EXPERT OPINION

Treatment of chlamydial infections: 2014 update

Stephan A Kohlhoff[†] & Margaret R Hammerschlag
[†]*SUNY Downstate Medical Center, Division of Pediatric Infectious Diseases, Department of Pediatrics, Brooklyn, NY, USA*

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

Expert Opin. Pharmacother. (2015) ***16****(2):205-212*

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 phylogenic 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.

informa
healthcare

10.1517/14656566.2015.999041 © 2015 Informa UK, Ltd. ISSN 1465-6566, e-ISSN 1744-7666

Article highlights.

- Chlamydiae are susceptible to antibiotics that interfere with DNA and protein synthesis, including tetracyclines, macrolides and quinolones.
- Since 2011, there have been major advances in diagnostic tests for *Chlamydia trachomatis* and the introduction of the first FDA-approved test for the detection of *C. pneumoniae* in respiratory samples.
- The options for treating *C. trachomatis* and *C. pneumoniae* infections are largely the same as they were in 2011.
- Azithromycin remains the drug of choice for uncomplicated *C. trachomatis* genital infection and trachoma.
- *In vitro* antibiotic resistance in *Chlamydia* spp. is very rare and does not appear to affect microbiologic efficacy *in vivo*.
- There several new drugs currently in preclinical development and early clinical trials, including solithromycin and a novel nonquinolone DNA gyrase inhibitor (AZD 0914) that may have a role in the treatment of chlamydial infections.

This box summarizes key points contained in the article.

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 glycopeptides. *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 peptidoglycan, 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.

Table 1. MIC of selected antimicrobial agents against *Chlamydia trachomatis* and *C. pneumoniae*.

Antimicrobial	*C. trachomatis*	*C. pneumoniae*
FDA-approved drugs		
Doxycycline	0.031 – 0.25	0.015 – 0.5
Tigecycline	0.03 – 0.125	0.125 – 0.25
Erythromycin	0.016 – 2	0.015 – 0.25
Azithromycin	0.6 – 2	0.05 – 0.25
Clarithromycin	0.015 – 0.125	0.004 – 0.125
Clindamycin	2 – 16	–
Ciprofloxacin	0.5 – 2	1 – 4
Levofloxacin	0.12 – 0.5	0.25 – 1
Moxifloxacin	0.5 – 1	0.125 – 1
Rifampin	0.005 – 0.25	0.0075 – 0.03
Trimethoprim	≥ 128	≥ 128
Sulfamethoxazole	0.5 – 4	≥ 500
Gentamicin	500	500
Vancomycin	1000	1000
Investigational drugs		
Solithromycin (CEM-101)	0.125 – 0.5	0.25 – 1
Sitafloxacin	0.031 – 0.063	0.031 – 0.125
Nemonoxacin	0.03 – 0.125	0.03 – 0.125
Delafloxacin	–	0.06 – 0.125
AZD0914	0.06 – 0.5	0.25 – 1
Rifalazil	0.00125 – 0.0025	0.00125

MIC range (μg/ml).
Data taken from [3,4,11-13,25-28,36,37].

AZD0914 (AstraZeneca) is a member of a new class of antibacterials which incorporates a novel spiropyrimidinetrione that also targets DNA gyrase/topoisomerase IV through novel mode of inhibition [9]. AZD0914 has potent *in vitro* antibacterial activity against fluoroquinolone-resistant and multidrug 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 macrolide resistance after biannual communitywide 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 communitywide 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 doxycyline for the treatment of non-gonoccocal 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 from1990 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 and ofloxacin [36], which are recommended by the CDC as alternative treatment regimens [1], especially as it requires multiple dosing which offers no advantages over doxycyline.

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 treated 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 L_1, L_2 or L_3 [1]. Most LGV infections seen in Europe and the US have been due to L_2 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 antichlamydial 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 antichlamydial, immunomodulatory effects, or a combination of the two. Recently, *in vitro* suppression of *C. pneumoniae*-induced cytokine and IgE responses by doxycycline independent of antichlamydial 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.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Centers for Disease Control and Prevention. 2014 Sexually transmitted diseases treatment guidelines. MMWR 2014;In press

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

2. Hammerschlag MR, Kohlhoff SA, Darville T. Chlamydia pneumoniae and Chlamydia trachomatis. In: Fratamico PM, Smith JL, Brogden KA, editors. Sequelae and long-term consequences of infectious diseases. American Society for Microbiology, Washington, DC; 2009;p. 27-52

3. Hammerschlag MR, Kohlhoff SA, Gaydos CA. Chlamydia pneumoniae. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases. 8th edition. Elsevier, Inc., Philadephia, PA; 2014;p. 2174-83

4. Hammerschlag MR, Kohlhoff SA. Treatment of chlamydial infections. Expert Opin Pharmacother 2011;13:542-52

5. Senn L, Hammerschlag MR, Greub G. Therapeutic approaches to Chlamydia infections. Expert Opin Pharmacother 2005;6:1-10

6. Suchland RJ, Geisler WM, Stamm WE. Methodologies and cell lines used for antimicrobial susceptibility testing of Chlamydia spp. Antimicrob Agents ?Chemother 2002;47:636-42

7. Sandoz KM, Rockey DD. Antibiotic resistance in Chlamydiae. Future Microbiol 2010;5:1427-42

8. Ghuysen JM, Goffin C. Lack of cell wall peptidoglycan versus penicillin sensitivity: new insights into the chlamydial anomaly. Antimicrob Agents Chemother 1999;43:2339-44

9. Jacobsson S, Golparian D, Alm RA, et al. High in-vitro activity of the novel spiropyrimidinetrione AZD0914, a DNA gyrase inhibitor, against multidrug resistant Neisseria gonorrhoeae isolates suggests a new effective option for oral treatment of gonorrhea. Antimicrob Agents Chemother 2014;58:5585-8

10. Huband MD, Otterson LG, Doig PC, et al. Benzisoxazoles: in vitro activity of new bacterial DNA gyrase/topoisomerase IV inhibitors against Gram-positive, fastidious Gram-negative, atypical, and anaerobic bacterial isolates. 53rd Annual ICAAC; 10 – 13 September 2013; Denver, CO, USA. Poster F-1220

11. Kohlhoff SA, Huban MD, Hammerschlag MR. In vitro activity of AZD0914, a novel DNA gyrase inhibitor, against Chlamydia trachomatis and Chlamydia pneumoniae. Antimicrob Agents Chemother 2014;58:7595-6

12. Chotikanatis K, Kohlhoff SA, Hammerschlag MR. In vitro activity of nemonoxacin, a novel nonfluorinated quinolone antibiotic, against Chlamydia trachomatis and Chlamydia pneumoniae. Antimicrob Agents Chemother 2014;58:1800-1

13. Hammerschlag MR, Roblin PM. The in vitro activity of a new fluoroquinolone, ABT-492, against recent clinical isolates of Chlamydia pneumoniae. J Antimicrob Chemother 2004;54:281-2

14. Dessus-Babus S, Bébéar CM, Charron A, et al. Sequencing of gyrase and topoisomerase IV quinolones sequence-determining regions of Chlamydia trachomatis and characterization of quinolones resistant mutants obtained in vitro. Antimicrob Agents Chemother 1998;42:2474-81

15. Morrissey I, Salman H, Bakker S, et al. Serial passage of Chlamydia spp. in subinhibitory fluoroquinolone concentrations. J Antimicrob Chemother 2002;49:757-61

16. Kutlin A, Kohlhoff S, Roblin P, et al. Emergence of resistance to rifampin and rifalazil in Chlamydophila pneumoniae and Chlamydia trachomatis. Antimicrob Agents Chemother 2005;49:903-7

17. Batteiger BE, Tu W, Ofner S, et al. Repeated Chlamydia trachomatis genital infections in adolescent women. J Infect Dis 2010;201:42-51

18. Rice RJ, Bhullar V, Mitchell SH, et al. Susceptibilities of Chlamydia trachomatis isolates causing uncomplicated female genital tract infections and pelvic inflammatory disease. Antimicrob Agents Chemother 1995;39:760-2

19. Samra Z, Rosenberg S, Soffer Y, et al. In vitro susceptibility of recent clinical isolates of Chlamydia trachomatis to macrolides and tetracyclines. Diagn Microbiol Infect Dis 2001;39:177-9

20. Ljubin-Sternak S, Mestrovic T, Vilibic-Cavlek T, et al. In vitro susceptibility of urogenital Chlamydia trachomatis strains in a country with high azithromycin consumption rate. Folia Microbiol (Praha) 2013;58:361-5

21. Hong KC, Schachter J, Moncada J, et al. Lack of macrolide resistance in Chlamydia trachomatis after mass azithromycin distributions for trachoma. Emerg Infect Dis 2009;15:1088-90

22. West SK, Moncada J, Munoz B, et al. Is there evidence for resistance of ocular Chlamydia trachomatis to azithromycin after mass treatment for trachoma control. J Infect Dis 2014;210:65-71

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

23. Seidman JC, Coles CL, Sibergeld EK, et al. Increased carriage of macrolide-resistant fecal E. coli following mass distribution of azithromycin for trachoma control. Int J Epidemiol 2014;43(4):1105-13

24. Coles CL, Mabula K, Seidman JC, et al. Mass distribution of azithromycin for trachoma control is associated with increased risk of azithromycin-resistant Streptococcus pneumoniae, carriage in young children 6 months after treatment. Clin Infect Dis 2013;56:1519-26

25. Roblin PM, Hammerschlag MR. Microbiologic efficacy of azithromycin and susceptibility to azithromycin of isolates of Chlamydia pneumoniae from adults and children with community acquired pneumonia. Antimicrob Agents Chemother 1998;42:194-6

26. Hammerschlag MR, Roblin PM. Microbiologic efficacy of levofloxacin for the treatment of community-acquired pneumonia due to Chlamydia pneumoniae. Antimicrob Agents Chemother 2000;44:1409

27. Hammerschlag MR, Roblin PM. Microbiologic efficacy of moxifloxacin for the treatment of community-acquired pneumonia due to Chlamydia pneumoniae. Int J Antimicrob Agents 2000;15:149-52

28. Roblin PM, Montalban G, Hammerschlag MR. Susceptibility to clarithromycin and erythromycin of isolates of Chlamydia pneumoniae from children with pneumonia. Antimicrob Agents Chemother 1994;38:1588-9

29. Lau C-Y, Qureshi AK. Azithromycin versus doxycycline for genital Chlamydia infections. A meta-analysis of randomized clinical trials. Sex Transm Dis 2002;29:497-502

30. Manhart LE, Gillespie CW, Lowens MS, et al. Standard treatment regimens for nogonococcal urethritis have similar but decline cure rates: a randomized controlled trial. Clin Infect Dis 2013;56:934-42

- **Recent study documenting lower microbiologic cure rates for *C. trachomatis* infection in men with NGU than previously reported.**

31. Kong FYS, Tabrizi SN, Law M, et al. Azithromycin versus doxycycline for the treatment of genital chlamydia infection: a meta-analysis of randomized controlled trials. Clin Infect Dis 2014;59:193-205

- **A detailed review and meta-analysis of treatment studies of genital *C. trachomatis* infections through 2013.**

32. Khosropour CM, Dombrowski JC, Barbee LA, et al. Comparing azithromycin and doxycycline for the treatment of rectal chlamydial infection: a retrospective cohort study. Sex Transm Dis 2014;41:79-85

33. Khosropour CM, Manhart LE, Colombara DV, et al. Sub-optimal adherence to doxycycline and treatment outcomes among men with non-gonococcal urethritis: a prospective cohort study. Sex Transm Infect 2014;90:3-7

34. Ito S, Ysuda M, Seike K, et al. Clinical and microbiological outcomes in treatment of men with non-gonococcal urethritis with 100 mg twice-daily dose regimen of sitafloxacin. J Infect Chemother 2012;18:414-18

35. Takahashi S, Hamasuna R, Yasuda M, et al. Clinical efficacy of sitafloxacin 100 mg twice daily for 7 days for patients with non-gonococcal urethritis. J Infect Chemother 2013;19:941-5

36. Miyashita N, Niki Y, Matsushima T. In vitro and in vivo activities of sitafloxacin against Chlamydia spp. Antimicrob Agents Chemother 2001;45:3270-2

37. Roblin PM, Reznik T, Kutlin A, et al. In vitro activity of rifamycin derivatives ABI-1648 (Rifalazil, KRM-1648), ABI-1657 and ABI-1131 against Chlamydia trachomatis and recent clinical isolates of Chlamydia pneumoniae. Antimicrob Agents Chemother 2003;47:1135-6

38. Geisler WM, Pascual ML, Mathew J, et al. Randomized, double-blind, multicenter safety and efficacy study of rifalazil compared with azithromycin for treatment of uncomplicated genital Chlamydia trachomatis infection in women. Antimicrob Agents Chemother 2014;58:4014-19

- **Only recent published treatment study of a new drug for *C. trachomatis* infection in women.**

39. de Vries HJC, Smelov V, Middleburg JG, et al. Delayed microbial cure of lymphogranuloma venereum proctitis with doxycycline treatment. Clin Infect Dis 2009;48:e53-6

40. Méchaï F, de Barbeyrac D, Aoun O, et al. Doxycycline failure in lymphogranuloma venereum. Sex Transm Infect 2010;86:278-9

41. Oud EV, de Vrieze NH, de Meij A, de Vries HJ. Pitfalls in the diagnosis and management of inquinal lymphogranuloma venereum: important lessons from a case series. Sex Transm Infect 2014;90:279-82

42. Vall-Mayans M, Isaksson J, Caballero E, et al. Bubonic lymphogranuloma venereum with multidrug treatment failure. Int J STD AIDS 2014;25:306-8

43. Nieuwenhuis RF, Ossewaarde JM, van der Meijden WI, et al. Unusual presentation of early lymphogranuloma venereum in an HIV-1 infected patient: effective treatment with 1 g azithromycin. Sex Transm Infect 2003;79:453-5

44. Kurz H, Gopfrich H, Huber K, et al. Spectrum of pathogens if inpatient children and youths with community-acquired pneumonia: a 3 year survey of a community hospital in Vienna, Austria. Wien Klin Wochenschr 2013;125:674-9

45. Conklin L, Adjemian J, Loo J, et al. Investigation of a Chlamydia pneumoniae outbreak in a federal correctional facility in Texas. Clin Infect Dis 2013;57:639-47

46. Capelestagui A, Espana PP, Bilbao A, et al. Poblational Study of Pneumonia (PSoP) Group. Etiology of community-acquired pneumonia in a population-based study: link between etiology and patients characteristics, process of care, clinical evolution and outcomes. BMC Infect Dis 2012;12:134

47. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Disease Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44:S27-71

48. Vergis EN, Indorf A, File TM, et al. Azithromycin vs cefuroxime plus erythromycin for empirical treatment of community-acquired pneumonia in hospitalized patients. Arch Intern Med 2000;160:1294-300

49. Pletz MW, Rohde G, Schutte H, et al. CAPNETZ-Studiengruppe. Epidemiology and aetiology of community-acquired pneumonia. Dtsch Med Wochenschr 2011;136:775-80

50. FDA website. Available from: http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm304177.htm

51. Dzhindzhikhashvili MS, Joks R, Smith-Norowitz T, et al. Doxycycline suppresses Chlamydia pneumoniae-mediated increases in ongoing immunoglobulin E and interleukin-4 responses by peripheral blood mononuclear cells of patients with allergic asthma. J Antimicrob Chemother 2013;68:2363-8

52. Johnston SL, Blasi F, Black PN, et al. The effect of telithromycin in acute exacerbations of asthma. N Engl J Med 2006;354:1589-600

53. Sutherland ER, King TS, Icitovic N, et al. A trial of clarithromycin for the treatment of suboptimally controlled asthma. J Allergy Clin Immunol 2010;126:747-53

Affiliation

Stephan A Kohlhoff[†1,2] MD &
Margaret R Hammerschlag[1,2] MD
[†]Author for correspondence
[1]SUNY Downstate Medical Center, Division of Infectious Diseases, Department of Pediatrics, 450 Clarkson Ave., Brooklyn, NY 11203-2098, USA
E-mail: skohlhoff@downstate.edu
[2]SUNY Downstate Medical Center, Division of Pediatric Infectious Diseases, Department of Medicine, Brooklyn, NY, USA