
Leading articles

Treatment of chlamydial genital infection

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Effective treatment is available for most sexually transmitted bacterial diseases, although in many cases it still falls short of being ideal. A major problem is that symptoms of genital infection are non-specific, being variations on the themes of genital ulcer or genital discharge, and it is difficult to make a precise aetiological diagnosis. Furthermore, the underlying cause is frequently polymicrobial. The specific treatment of chlamydial genital infection is therefore inextricably entwined with the syndromic management of genital disease. Lower genital tract infection usually precedes infection of the upper genital tract, and it is the latter which is responsible for the more serious consequences of chlamydial genital infection, for example infertility, increased risk of ectopic pregnancy and persistent pelvic pain following pelvic inflammatory disease (PID) in women. Reactive arthritis may be a debilitating consequence of sexually acquired chlamydial infection in either sex. Because of the likelihood of further sexual transmission and the possibility of development of upper genital infection and its sequelae in patients with only minimal symptoms or signs, it is important to treat *Chlamydia trachomatis* infection whenever it is detected, and to ensure that treatment schedules for the management of all genital infections include adequate cover for possible *C. trachomatis* infection.

Tetracyclines have been the mainstay of antichlamydial therapy, and of non-specific genital infection, for over 20 years. The current Centers for Disease Control and Prevention (CDC) recommendation is oral doxycycline 100 mg bd for 7 days.¹ It should be noted that this regimen differs from the 100 mg once-daily dosage of doxycycline used for most other conditions. There is no advantage in prolonging the course. For acute upper genital tract infection, e.g. PID, intravenous therapy may be necessary. Intravenous preparations of doxycycline are not available in the UK, necessitating the use of parenteral tetracycline hydrochloride.

The current widely used alternative to oral doxycycline is erythromycin, usually recommended as erythromycin base 500 mg 6 hourly for 7 days. However, a large number of

patients will experience gastrointestinal side-effects on this regimen. Another option is to give erythromycin as the stearate 500 mg bd for 10 days. The incidence of gastrointestinal side-effects with either the tetracyclines or erythromycin is a cause for concern, resulting in unreliable compliance. Furthermore, although the eradication of *C. trachomatis* approaches 100%, the clinical cure rate is approximately 80%, a figure not significantly different from the clinical cure rate obtained with the same agents in non-gonococcal, non-chlamydial genital infections, such as non-specific urethritis and cervicitis. Decreased sensitivity to tetracyclines and macrolides has been reported, but its clinical relevance remains uncertain.² Tetracyclines are usually active against *Mycoplasma hominis* and *Urea-plasma urealyticum*, although the precise role of these organisms in genital infection continues to be contentious. In contrast, erythromycin and most other macrolides are inactive against *M. hominis*. There is, therefore, room for improvement, and the development of new macrolides and fluoroquinolones with clinically useful activity against *C. trachomatis* is to be welcomed.

The use of penicillins for chlamydial infections continues to be controversial. Amoxycillin has the CDC seal of approval in a dose of 500 mg orally tds for 7–10 days.¹ The recommendation is qualified with the statement that it should only be used for pregnant women with chlamydial infection who are unable to tolerate erythromycin.¹ Alary and colleagues³ recently compared amoxycillin and erythromycin for chlamydial infection in pregnancy, and found that the former was better tolerated. Whilst both drugs were highly effective in eradicating the organism, 12 of 99 treated with erythromycin stopped medication because of side-effects, compared with one of 100 treated with amoxycillin.³ Other penicillins, and all cephalosporins, have no role in the management of chlamydial infections. Indeed, it must be stressed that any sexually transmitted disease treatment regimen involving cephalosporins must be supplemented with an antibiotic effective against chlamydiae (mycoplasmas are also intrinsically resistant to all β -lactam antibiotics).

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Quinolone antibiotics are usually bactericidal against *C. trachomatis*, at or around the MIC. However, their clinical efficacy has been somewhat disappointing. The first quinolone antibiotic to show potentially useful activity against *C. trachomatis* was ciprofloxacin, and initial studies were encouraging.⁴ However, it soon became apparent that ciprofloxacin was not reliable for chlamydial infections, and should not be used for this purpose, along with other quinolones with less in-vitro activity against *C. trachomatis*, for example norfloxacin, fleroxacin, lomefloxacin and pefloxacin.⁵ A short report by van der Willigan *et al.*⁶ demonstrated that clinical failure with ciprofloxacin was not associated with development of resistance during therapy. Ofloxacin, which is only twice as active as ciprofloxacin *in vitro*,⁵ is highly effective in eradicating *C. trachomatis*. Blomer *et al.*⁷ treated 356 women with chlamydial genital infection orally with either 200 mg bd or 400 mg once daily for 9 days, and 354 were cured at the end of therapy. Hooton and co-workers⁸ used 300 mg bd for 7 days to treat cervical chlamydial infection.⁸ At 28 days' follow-up, 26 of 28 women were cured of infection, with one of the two failures admitting to unprotected intercourse during the follow-up. The use of a single daily dose has the advantage of improved compliance, and a study by Kitchen *et al.*⁹ of 400 mg once daily for 7 days yielded 100% microbiological cure in ten men and 28 women. Whilst authorities appear to accept the use of a 400 mg single oral dose of ofloxacin for treating gonorrhoea, the CDC recommends 300 mg bd for 7 days for chlamydial infection, not 400 mg (either as a single or divided daily dosage) for 7 days as suggested by the studies reported above.¹ Not only is a 300 mg regimen incompatible with the 400 mg single dose for gonorrhoea, but ofloxacin is not marketed in the UK in a 300 mg formulation. Further studies are required to confirm the ideal regimen, particularly with regard to the efficacy of single daily dosage, the length of course, and prolonged follow-up with particular emphasis on clinical cure in contrast to organism eradication.

Reports on the in-vitro activity of newer quinolones continue to appear,^{5,10-13} but reports of good clinical studies are few. Tanaka and colleagues¹⁴ treated 29 men with chlamydial urethritis, and nine men with chlamydia-negative urethritis with 300 mg sparflaxacin daily for 7 or 14 days. At the end of therapy, all patients were clinically cured, and *C. trachomatis* could not be isolated from any patient. Phillips *et al.*¹⁵ reported the results of a double-blind multicentre study of sparflaxacin or doxycycline for men with urethritis. Patients received sparflaxacin, 200 mg on day 1 followed by 100 mg daily for a total of 3 or 7 days, with 243 patients in each group, or doxycycline 200 mg daily for 7 days (239 patients). Final follow-up was on day 25. Although the 7 day regimen was more effective than the 3 day regimen in eradicating this organism, clinical cure for all three regimens was approximately 80%, irrespective of the presence or absence of *C. trachomatis* at the start of treatment.

Trovaflaxacin, a fluoronaphthyridone antibiotic, shows excellent activity against *C. trachomatis*.^{12,16} The peak serum concentration of this compound after a 200 mg dose is 2.2 mg/L, some 30 times the MIC for chlamydiae, and with a half-life of 10 h, a single daily dosage regimen should be effective. Dose ranging studies reported by Martin *et al.*¹⁶ indicate that 200 mg once daily for 5-7 days will eradicate *C. trachomatis* from the lower genital tract in men and women. Thirty of 31 men with non-gonococcal urethritis were clinically cured.¹⁶

As indicated earlier, activity against *C. trachomatis* is only part of the story. The in-vitro activity of quinolones against *M. hominis* and *U. urealyticum* is variable, with generally greater activity against *M. hominis*. There is often a four- to eight-fold range of MICs for each species⁵ and unreliable activity against the genital mycoplasmas may explain the disappointing lack of clinical cure in non-gonococcal infections (NGI) treated with quinolones effective against *C. trachomatis*. Whilst a >95% cure rate is demanded of a single dose treatment for uncomplicated gonorrhoea, a 80% clinical cure is still regarded as acceptable following a course of therapy for NGI, even when *C. trachomatis* has been eradicated. Furthermore a failing of many NGI studies is that the follow-up period is too short to detect clinical relapse.

The spectrum of activity of quinolones suggests that they may have a role in the treatment of PID. PID is a polymicrobial condition, and although *C. trachomatis* is the major pathogen, therapy should also be active against *Neisseria gonorrhoeae*, *M. hominis*, coliforms and the non-sporeforming anaerobes. It is thus apparent that only the more recently developed quinolones are likely to be effective. Since the accuracy of diagnosis on clinical criteria alone is poor, PID studies frequently suffer from a lack of strict standardized protocols, which can make interpretation of the results difficult, and may give a false impression of efficacy.¹⁷ Studies that do not involve laparoscopic confirmation of disease, or have inadequate microbiological investigations, must be interpreted with caution. Soper and co-workers¹⁸ treated women with laparoscopically confirmed PID with parenteral ofloxacin 400 mg bd for at least 3 days, followed by 400 mg bd orally for a total of 10-14 days. *N. gonorrhoeae* was present in 69.4%, and *C. trachomatis* in 16.7% of patients. All 30 patients followed up were culture-negative for *N. gonorrhoeae*. One woman initially negative for *C. trachomatis* was positive at follow-up, but admitted to unprotected intercourse. All patients responded clinically.¹⁸ Much PID is treated on an ambulant basis and there is a need for single oral agent therapy. Wendel *et al.*¹⁹ treated 37 women with 400 mg ofloxacin bd for 10 days. Thirty-five women (95%) were clinically cured. Ofloxacin eradicated all 21 gonococcal infections, and six of seven *C. trachomatis* infections (the one failure may have been a reinfection).¹⁹ Faro²⁰ suggested that anaerobes and aerobic bacteria other than *N. gonorrhoeae* and *C. trachomatis* were usually not

involved in early salpingitis, only becoming important when peritonitis developed. This, he argues, may justify the use, for outpatient therapy, of a drug such as ofloxacin that does not have activity against anaerobes, although he indicates that additional oral therapy with clindamycin or metronidazole might be necessary.²⁰ This view is endorsed in the 1993 CDC sexually transmitted diseases treatment guidelines.²¹

A multicentre study of 249 women with PID, treated with oral ofloxacin or cefoxitin/doxycycline, found *N. gonorrhoeae* in 16% and *C. trachomatis* in 12% of patients.²² All patients were clinically improved on follow-up and *N. gonorrhoeae* and *C. trachomatis* were eradicated from all patients treated with ofloxacin.²² The majority of the women in this study had non-gonococcal, non-chlamydial PID, and the authors interpret this as indicating that the need for activity against anaerobes when treating outpatient PID is questionable, irrespective of the presence or absence of gonococcal or chlamydial infection. Although ofloxacin is now an acceptable single-agent outpatient therapy for PID, the anaerobe controversy will continue. Whether studies with compounds with greater in-vitro activity against anaerobic organisms, for example clinafloxacin or trovafloxacin, will demonstrate superior clinical results remains to be seen. Nielson *et al.*²³ failed to demonstrate any advantage of giving women undergoing first trimester abortion a single oral dose of 400 mg ofloxacin 1.5–2 h beforehand, compared with a placebo.²³ The lack of efficacy may be due to unfavourable pharmacokinetics, and quinolones with similar antimicrobial activity and longer half-life may prove more effective.

The successful treatment regimens for the macrolides roxithromycin, josamycin and clarithromycin in chlamydial and non-chlamydial, non-gonococcal, lower genital tract infection have been reviewed by Handsfield²⁴ and Ridgway.²⁵ In essence, all three are effective when given in standard doses twice daily for 7–10 days. Josamycin has been used in pregnancy for the treatment of chlamydial lower genital tract infection. The results are similar to those obtained with standard doxycycline therapy, both with regard to eradication of *C. trachomatis* and clinical cure. Therefore, other than their reduced gastrointestinal side-effects compared with erythromycin, there appears to be little advantage in using these regimes over conventional therapies.

The azalide azithromycin (9-deoxy-9a-methyl-9a-aza-9a-homoerythromycin) has a 15-membered ring with a methyl substituted nitrogen in the aglycone ring. Apart from conferring acid stability, other notable features are high tissue penetration, low serum levels and a prolonged half-life.²⁶ This makes single-dose therapy of organisms with a long generation time, such as *C. trachomatis*, possible. Such a possibility, if borne out in clinical practice, could have dramatic benefits in the treatment of non-gonococcal genital infection. A number of well conducted, large studies have demonstrated that this is indeed so.²⁷ A

single 1 g oral dose of azithromycin is of equivalent efficacy as oral doxycycline 100 mg bd for 7 days, and is recommended as a first-line treatment for uncomplicated urethral, cervical and rectal chlamydial infection.¹ It may seem that a major drawback to azithromycin therapy is cost. The approximate cost of 1 g azithromycin is £7–9, compared with £3–5 for a week's course of doxycycline (100 mg bd). However, acquisition cost is only one component of the treatment costs. Carlin & Barton²⁸ looked not only at drug costs, but also at the cost of follow-up clinic visits. They found that for every 100 patients there was an overall saving of £360 in the azithromycin-treated group compared with a conventional doxycycline-treated group.

As discussed earlier, eradication of *C. trachomatis* does not necessarily equate with clinical cure. Azithromycin appears to be neither better nor worse than other treatments in this respect. Thorpe *et al.*²⁹ recently reported a multicentre study of chlamydial cervicitis and urethritis. Of 347 patients treated with single-dose azithromycin, 338 (97%) were bacteriologically cured, compared with 161 of 163 (99%) patients treated with conventional doxycycline. At 2 weeks, the clinical cure rates were 86% and 83% respectively.²⁹ That is a disappointingly low level. The syndromic approach to treating non-gonococcal urethritis with azithromycin was specifically addressed in the multicentre study reported by Stamm and colleagues.³⁰ As expected, eradication of *C. trachomatis* was similar in the azithromycin- and doxycycline-treated groups, although it is noteworthy that three patients in the former group, apparently clear of the organism at 2 weeks' follow-up, were infected at week 5. Only one of these patients admitted re-exposure, raising the possibility of suppression rather than eradication of the organism by azithromycin. Cumulative clinical cure rates overall were 81% for azithromycin and 77% for doxycycline. The presence of *C. trachomatis* or *U. urealyticum* made no difference to likely clinical outcome. Indeed, despite good in-vitro activity of both azithromycin and doxycycline against *U. urealyticum*, overall microbiological cure rates were 45% and 47% respectively.³⁰

The role of azithromycin in PID is less clear, although preliminary studies suggest that it may be at least equivalent to conventional therapy, albeit in a shorter multidose course.²⁷

We clearly still have much to learn about both the pathogenesis and the therapy of genital infection associated with *C. trachomatis*. New therapies have advantages with regard to compliance and side-effects profile, but still do not offer optimal clinical cure. To the patient, eradication of a known pathogen is cold comfort if symptoms persist and the clinician cannot explain why, or guarantee cure.

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