumonia in children without toxic signs. Because the experience of using clarithromycin in children with pneumonia is still limited, the present study was conducted with the aim of comparing the efficacy and safety of clarithromycin and erythromycin in the treatment of community-acquired pneumonia in children.

Methods

Patients

Eligible children were those aged below 15 years with community-acquired pneumonia confirmed by chest X-ray or by the presence of crackles on physical examination. Children with known sensitivity to macrolide antibiotics were excluded from the study. Informed consents were obtained from parents of enrolled children.

Treatment schedule

Enrolled children were randomly assigned to receive either clarithromycin or erythromycin. Clarithromycin suspension (Abbott Laboratories Taiwan Limited, Taipei, Taiwan) was used for 10 days at a dose of 15 mg/kg/day given twice daily. Erythromycin ethylsuccinate suspension (Abbott Laboratories) was used for 10 days at a dose of 30-50 mg/kg/day given 4 times daily.

Clinical assessments

Full medical history was recorded at enrollment. Peak body temperature and duration of fever before and after treatment were recorded to compare clinical efficacy between the two treatment groups. The presence of fever was defined as a rectal temperature or tympanic temperature above 38.0°C. Delayed defervescence was defined as a persistent fever lasting for more than 72 h after the start of therapy. All adverse reactions that were possibly related to study drugs were monitored and recorded. If the adverse reaction was not tolerable, the other comparative agent was used instead.

Laboratory assessments

Appropriate specimens were sent for culture and serological tests. Virus culture of throat swab and antibodies against *M. pneumoniae* and *C. pneumoniae* were examined. Laboratory tests, including hemoglobin, leukocyte count with differential, platelet count, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), blood urea nitrogen, creatinine and urinalysis, were performed before and after treatment. C-reactive protein was examined before treatment. Cerebrospinal fluid analysis was done for patients with meningoencephalitis.

M. pneumoniae antibody was determined by complement fixation test. Immunoglobulin M (IgM) antibody to *M. pneumoniae* was tested by an IgM-capture enzyme-linked immunosorbent assay (IgM-Mp test; Diatech Diagnostica Ltd., Ness Ziona, Israel). Microimmunofluorescence assays were used to determine the presence of IgM, immunoglobulin A (IgA), and immunoglobulin G (IgG) antibody to *C. pneumoniae* (Chlamydia IgM SeroFIA™, Chlamydia IgA SeroFIA™ and Chlamydia IgG SeroFIA™; Savyon Diagnostic Ltd, Ashdod, Israel). Antigen of *C. pneumoniae* was detected by a direct immunofluorescence test (*C. pneumoniae* fluorescein isothiocyanate research reagent; Dako Diagnostics Ltd., Cambridgeshire, UK).

Diagnostic criteria

Diagnosis of bacterial infections was confirmed by appropriate cultures. Diagnosis of *M. pneumoniae* infection was made when IgM antibody was positive and/or complement fixation antibodies in paired sera showed at least a four-fold rise. According to the manual of *C. pneumoniae* detection kits, the diagnosis of recent *C. pneumoniae* infection was based on a positive result of *C. pneumoniae* antigen detection, the presence of IgM or IgA antibody against *C. pneumoniae*, or a four-fold rise of IgG antibody against *C. pneumoniae*.

Statistical analysis

For the analysis of treatment efficacy, only children with a confirmed diagnosis of *M. pneumoniae* or *C. pneumoniae* infection were included. Data of all enrolled children were included in analyses of biochemical profiles and drug-associated adverse reactions.

Because most data in this study were not normally distributed, non-parametric tests were used to compare the differences between groups. However, numerical data were expressed as mean ± standard deviation. Mann-Whitney test was used to examine the differences

between the two groups of independent numerical data. For paired numerical data, Wilcoxon signed rank test was used. Differences in frequency between groups were examined by chi-squared test with Yates' correction.

Results

Enrolled children

A total of 97 children, including 58 boys and 39 girls, were enrolled. Seventy six of them were hospitalized during treatment and 21 were treated as outpatients. Their ages ranged between 0.5 and 14.5 years old (median, 4.9 years). In 17 patients, the illness was complicated by meningoencephalitis. The etiology was identified in 55 children, and included *M. pneumoniae* (26 cases), *C. pneumoniae* (15 cases), both mycoplasma and chlamydia (6 cases), *Streptococcus pneumoniae* (1 case), group A *Streptococcus* (1 case), *Streptococcus mitis* (1 case), respiratory syncytial virus (1 case), influenza A (2 cases), and influenza B (2 cases). The etiology of the remaining 42 infections was not known. Analysis of therapeutic efficacy was limited to 47 children with either mycoplasma or chlamydia infections.

At enrollment, 48 and 49 children were randomly assigned to receive clarithromycin and erythromycin, respectively. Two children had intolerable abdominal pain after taking a few doses of erythromycin. After changing their antibiotic treatment to clarithromycin, drug-related gastrointestinal upset did not recur. Therefore, the total number of children in the clarithromycin and erythromycin treatment groups at completion of the study was 50 and 47, respectively. Among 47 children with mycoplasma or chlamydia infection, 25 children received clarithromycin and 22 children received erythromycin therapy. For analysis of drug-related adverse reactions, the number of children in the erythromycin group was 49 (including the 2 children with intolerable adverse reactions). Basic features and identified etiologies of infections were similar between the two groups (Table 1).

Three children discontinued testing drugs, clarithromycin in two and erythromycin in one, because of a grave clinical condition and a culture result of resistant bacteria. One of them had lobar pneumonia caused by *S. pneumoniae*, one had *S. mitis* empyema, and one had group A *Streptococcus* bacteremia. Three children with pneumonia of unknown etiology were lost to follow-up after treatment, including one on clarithromycin treatment and two on erythromycin treatment.

Clinical manifestations

Among all enrolled children, the most common clinical manifestations were fever (89%), cough (56%), rhinorrhea (45%), vomiting (37%), tachypnea (24%), diarrhea (21%), and crackles (91%) and wheezing (38%) on chest auscultation. Seizures were observed in 5 children (10%) receiving clarithromycin treatment and in 6 children (13%) receiving erythromycin treatment.

Table 1. Basic features and diagnosis of 97 children with community-acquired pneumonia

Variable	Treatment (number of cases)		Total (number of cases)
	Clarithromycin	Erythromycin	
Total	50	47	97
Male:female gender	30:20	28:19	58:39
Inpatient:outpatient	37:13	39:14	76:27
Diagnosis			
Pneumonia	44	36	80
Pneumonia with meningoencephalitis	6	11	17
Etiology			
Mycoplasma	14	12	26
Mycoplasma + chlamydia	2	4	6
Chlamydia	9	6	15
Respiratory syncytial virus	1	0	1
Influenza A	2	0	2
Influenza B	1	1	2
Streptococcus mitis	1	0	1
Group A *Streptococcus*	1	0	1
Streptococcus pneumoniae	0	1	1
Unknown	19	23	42

Observed frequencies of most clinical manifestations were similar between the two treatment groups, except that hepatomegaly was noted at a slightly higher frequency in the erythromycin group than in the clarithromycin group, with a borderline statistical significance (17% vs 4%, p=0.076). When only the 47 children with mycoplasma or chlamydia infection were analyzed, the frequency of all manifestations did not differ significantly between the two treatment groups.

Laboratory findings

Anemia and leukocytosis with a neutrophil predominance were frequently observed. All laboratory findings before treatment were similar between the two treatment groups, including hemoglobin, leukocyte count and differential, platelet, bilirubin, AST, ALT, ALP, blood urea nitrogen, creatinine, urinalysis, C-reactive protein, and cerebrospinal fluid findings. This was also true for those with confirmed mycoplasma or chlamydia infections.

Most laboratory tests after treatment were not significantly different between the two treatment groups. Five of 27 children (19%) treated with erythromycin had an AST level higher than 55 U/L after treatment. This rate was significantly higher than that of children treated with clarithromycin (0/34; p=0.032). Three of 5 children with abnormal post-treatment AST level had an AST level >55 U/L before treatment.

Abnormal post-treatment ALT level was also more frequently observed in the erythromycin group (5/27, 19%) than in the clarithromycin group (2/34, 6%), but the difference was not statistically significant. Two children had conjugated hyperbilirubinemia after erythromycin treatment. Excluding 10 children with abnormal serum levels of bilirubin or ALT before treatment, post-treatment liver function abnormalities were observed in only 1 erythromycin-treated child with *C. pneumoniae* infection and proteinuria.

By using Wilcoxon signed rank test to compare paired laboratory data before and after treatment, normalizing laboratory findings with a statistical significance were noted for hemoglobin, leukocyte count, segmented neutrophil proportion, and lymphocyte proportion in both treatment groups. Significantly decreased levels of total bilirubin, direct bilirubin, and AST were also noted in the clarithromycin group. Liver function profiles, including ALP, were not significantly affected after erythromycin treatment. Post-treatment eosinophil counts and platelet counts tended to be elevated after treatment in both groups (Table 2 and Table 3).

Chest X-ray findings in 95 enrolled children included interstitial infiltration (55%), patch (23%), consolidation (21%), and pleural effusion (7%). Patterns of chest X-ray findings were similar between the two treatment groups, as assessed either by analyzing all enrolled children or by analyzing those with confirmed mycoplasma or chlamydia infections.

Treatment outcomes

Among 47 children with mycoplasma or chlamydia infection, the two treatment groups were comparable in the duration of fever before treatment. Peak body

Table 2. Laboratory findings in children treated with clarithromycin

Variable (mean ± SD)	No. of evaluable patients	Before treatment	After treatment	p^a
Hemoglobin (g/dL)	36	11.4 ± 1.2	12.0 ± 1.1	0.002
Leukocyte count (/mm^3)	36	12,703 ± 6733	7939 ±2488	<0.001
Leukocyte differential				
Band neutrophil (%)	33	0.6 ± 1.5	0.7 ± 1.8	NS
Segmented neutrophil (%)	33	70.6 ± 20.4	46.7 ± 15.3	<0.001
Lymphocyte (%)	33	19.8 ± 17.7	39.7 ± 17.1	<0.001
Eosinophil count (/mm^3)	33	79 ± 165	237 ± 275	<0.001
Platelet count (× 10^3/mm^3)	34	301 ± 146	488 ± 179	<0.001
Total bilirubin (mg/dL)	31	0.6 ± 0.4	0.4 ± 0.1	0.004
Direct bilirubin (mg/dL)	22	0.3 ± 0.2	0.2 ± 0.1	0.012
Aspartate aminotransferase (U/L)	34	44.6 ± 66.9	28.2 ± 7.3	0.007
Alanine aminotransferase (U/L)	25	31.3 ± 51.3	18.6 ± 16.5	NS
Alkaline phosphatase (U/L)	22	385 ± 336	370 ± 156	NS
Blood urea nitrogen (mg/dL)	34	10.4 ± 4.0	12.1 ± 3.8	NS
Creatinine (mg/dL)	34	0.6 ± 0.2	0.6 ± 0.1	NS

Abbreviations: SD = standard deviation; NS = not significant (p>0.05)

[a]Wilcoxon signed rank test.

Table 3. Laboratory findings in children treated with erythromycin

Variable (mean ± SD)	No. of evaluable patients	Before treatment	After treatment	p^a
Hemoglobin (g/dL)	29	11.3 ± 2.1	12.3 ± 1.5	<0.001
Leukocyte count (/mm^3)	29	11,849 ± 5429	8870 ± 3016	0.013
Leukocyte differential				
Band neutrophil (%)	28	2.6 ± 11.9	1.0 ± 3.2	NS
Segmented neutrophil (%)	28	63.8 ± 20.9	50.8 ± 12.4	0.007
Lymphocyte (%)	28	25.6 ± 15.3	38.9 ± 11.7	0.001
Eosinophil count (/mm^3)	28	142 ± 255	220 ± 184	0.014
Platelet count (× 10^3/mm^3)	28	309 ± 129	396 ± 175	0.056
Total bilirubin (mg/dL)	21	1.3 ± 2.1	1.4 ± 3.8	NS
Direct bilirubin (mg/dL)	10	1.0 ± 2.2	1.7 ± 4.8	NS
Aspartate aminotransferase (U/L)	26	59.5 ± 64.6	46.5 ± 39.5	NS
Alanine aminotransferase (U/L)	16	25.1 ± 16.5	25.4 ± 22.3	NS
Alkaline phosphatase (U/L)	12	393 ± 249	380 ± 81	NS
Blood urea nitrogen (mg/dL)	25	10.4 ± 5.1	12.3 ± 3.7	NS
Creatinine (mg/dL)	25	0.5 ± 0.1	0.6 ± 0.2	NS

Abbreviations: SD = standard deviation; NS = not significant (p>0.05)

[a]Wilcoxon signed rank test.

temperature was on average slightly higher in the clarithromycin group than in the erythromycin group (p=0.037). Duration of fever after treatment was not significantly different between the two groups (Table 4).

Among children with a known duration of fever after treatment, delayed defervescence, as defined by a fever lasting for more than 72 h after treatment, was observed in 4 of 22 clarithromycin-treated children (18%) and in 3 of 15 erythromycin-treated children (20%) [p>0.05; Table 4]. Three of them were infected by *M. pneumoniae* and four were infected by *C. pneumoniae*. All of the 7 children with delayed defervescence after treatment had either a severe pneumonic change (consolidation and/or pleural effusion in 4 children) or some extrapulmonary manifestations (encephalitis in 2 children and hepatitis in 1 child).

Adverse reactions

Gastrointestinal side effects, including vomiting, abdominal pain and diarrhea, were observed in 3 of 50 (6%) children receiving clarithromycin and in 11 of 49 (22%) children receiving erythromycin. The incidence of the overall gastrointestinal adverse reactions was significantly higher in those receiving erythromycin (p=0.032). Two children with erythromycin treatment could not tolerate the accompanying abdominal pain. Their antibiotics were changed to clarithromycin and the adverse reaction did not recur.

Discussion

The macrolide erythromycin is considered to be the drug of choice for the treatment of mycoplasma pneumonia

Table 4. Fever in 47 children with mycoplasma or chlamydia infection

	Treatment				p^a
	Clarithromycin		Erythromycin		
		No. of evaluable patients		No. of evaluable patients	
Peak body temperature (°C) [mean ± SD; range]	39.6 ± 1.0 (37.0-2.0)	23	39.1 ± 0.9 (37.0- 40.7)	17	0.037
Duration of fever before treatment (days; mean ± SD) [range]	4.8 ± 3.6 (0.5-14.0)	24	5.8 ± 4.4 (0.5-14.0)	18	NS
Duration of fever after treatment (days; mean ± SD) [range]	2.5 ± 2.6 (0.5- 12.0)	22	2.4 ± 2.4 (0.5-10.0)	15	NS
Fever >3 days after treatment (no.) [%]	4 (18)	22	3 (20)	15	NS

Abbreviations: SD = standard deviation; NS = not significant (p>0.05)

[a]Mann-Whitney test or chi-squared test with Yates' correction.

and chlamydia pneumonia, because of its good in vitro activity and its high intracellular concentration [10]. One study evaluating community-acquired pneumonia in 260 children in the United States showed that *M. pneumoniae* and *C. pneumoniae* accounted for 27% and 28% of these infections, respectively [8]. The present study showed a similar finding: that 49 of 107 children (46%) with community-acquired pneumonia had either *M. pneumoniae* or *C. pneumoniae* infection. A laboratory diagnosis of mycoplasma or chlamydia infection depends on serological tests that are time-consuming. It is not practical to withhold antibiotic treatment until a bacteriological diagnosis has been confirmed. Since about one-half of children with community-acquired pneumonia were infected by mycoplasma or chlamydia, macrolide antibiotics should be considered the empiric antibiotic choice for these infections. However, standard erythromycin therapy is to be administered for 10 to 14 days with 4 doses daily. Such a regimen is inconvenient, especially for pediatric patients.

Because of the limitation of laboratory diagnosis, clinical efficacy of antibiotic treatment for mycoplasma and chlamydia pneumonia cannot be evaluated by bacteriological eradication. Previous studies have demonstrated that the clinical efficacy of antibiotic treatment for such infections can be reflected by a shortened duration of fever [11,12]. In the present study, all except seven children with mycoplasma or chlamydia infection had a resolution of fever within three days after the start of antibiotic therapy, and the rate of defervescence was not significantly different between the two treatment groups.

It has been shown that macrolide resistance of *M. pneumoniae* and *C. pneumoniae* is extremely rare [1,2,13,14], and such resistance has not affected the clinical course of the illness [15,16]. On the other hand, it is noteworthy that all seven children with delayed defervescence in the present study had either a severe pneumonic change or some extrapulmonary manifestations. It was reported that patients with mycoplasma pneumonia tended to run a severe and prolonged course if pleural effusion was present [17]. High serum levels of interleukin-6 and C-reactive protein were shown to correlate with a longer duration of fever in patients with community-acquired pneumonia [18]. Therefore, the lack of immediate clinical response may result from some disease-associated factors rather than a true antibiotic resistance. It may be concluded that twice-a-day dosing of clarithromycin was equally effective as erythromycin in the treatment of mycoplasma pneumonia and chlamydia pneumonia.

As shown by this study, clarithromycin is not only more convenient to administer, but also associated with fewer side effects. Gastrointestinal disturbance is a well-known adverse reaction of erythromycin, with an incidence between 10% and 20% [19]. The present study showed a similar rate of 22%. By comparison, such adverse reactions occurred in only 6% of children receiving clarithromycin, which was also similar to previous reports [7,20,21]. In addition, two children who could not tolerate erythromycin did not experience similar gastrointestinal disturbance after changing to clarithromycin.

Early investigations demonstrated that erythromycin increased gastrointestinal motility, and more recent studies suggest that it beneficially binds to and stimulates the receptor for the gastrointestinal peptide motilin [22]. Gastrointestinal side effects induced by erythromycin are sometimes too severe to be tolerated. This may not cause therapeutic difficulties in adult patients because alternative agents are available, such as tetracyclines and some fluoroquinolones that are also active against mycoplasma and chlamydia. However, both tetracyclines and fluoroquinolones are not recommended for use in children, because of their potential to damage developing bones, cartilage and teeth. In the past, when only erythromycin was available, there was no appropriate alternative drug for children with atypical pneumonia. With a low incidence of adverse reactions, clarithromycin is thus a solution to this problem.

It is known that macrolide antibiotics, especially erythromycin estolate, are associated with hepatic toxicity [23-25]. However, the estimated risk of significant cholestatic jaundice associated with erythromycin is only about 3.6 per 100,000 users [26]. In the present study, possible drug-related liver dysfunction was observed in only one child treated with erythromycin. Interpretation of such data is complicated by the fact that the infectious agent per se may cause hepatitis, including *M. pneumoniae*, *C. pneumoniae*, and others [27-29]. In fact, analyses of paired data suggest that the overall liver function profiles were improving, rather than deteriorating, after treatment. Therefore, neither of the tested drugs in this study showed evidence of hepatoxicity.

Analysis of paired data before and after treatment showed post-treatment eosinophil count to be significant elevated in both groups. This finding may be of

minor clinical significance, because most children still had a normal eosinophil count after treatment. The rate of thrombocytosis increased from 19-24% before treatment to 50-62% after treatment. Post-treatment elevation of platelet counts was also demonstrated by analysis of paired pre- and post-treatment data. It is known that a severe inflammatory process may lead to thrombocytosis that may be related to the effect of interleukin-6 [30,31]. Mycoplasma pneumonia has also been shown to be associated with a high rate of thrombocytosis [32]. Therefore, thrombocytosis was probably induced by the infection itself rather than the tested drugs.

Azithromycin is another macrolide derivative introduced in recent years. According to the literature, clarithromycin and azithromycin have similar therapeutic efficacy and a similar incidence of adverse effects in the treatment of common respiratory tract infections. However, clarithromycin is more effective against non-tuberculous mycobacteria infection and *Helicobacter pylori* infection [33,34]. In such infections, the therapeutic role of clarithromycin cannot be substituted by azithromycin or other macrolide antibiotics.

In conclusion, twice-a-day dosing of clarithromycin showed efficacy equivalent to erythromycin in the treatment of mycoplasma and chlamydia pneumonia in children. However, clarithromycin was associated with fewer gastrointestinal side effects than the alternative agent. The better tolerability and more convenient dosage regimen of clarithromycin indicate that it is superior to erythromycin in this clinical setting.

References

1. Roblin PM, Montalban G, Hammerschlag MR. Susceptibilities to clarithromycin and erythromycin of isolates of *Chlamydia pneumoniae* from children with pneumonia. Antimicrob Agents Chemother. 1994;38:1588-9.
2. Welsh L, Gaydos C, Quinn TC. In vitro activities of azithromycin, clarithromycin, erythromycin, and tetracycline against 13 strains of *Chlamydia pneumoniae*. Antimicrob Agents Chemother. 1996;40:212-4.
3. Hardy RD, Rios AM, Chavez-Bueno S, Jafri HS, Hatfield J, Rogers BB, et al. Antimicrobial and immunologic activities of clarithromycin in a murine model of *Mycoplasma pneumoniae*-induced pneumonia. Antimicrob Agents Chemother. 2003;47:1614-20.
4. Klein JO. Clarithromycin: where do we go from here? Pediatr Infect Dis J. 1993;12(12 Suppl 3):S148-51.
5. Hardy DJ, Swanson RN, Rode RA, Marsh K, Shipkowitz NL, Clement JJ. Enhancement of the in vitro and in vivo activities of clarithromycin against *Haemophilus influenzae* by 14-hydroxy-clarithromycin, its major metabolite in humans. Antimicrob Agents Chemother. 1990;34:1407-13.
6. Neu HC. The development of macrolides: clarithromycin in perspective. J Antimicrob Chemother. 1991;27(Suppl A):1-9.
7. Chien SM, Pichotta P, Siepman N, Chan CK. Treatment of community-acquired pneumonia. A multicenter, double-blind, randomized study comparing clarithromycin with erythromycin. Canada-Sweden Clarithromycin-Pneumonia Study Group. Chest. 1993;103:697-701.
8. Block S, Hedrick J, Hammerschlag MR, Cassell GH, Craft JC. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in pediatric community-acquired pneumonia: comparative efficacy and safety of clarithromycin vs. erythromycin ethylsuccinate. Pediatr Infect Dis J. 1995;14:471-7.
9. Still JG, Hubbard WC, Poole JM, Sheaffer CI, Chartrand S, Jacobs R. Comparison of clarithromycin and penicillin VK suspensions in the treatment of children with streptococcal pharyngitis and review of currently available alternative antibiotic therapies. Pediatr Infect Dis J. 1993;12(12 Suppl 3):S134-41.
10. Modai J. The clinical use of macrolides. J Antimicrob Chemother. 1988;22(Suppl B):145-53.
11. Kingston JR, Chanock RM, Mufson MA, Helman LP, James WD, Fox HH, et al. Eaton agent pneumonia. JAMA. 1961;176:118-23.
12. Sterner G, Fransén H, Tunevall G, Svedmyr A. A comparative trial of cephaloridine and erythromycin in hospitalized pneumonic patients. Postgrad Med J. 1967;43:53-4.
13. Cassell GH, Waites KB, Pate MS, Canupp KC, Duffy LB. Comparative susceptibility of *Mycoplasma pneumoniae* to erythromycin, ciprofloxacin, and lomefloxacin. Diagn Microbiol Infect Dis. 1989;12:433-5.
14. Kuo CC, Jackson LA, Lee A, Grayston JT. In vitro activities of azithromycin, clarithromycin, and other antibiotics against *Chlamydia pneumoniae*. Antimicrob Agents Chemother. 1996;40:2669-70.
15. Niitu Y, Hasegawa S, Suetake T, Kubota H, Komatsu S, Horikawa M. Resistance of *Mycoplasma pneumoniae* to erythromycin and other antibiotics. J Pediatr. 1970;76: 438-43.
16. Stopler T, Gerichter CB, Branski D. Antibiotic-resistant mutants of *Mycoplasma pneumoniae*. Isr J Med Sci. 1980; 16:169-73.
17. Nagayama Y, Sakurai N, Yamamoto K. Clinical observations of children with pleuropneumonia due to *Mycoplasma pneumoniae*. Pediatr Pulmonol. 1990;8:182-7.
18. Ortqvist A, Hedlund J, Wretlind B, Carlström A, Kalin M.

Diagnostic and prognostic value of interleukin-6 and C-reactive protein in community-acquired pneumonia. Scand J Infect Dis. 1995;27:457-62.
19. Periti P, Mazzei T, Mini E, Novelli A. Adverse effects of macrolide antibacterials. Drug Saf. 1993;9:346-64.
20. Craft JC, Siepman N. Overview of the safety profile of clarithromycin suspension in pediatric patients. Pediatr Infect Dis J. 1993;12(12 Suppl 3):S142-7.
21. Piscitelli SC, Danziger LH, Rodvold KA. Clarithromycin and azithromycin: new macrolide antibiotics. Clin Pharm. 1992;11:137-52.
22. Weber FH Jr, Richards RD, McCallum RW. Erythromycin: a motilin agonist and gastrointestinal prokinetic agent. Am J Gastroenterol. 1993;88:485-90.
23. Carson JL, Strom BL, Duff A, Gupta A, Shaw M, Lundin FE, et al. Acute liver disease associated with erythromycins, sulfonamides, and tetracyclines. Ann Intern Med. 1993;119: 576-83.
24. Wilson WR, Cockerill FR 3rd. Tetracyclines, chloramphenicol, erythromycin, and clindamycin. Mayo Clin Proc. 1983;58:92-8.
25. Brown BA, Wallace RJ Jr, Griffith DE, Girard W. Clarithromycin-induced hepatotoxicity. Clin Infect Dis. 1995;20:1073-4.
26. Derby LE, Jick H, Henry DA, Dean AD. Erythromycin-associated cholestatic hepatitis. Med J Aust. 1993;158: 600-2.
27. Arav-Boger R, Assia A, Spirer Z, Bujanover Y, Reif S. Cholestatic hepatitis as a main manifestation of *Mycoplasma pneumoniae* infection. J Pediatr Gastroenterol Nutr. 1995;21:459-60.
28. Sundelöf B, Gnarpe H, Gnarpe J. An unusual manifestation of *Chlamydia pneumoniae* infection: meningitis, hepatitis, iritis and atypical erythema nodosum. Scand J Infect Dis. 1993;25:259-61.
29. Ali NJ, Sillis M, Andrews BE, Jenkins PF, Harrison BD. The clinical spectrum and diagnosis of *Mycoplasma pneumoniae* infection. Q J Med. 1986;58:241-51.
30. Tefferi A, Ho TC, Ahmann GJ, Katzmann JA, Greipp PR. Plasma interleukin-6 and C-reactive protein levels in reactive versus clonal thrombocytosis. Am J Med. 1994; 97:374-8.
31. Gangarossa S, Romano V, Munda SE, Sciotto A, Schilirò G. Low serum levels of interleukin-6 in children with post-infective acute thrombocytopenic purpura. Eur J Hematol. 1995;55:117-20.
32. Marrie TJ. *Mycoplasma pneumoniae* pneumonia requiring hospitalization, with emphasis on infection in the elderly. Arch Intern Med. 1993;153:488-94.
33. Markham A, McTavish D. Clarithromycin and omeprazole as *Helicobacter pylori* eradication therapy in patients with *H. pylori*-associated gastric disorders. Drugs. 1996;51: 161-78.
34. Barradell LB, Plosker GL, McTavish D. Clarithromycin. A review of its pharmacological properties and therapeutic use in *Mycobacterium avium-intracellulare* complex infection in patients with acquired immune deficiency syndrome. Drugs. 1993;46:289-312.