Treatment of chlamydial infections: 2014 update

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**Introduction:** Chlamydiae are obligate intracellular bacterial pathogens whose entry into mucosal epithelial cells is required for intracellular survival and subsequent growth. The life cycle of *Chlamydia* spp. and the ability to cause persistent, often subclinical infection, has major ramifications for diagnosis and treatment of *Chlamydia trachomatis* and *C. pneumoniae* infections in humans.

**Areas covered:** This paper reviews the current literature on the antimicrobial susceptibilities and treatment of genital infections due to *C. trachomatis* and respiratory infections due to *C. pneumoniae* published since 2011.

**Expert opinion:** Chlamydiae are susceptible to antibiotics that interfere with DNA and protein synthesis, including tetracyclines, macrolides and quinolones, which are the compounds that have been most extensively studied and used for treatment of human infection. Since our original review was published in 2011, there have been some major advances in diagnostic tests for *C. trachomatis* and the introduction of the first FDA-approved test for the detection of *C. pneumoniae* in respiratory samples. However, the options for treating chlamydial infections have largely remained the same. There are a small number of new drugs currently in preclinical development and early clinical trials that may have a role in the treatment of chlamydial infections.

**Keywords:** antibiotics, *Chlamydia pneumoniae*, *Chlamydia trachomatis*, Chlamydiae


**1. Introduction**

Chlamydiae are obligate intracellular bacterial pathogens whose entry into mucosal epithelial cells is required for intracellular survival and subsequent growth. Chlamydiae cause a variety of diseases in animal species at virtually all phylogenetic levels, from amphibians and reptiles to birds and mammals. The chlamydial species that most frequently cause disease in humans are *Chlamydia trachomatis* and *C. pneumoniae*. *C. trachomatis* is a major cause of sexually transmitted infections including non-gonococcal urethritis (NGU) and epididymitis in men, cervicitis and pelvic inflammatory disease in women, and conjunctivitis and pneumonia in infants born to women with active genital infection [1,2]. *C. pneumoniae* is primarily a respiratory pathogen and is a frequent cause of community-acquired pneumonia (CAP) in adults and children [3]. The organism has also been implicated as an infectious trigger in asthma [2,3]. The majority of *C. trachomatis* and *C. pneumoniae* infections are asymptomatic and frequently of long duration.

This topic was last reviewed in *Expert Opinion in Pharmacotherapy* in 2011 [4]. The present review covers advances in the management of infections due to *C. trachomatis* and *C. pneumoniae* published since 2011.
2. Antimicrobial susceptibility of Chlamydia spp.

The biology of Chlamydiae was reviewed in detail by Hammerschlag and Kohlhoff in 2011 [4]. Chlamydiae are susceptible to a wide variety of antibiotics that interfere with DNA and protein synthesis, including tetracyclines, macrolides, quinolones, rifamycins and clindamycin (Table 1). Although there are no standardized methods for in vitro susceptibility testing of Chlamydia spp., results have been largely consistent [5-7]. Chlamydia spp. are resistant to trimethoprim, aminoglycosides and glycopeptidases. C. trachomatis is sensitive to sulfonamides but C. pneumoniae and C. psittaci are resistant. Genomic analysis has revealed that C. trachomatis and C. pneumoniae encode for proteins forming a nearly complete pathway for the synthesis of peptideoglycan, including three penicillin-binding proteins, thus penicillin and amoxicillin have been found to have some activity in vitro, this has been called the chlamydial paradox or anomaly [8]. Amoxicillin has been recommended as an alternative regimen for treating C. trachomatis infection in pregnant women and has been found to be as effective and better tolerated than erythromycin [1].

The intracellular location of Chlamydia spp. requires that antimicrobial agents need to achieve adequate intracellular penetration and concentration to be effective. Efficacy is generally defined by a MIC of 1 µg/ml or less, but an antibiotic with an MIC of 0.1 µg/ml may not necessarily have greater microbiologic efficacy in vivo than one with an MIC of 1 µg/ml [4].

There are several new antibiotics with anti-chlamydial activity that are currently in early clinical development.

AZD0914 (AstraZeneca) is a member of a new class of anti-bacterials which incorporates a novel spiroprimidinetriene that also targets DNA gyrase/topoisomerase IV through novel mode of inhibition [9]. AZD0914 has potent in vitro antibacterial activity against fluoroquinolone-resistant and multi-drug resistant MRSA, Streptococcus pneumoniae and Neisseria gonorrhoeae [9,10]. Preliminary data have also demonstrated good activity against C. trachomatis and C. pneumoniae [11]. In addition, there are two quinolones, nemonoxacin and delafloxacin which are being fast-tracked by the FDA for treatment of gonorrhea. These compounds also retain activity against quinolone-resistant N. gonorrhoeae and are active against Chlamydia spp [12,13]. Both are currently in Phase III clinical trials for treatment of gonococcal infection. Solithromycin (CEM-101) is a ketolide antibiotic that is currently in Phase III clinical trials for treatment of CAP. It has good in vitro activity against both C. trachomatis and C. pneumoniae [4], but the efficacy against CAP due to C. pneumoniae is not being assessed in these treatment studies.

2.1 Antibiotic resistance in C. trachomatis and C. pneumoniae

Although resistance to quinolones and rifamycins can be induced in C. trachomatis and C. pneumoniae in vitro by serial passage in subinhibitory concentrations of antibiotics [14-16], antibiotic resistance in both species appears to be very rare in vivo. The number of passages needed to select for resistant mutants varied by species, strain and antibiotic. The role of
antimicrobial resistance in treatment failures or persistent infection is not clear. The potential of the organism to develop antimicrobial resistance in vivo has not been well studied, mostly limited to a few case reports that suggested that resistance was a possible cause of clinical treatment failure; however, the possible mechanisms of resistance were not well defined [7].

Most recurrent C. trachomatis infections result from re-infection from an untreated partner or new infection from a new sexual partner [17]. Studies examining the in vitro susceptibilities of clinical isolates from patients with C. trachomatis infection seen in the US and Israel in 2005 and 1995 did not reveal any resistant organisms [18,19]. A more recent survey from Croatia, which has the highest consumption of azithromycin in Europe, did not find any resistance to azithromycin or doxycycline in 24 recent clinical urogenital isolates of C. trachomatis [20]. The MICs for azithromycin and doxycycline ranged from 0.064 to 0.125 µg/ml and 0.016 – 0.064 µg/ml, respectively. Two large surveys of C. trachomatis isolates from patients with trachoma did not detect development of macro-lide resistance after biannual community-wide distributions of azithromycin for control of trachoma [21,22]. In 2009, Hong et al. [21] investigated the susceptibilities of C. trachomatis isolates 18 months after four biannual community-wide antibiotic distributions in Ethiopia. These distributions involved hundreds of individuals 1 year of age receiving a single dose azithromycin, 20 mg/kg in children or 1 g in adults twice a year, which could conceivably provide selective pressure which might enable expansion of resistant clones of C. trachomatis. The investigators found no significant differences in in vitro susceptibilities of C. trachomatis isolates from these patients to azithromycin and doxycycline. More recently, West et al. [22] reported similar findings after 3 yearly mass distributions of azithromycin in 32 communities in Tanzania. They identified 30 children with trachoma who remained positive for C. trachomatis. In vitro susceptibility testing was performed on 15 paired C. trachomatis isolates from these children. The average MIC was 0.26 µg/ml for azithromycin before, and 0.20 µg/ml after mass distribution of azithromycin. The authors concluded that other potential causes of persistent infection needed to be evaluated. It should be noted that the community-wide azithromycin exposure with treatment of chlamydial genital infections is significantly less than the mass treatments required for control of trachoma.

In contrast, mass distribution of azithromycin for control of trachoma has been associated with increased carriage of azithromycin-resistant fecal Escherichia coli [23] and increased carriage of azithromycin-resistant S. pneumoniae in young children [24].

Similar data have been reported for treatment of C. pneumoniae respiratory infections. Results of several multicenter treatment studies that utilized culture demonstrated 70 – 86% efficacy of treatment with erythromycin, clarithromycin, azithromycin, levofloxacin and moxifloxacin in eradicating C. pneumoniae from the nasopharynx of children and adults with CAP [3]. Most patients improved clinically despite persistence of the organism. Persistence did not appear to be secondary to the development of antibiotic resistance, as the MICs of the isolates obtained after treatment did not change [25-28].

3. Treatment of genital C. trachomatis infections in adults and adolescents

Because of the long life cycle of C. trachomatis, 48 – 72 h depending on biovar and strain, treatment has in the past required multiple dose treatment regimens. For decades, 7-day courses of doxycycline and erythromycin were standard treatment [1]. The need for multiple dose regimens has raised concerns about the impact on compliance. The introduction of azithromycin with its long half-life in tissue has allowed for single-dose treatment of genital C. trachomatis infections [1]. Currently, the centers for disease control and prevention (CDC) recommends either single dose azithromycin or 7-day course of doxycycline as first-line regimens for the treatment of uncomplicated genital C. trachomatis infection in adolescent and adult men and women [1]. Alternative regimens include 7-day course of erythromycin base or ethylsuccinate. Erythromycin is has a higher rate of gastrointestinal side effects than either azithromycin or doxycycline, which may contribute to lower efficacy seen in a number of studies. Levofloxacin and ofloxacin are also listed as alternatives treatment regimens; however, they are more expensive and require multiple dosing which offers no advantages over the first-line recommendations. These recommendations have not changed since 1993. A meta-analysis of 12 randomized clinical trials, published in 2002, comparing single dose azithromycin to a 7-day course of doxycycline found a rate of microbiologic eradication of 97% for azithromycin and 98% for doxycycline [29]. Manhart et al. [30] in a study published in 2013, evaluating azithromycin and doxycycline for the treatment of non-gonococcal urethritis found that although both regimens had a similar microbiologic cure rate, it was lower than what had previously been reported. The microbiologic cure rates for C. trachomatis were 86% for azithromycin and 90% for doxycycline, which were substantially lower than earlier studies. Although the authors describes various reasons why their results were different, including: it was a single site study and variations in duration of follow up and timing of test of cure specimens, the most likely explanation is that the earlier trials used culture or immunoassays to detect C. trachomatis, whereas the current study used a nucleic acid amplification test (NAAT). NAATs are significantly more sensitive than culture for detection of C. trachomatis in urogenital specimens. The use of less sensitive methods, including culture and immunoassays, may have led to overestimation of microbiologic efficacies. Recently, Kong et al. [31] conducted another meta-analysis of trials comparing azithromycin to doxycycline published from 1990 through 2013. They found a 3% increased efficacy overall for doxycycline compared to
azithromycin for the treatment of urogenital chlamydial infections in men and women. However, as with many meta-analyses, the quality of the evidence varied considerably but, they felt that with the increasing concern about potential azithromycin failure, additional studies are needed.

Efficacy of treatment regimens may also vary by anatomic site. Khosropour et al. [32], in a retrospective cohort study, compared azithromycin to doxycycline for the treatment of rectal C. trachomatis infection in men. They found that persistent or recurrent infection was higher among men treated with azithromycin compared to doxycycline, 8% for azithromycin, versus 0% for doxycycline, 14–30 days after treatment. However, it is possible that some of these men may have had lymphogranuloma venereum (LGV).

On the other hand, as treatment with doxycycline requires a multi-dose regimen, compliance is always a concern. In another study from the same group, the investigators documented that sub-optimal adherence to doxycycline therapy was associated with microbiologic failure in men with NGU who had C. trachomatis infection [33]. Sub-optimal therapy was defined as missing at least 1 dose of doxycycline in 7 days. Approximately 28% of the men were non-adherent and 20% of them had C. trachomatis detected at follow-up compared to <3% of men who reported being adherent.

There have been very few studies of new antibiotics for the treatment of genital C. trachomatis infection and none of these compounds are currently in clinical development in the US. Two relatively small studies from Japan [34,35] evaluated a quinolone, sitafloxacin, 100 mg twice a day for 7 days for treatment of NGU. The microbiologic eradication rates for C. trachomatis were 95.7 and 100%, in a total 69 patients with C. trachomatis infection from both studies. Detection of C. trachomatis was done by NAAT. Sitafloxacin offers no advantages over levofloxacin or ofloxacin [36], which are recommended by the CDC as alternative treatment regimens [1], especially as it requires multiple dosing which offers no advantages over doxycycline.

Rifalazil is a long-acting rifamycin with excellent in vitro activity against both C. trachomatis and C. pneumoniae [37]. Geisler et al., recently reported the results of a Phase II double-blind, multi-centre study comparing single dose rifalazil to azithromycin for the treatment of uncomplicated genital C. trachomatis infection in women [38]. Rifalazil was well tolerated and efficacious. A single 25 mg dose of rifalazil was equivalent to 1 g of azithromycin with C. trachomatis eradication rates of 84.8% compared to 92.1% for azithromycin at the test-of-cure visit, 22–26 days after treatment. However, as stated above, rifalazil is no longer in clinical development in the US.

3.1 Treatment of LGV

LGV is a systemic, invasive chlamydia infection caused by the C. trachomatis serovars L1, L2, or L3 [1]. Most LGV infections seen in Europe and the US have been due to L2 strains. If not treated early and appropriately, LGV can lead to serious sequelae in men and women, including colorectal fistulas, strictures and elephantiasis. Unlike uncomplicated genital infection due to trachoma biovar strains of C. trachomatis, treatment of LGV requires a prolonged course of therapy. The CDC currently recommends doxycycline, 100 mg orally twice daily for 21 days as the first-line treatment regimen [1]. Erythromycin base, 500 mg orally four times daily for 21 days is the alternative regimen for use in pregnancy.

Published studies have demonstrated persistent C. trachomatis RNA in rectal samples from patients with LGV proctocolitis after 2 weeks of doxycycline, in comparison, C. trachomatis DNA was undetectable by 7 days of treatment in patients with proctitis due to trachoma biovar strains [39]. Although 21-day treatment with doxycycline appears to be very effective, there have been reports of failure, usually in men co-infected with HIV [40–42]. Oud et al. [41] reported four patients with LGV presenting with inguinal lymphadenopathy, all were men who have sex with men (MSM), three of whom were HIV positive, who failed a 3-week course of doxycycline. The patients responded after an additional 6–12 weeks of doxycycline plus aspiration of the buboes. Vall-Mayans et al. [42] reported a 47-year-old MSM with LGV proctitis and inguinal lymphadenopathy who in addition to 3 weeks of doxycycline, required additional treatment with 20 days of azithromycin followed by 12 days of moxifloxacin.

Data on use of other antibiotics, including azithromycin and quinolones are limited to anecdotal reports, although in vitro susceptibilities against C. trachomatis suggest that they would be effective (Table 1). Regimens of azithromycin used have included a single 1-g dose and 1 g weekly for 3 weeks [1,43]. The question of what is the optimal treatment for LGV will not be resolved until we have data from controlled trials.

4. Treatment of acute respiratory
C. pneumoniae infection

C. pneumoniae is a common cause of respiratory infections including CAP and is frequently described as the cause of community outbreaks [44–46]. Guidelines for the treatment of CAP typically include antibiotics with activity against C. pneumoniae [47]. However, most studies evaluating regimens including antimicrobial agents for the empirical treatment of CAP did not include sufficient numbers of patients with proven C. pneumoniae infection to establish that inclusion of such agents is essential [48,49]. Further limitations to the analysis of CAP treatment studies are the lack of uniform diagnostic parameters and use of serology alone for diagnosis of C. pneumoniae infection, which is at best a clinical end point, in the majority of published pneumonia treatment studies.

Recently, the first FDA-approved molecular diagnostic test for respiratory pathogens that includes C. pneumoniae has become available (BioFire FilmArray Respiratory Panel) [50]. This may allow more widespread and standardized testing
and targeted treatment in patients with respiratory infection in the future.

Results of several multi-centre treatment studies that utilized direct detection by culture and included microbiologic endpoints demonstrated 70–86% efficacy of treatment with erythromycin, clarithromycin, azithromycin, levofloxacin and moxifloxacin in eradicating *C. pneumoniae* from the nasopharynx of children and adults with CAP [25-28]. On the basis of the few studies using microbiologic end points, the following regimens can be used for respiratory infection due to *C. pneumoniae*: in adults, doxycycline, 100 mg orally twice daily for 14–21 days, tetracycline, 250 mg orally 4 times daily for 14–21 days, azithromycin, 1.5 g orally over 5 days, clarithromycin, 500 mg orally, twice a day for 10 days, levofloxacin, 500 mg, intravenously or orally, once a day for 7–14 days, or moxifloxacin, 400 mg orally, once a day for 10 days. For children, erythromycin suspension, 50 mg/kg/day for 10–14 days, clarithromycin suspension, 15 mg/kg/day for 10 days, or azithromycin suspension, 10 mg/kg once on day one followed by 5 mg/kg, once daily for 4 days. Some patients may require re-treatment.

### 4.1 Treatment of *C. pneumoniae* in chronic disease

Chronic, persistent infection with *C. pneumoniae* has been implicated in the pathogenesis of several chronic diseases, initially not thought to be infectious. However, studies of the association of *C. pneumoniae* and these disorders have been hampered by difficulty in diagnosing chronic, persistent infection with the organism due to a lack of standardized methods. This makes it very difficult to determine the efficacy of intervention. Probably, the most widely accepted association is between infection with *C. pneumoniae* and exacerbation of asthma, which has been documented by a large number of epidemiologic and clinical studies (reviewed in [2]). Several studies have addressed the question whether antibiotic treatment of *C. pneumoniae* infection in asthmatics leads to improvement in disease activity (reviewed in [2]). The study design has been complicated by the fact that macrolides, quinolones, ketolides and tetracyclines all have immunomodulatory activity independent of their antimicrobial activity. Any positive treatment outcomes may therefore be due to anti-chlamydial, immunomodulatory effects, or a combination of the two. Recently, *in vitro* suppression of *C. pneumoniae*-induced cytokine and IgE responses by doxycycline independent of anti-chlamydial activity in peripheral blood mononuclear cells from subjects with asthma was demonstrated; this suggests an important role of anti-inflammatory properties for antibiotics used in patients with chronic respiratory symptoms [51]. Several randomized controlled trials were underpowered to show a benefit of macrolide treatment in *C. pneumoniae* infected asthmatics due to low numbers of study subjects with proven infection [52,53].

In conclusion, while diagnosis and treatment of documented *C. pneumoniae* infections in asthmatics with signs and symptoms of an airway infection should follow the above recommendations for acute respiratory infection, the benefits of using antibiotics with activity against atypical bacteria in asthmatics without evidence of acute infection remains controversial. Currently, there are no indications for the treatment of any other chronic diseases for presumed infection with *C. pneumoniae*.

### 5. Expert opinion

Chlamydiae are susceptible to antibiotics that interfere with DNA and protein synthesis, including tetracyclines, macrolides and quinolones, which are the compounds that have been most extensively studied and used for treatment of human infection. The recommendations for the treatment of *C. trachomatis* and *C. pneumoniae* infection remain essentially the same as when we last reviewed this subject in 2011 [4]. Current data also confirm that antibiotic resistance essentially does not occur in *C. trachomatis* and does not appear to effect microbiologic efficacy *in vivo*. This was confirmed with the community-wide azithromycin treatment for trachoma, where development of resistance in *C. trachomatis* isolates before and after treatment was not found [22]. Similar data have reported for treatment of *C. pneumoniae* infections, the MICs of isolates obtained after treatment were the same as the isolates at baseline [25-28]. Thus, persistence after treatment is probably due to other factors. The lower microbiologic efficacy rates of azithromycin and doxycycline reported in recent studies of genital infection may be secondary to the use of more sensitive molecular diagnostic tests for *C. trachomatis* [30,31].

There are few new agents under investigation that are being evaluated for treatment of *C. trachomatis* or *C. pneumoniae* infection. Unfortunately, two compounds that were evaluated in clinical trial for treatment of *C. trachomatis* genital infection, sitafloxacin and rifalazil, are not currently in clinical development in the US or Europe [34,35,38]. All existing antibiotics remain good treatment options with good safety record and with no clinical demonstration of resistance. Future areas of research include redefining the epidemiology of *C. pneumoniae* infection and the development of reliable diagnostic tests for *C. pneumoniae* in order to better target treatment.

### Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

**2014 edition of important reference for treatment of STDs, including Chlamydia trachomatis infection.**


**Detailed study which documents the lack of development of antibiotic resistance in C. trachomatis after community-wide treatment with azithromycin.**


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