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Activity of Quinolones Against *Chlamydia pneumoniae*

Margaret R. Hammerschlag

Division of Infectious Diseases, Department of Pediatrics, SUNY Health Science Center at Brooklyn, Brooklyn, New York, USA

Abstract

Quinolones are currently being used as empirical therapy for the treatment of community-acquired pneumonia and other respiratory infections as they cover a broad range of conventional bacterial and 'atypical' pathogens, including *Chlamydia pneumoniae. C. pneumoniae* has been associated with 10 to 20% of community-acquired pneumonia in adults and recently has been implicated as being associated with several nonrespiratory conditions, including atherosclerosis. However, data on the treatment of even respiratory infection due to *C. pneumoniae* are limited. Although currently available quinolones have good activity against *C. pneumoniae in vitro*, all published treatment studies have relied on serological diagnosis, thus microbiological efficacy has not been assessed. Anecdotal experience suggests that *in vitro* activity may not always correlate with efficacy *in vivo*.

Chlamydia pneumoniae, also known as TWAR, was first described as a respiratory tract pathogen by Grayston and colleagues in 1986.[1] The genus Chlamydiae is a group of obligate intracellular parasites that have a unique developmental cycle with morphologically distinct infectious and reproductive forms. All members of the genus have a Gram-negative envelope without peptidoglycan, share a genus-specific lipopolysaccharide (LPS) antigen, and utilise host ATP for the synthesis of chlamydial protein. The genus now contains four species, *Chlamydia psittaci, C. trachomatis, C. pneumoniae* and *C. pecorum*.

C. pneumoniae appears to be a primary human pathogen.[2] Attempts to identify zoonotic reservoirs have been unsuccessful. Mode of transmission remains uncertain but is probably via infected respiratory secretions. Serological surveys have documented a rising prevalence of antibody to *C. pneumoniae* with increasing age from 10% for children 5 to 10 years of age, reaching 30 to 45% by adolescence and often exceeding 80% in the elderly.[2] The proportion of community-acquired pneumonia (CAP) associated with *C. pneumoniae* infection ranges from 6 to 22%, varying with geographic location, age group examined and diagnostic methods used.[3-10] Most of these studies were based on serology alone. *C. pneumoniae* has also been associated with other respiratory infections, including acute exacerbations of chronic bronchitis, otitis media, sinusitis and reactive airway disease.[11-13] Although initial studies suggested that infection with *C. pneumoniae* was uncommon in young children, subsequent studies utilising culture methods, found the prevalence to be similar to that observed in adults.[9,10] Persistent nasopharyngeal infection with *C. pneumoniae* following acute respiratory infection has been documented in adults for periods of up to several years.[14,15]

Recently, *C. pneumoniae* has been implicated as being associated with disseminated disease outside the respiratory tract, notably atherosclerosis.[16] Although the organism has been identified in atheromatous tissue, causality has not been directly established. Interpretation of many studies is made more difficult by the lack of standardised serological and nonculture methods for the detection of the organism. These problems also impact on efforts to study treatment of *C. pneumoniae* infections.

1. *In Vitro* Activity of Quinolones Against *C. pneumoniae*

C. pneumoniae is susceptible *in vitro* to agents that affect protein or DNA synthesis; macrolides, tetracyclines and fluoroquinolones (table I).[17-24] Unlike *C. trachomatis, C. pneumoniae* is resistant to sulfonamides. The methods used for *in vitro* susceptibility testing of *C. pneumoniae* have largely been adapted from those used for *C. trachomatis*. The methods are

not standardised and the results can be influenced by a number of variables including tissue culture system used, inoculum size, timing of the addition of the antibiotic, and the number and type of isolates that are used for testing. Many *in vitro* studies reported in the literature have used ≤5 isolates of *C. pneumoniae*, many have used only one, usually a laboratory strain. There are a limited number of studies that have tested large numbers of clinical isolates. Extrapolating from studies with *C. trachomatis*, DNA gyrase is probably the primary target of action for quinolones.[25] In general, the older quinolones have been less active *in vitro* than macrolides and tetracyclines. Ciprofloxacin, fleroxacin and lomefloxacin have moderate activity against *C. pneumoniae*, with MICs and MCCs ranging from 1 to ≥16 mg/L.[17,18] Ofloxacin is slightly more active with MIC values of 1 to 2 mg/L. Levofloxacin, trovafloxacin and moxifloxacin are slightly more active than ofloxacin, with MICs of 0.25 to 1 mg/L.[20,21,23] Sparfloxacin, grepafloxacin, gatifloxacin and SB265805, appear to be the most active compounds that are FDA approved or currently in phase III clinical trials, with MICs of 0.03 to 0.5 mg/L.[18,19,22,23,26] There are a number of other compounds that are more active, such as Y-688 and S-34109, with MIC and MCC values of 0.03 to 0.06 mg/L, but these compounds may not be developed clinically.[27,28]

Although *C. pneumoniae* resistance to quinolones has, as yet, not been reported, Dessus-Babus et al.[25] recently described 2 strains of *C. trachomatis* which became resistant to sparfloxacin and ofloxacin after 4 passages at subinhibitory concentrations of these drugs. Resistance appeared to be due to a point mutation in the *gyrA* quinolone resistance-determining region. The authors suggested that selection of quinolone-resistant strains of *C. trachomatis* may occur *in vivo* during quinolone therapy.

2. Use of Quinolones for Treatment of *C. pneumoniae* Infection

There have been few published data describing the response of *C. pneumoniae* infection to antibiotic therapy. Optimum dose and duration of therapy are uncertain. Anecdotal data suggest that prolonged therapy (ie. at least 2 weeks) may be desirable since recrudescent symptoms and persistent positive cultures have been described following 2-week courses of erythromycin and even after 30 days of tetracycline or doxycycline.[14,15] Practically all treatment studies evaluating quinolones that have been presented or published to date have used serology alone for diagnosis. In 1990, Lipsky et al.[29] described 4 patients with bronchitis and pneumonia, treated with a 10-day course of ofloxacin who were retrospectively identified as having serological evidence of acute *C. pneumoniae* infection (4-fold rise in IgG/IgM, single IgM ≥16 or IgG ≥512). All patients reportedly demonstrated marked clinical improvements. Based on the MICs of 3 laboratory strains to ofloxacin (1 to 2 mg/L), the authors concluded that ofloxacin was effective in these patients as the MICs were less than the achievable serum levels. Subsequent treatment trials have all utilised serology for diagnosis, essentially limiting themselves to clinical end-points. Using the same criteria as Lipsky et al.,[29] Plouffe et al.[30] reported a clinical response rate of 83% in patients with CAP with serological evidence of *C. pneumoniae* infection, who were treated with ofloxacin, compared with 75% of patients receiving standard therapy (a beta-lactam antibiotic plus a macrolide or tetracycline). Similarly, File et al.[31] reported a clinical cure rate of 98% among patients who were treated with levofloxacin compared with 93% of those treated with ceftriaxone and/or cefuroxime axetil. In addition, either erythromycin or doxycycline was added to the treatment regimen at the discretion of the investigator. In the latter ceftriaxone

Table I. *In vitro* activity of various antibiotics against *Chlamydia pneumoniae*

Drug	MIC (range)	MIC_{90} (mg/L)	MBC_{90}
Erythromycin	0.06-0.25	0.25	0.25
Doxycycline	0.06-0.25	0.25	0.25
Azithromycin	0.05-0.25	0.25	0.25
Clarithromycin	0.004-0.03	0.03	0.03
Ciprofloxacin	1-2	2	4
Ofloxacin	0.5-2	1	1
Levofloxacin	0.25-1	0.5	0.5
Sparfloxacin	0.031-0.125	0.06	0.06
Grepafloxacin	0.25-0.5	0.5	0.5
Trovafloxacin	0.5-1	1	1
Moxifloxacin	0.5-1	0.5	0.5
Gatifloxacin	0.125-0.25	0.25	0.25
SB265805	0.06-0.12		
Sulfamethoxazole	>500		

MBC = minimum bactericidal concentration; **MIC** = minimum inhibitory concentration.

group, the response rate of patients with serological evidence of *C. pneumoniae* infection did not differ between those patients who had erythromycin or doxycycline added to their treatment regimen. There was also no difference in the response rate among those patients who had definite infection, ie. a 4-fold rise in microimmunofluorescence (MIF) IgG or IgM, compared with those who had probable infection, i.e. a single IgG ≥512 or IgM ≥32.

A recent study by Leophonte et al.[32] comparing 2 trovafloxacin regimens with amoxicillin/clavulanic acid for the treatment of acute exacerbations of chronic bronchitis, found a similar clinical response rate for all 3 regimens and claimed that *C. pneumoniae* was successfully eradicated from 80 to 100% of patients at the end of treatment, with all 3 regimens. The investigators stated that 'atypical respiratory pathogens, which were identified by serological testing (a 4-fold increase in antibody titre) were presumed eradicated if the patient's clinical response was cure or improvement'.[32] Similar claims of eradication have been made by Deabate et al.[33] in a study comparing sparfloxacin with ofloxacin for the same indication. As with the study of Leophonte et al.,[32] *C. pneumoniae* infection was diagnosed serologically, no cultures were obtained.

There also remains a question over the apparent success of regimens using antibiotics that have poor or no activity against *C. pneumoniae in vitro*, such as cephalosporins. This may be due in part to the poor specificity of serological criteria used to diagnose *C. pneumoniae* infection. Several recent studies have found a poor correlation between the results of MIF serology and culture.[9,10,14,34]There is one anecdotal report of treatment with a quinolone where cultures were obtained. Roblin et al.[19] treated 3 patients with culture documented *C. pneumoniae* infection (bronchitis and pneumonia) with grepafloxacin. Two of the 3 patients remained culture positive and symptomatic despite 2 weeks of treatment with the drug. These 2 culture positive patients did not meet the serological criteria for acute *C. pneumoniae* infection. Grepafloxacin is 2- to 4-fold more active *in vitro* than trovafloxacin or ofloxacin.

The only published studies that have utilised cultures and assessed microbiological efficacy used macrolides. Block et al.[9] found that treatment with erythromycin suspension eradicated *C. pneumoniae* from the nasopharynx of 86% and clarithromycin suspension from 79% of culture positive children with CAP. All these children improved clinically despite persistence of the organism. Persistence was not related to the development of antibiotic resistance as all the isolates remained susceptible to erythromycin and clarithromycin during and after treatment.[35] Clarithromycin is 10- to 100-fold more active than erythromycin *in vitro* and has superior pharmacokinetics and tissue penetration, yet was no more effective than erythromycin in eradicating *C. pneumoniae* from the respiratory tract. The experience with azithromycin has been similar. In an open, noncomparative multicentre pneumonia treatment study,[36] adolescents and adults ≥12 years of age were given 1.5g of azithromycin orally over 5 days. *C. pneumoniae* was eradicated from the nasopharynx of 7 (70%) of the 10 culture positive patients after treatment. Harris et al.[10] reported that *C. pneumoniae* was eradicated after treatment from the nasopharynx of 19/23 (83%) evaluable children who received azithromycin, and 4/4 and 7/7 patients who received amoxicillin/clavulanic acid and erythromycin, respectively ($p = 0.9$, Chi square). The MICs and MCCs of 3 out of 9 isolates, obtained after treatment of 2/7 persistently infected patients in both studies who were treated with azithromycin, increased 4-fold after treatment although they were still within the range considered to be susceptible to the antibiotic.[36] It is not clear if this is an isolated event or suggestive of the possible development of resistance. All patients improved clinically despite persistence of the organism.

3. Conclusion

These studies illustrate several important issues dealing with the treatment of *C. pneumoniae* infections. *In vitro* activity does not always predict microbiological efficacy. Unless cultures are obtained and microbiological efficacy is assessed, we may never be able to survey for, or document the emergence of, resistance. The use of quinolones for empirical treatment of CAP is becoming a popular option as these drugs have activity against conventional and 'atypical' pathogens.[37] These issues need to be taken into account when evaluating the efficacy of quinolones for the treatment of *C. pneumoniae* infection.

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Correspondence and reprints: Dr *Margaret R. Hammerschlag*, 450 Clarkson Ave., Box 49, Brooklyn, NY 11203-2098, USA.
E-mail: mhammerschlag@pol.net