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Concurrent Gonococcal and Chlamydial Infection

How Best to Treat

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Abstract

Clinicians treating concurrent gonococcal and chlamydial infections have a variety of drugs to choose from. *Neisseria gonorrhoeae* is adept at developing resistance and the choice of antibiotic must be dictated to some extent by the patterns of resistance in the locality of the clinician. In contrast, resistance of *Chlamydia trachomatis* to some classes of drugs has been shown *in vitro* but does not appear to be clinically important at present.

The success of treatment depends on patient compliance with the drug administration schedule. With these organisms, which can be carried asymptomatically, many patients are unlikely to comply with courses of antibiotics.

Although single-dose therapy with azithromycin is available and established for chlamydial genital infection, it is more expensive and difficult to justify in a cash limited Healthcare system, and its efficacy for treating concurrent gonococcal infection requires further study. In patients where compliance is likely to be of concern, its use may be justified.

Another major deterrent for completing antibiotic courses is the adverse effect profile. Most of the available drugs cause only minor adverse effects, in particular gastrointestinal. Ofloxacin has a better profile than doxycycline but is considerably more expensive. Newer fluoroquinolones, found to be effective *in vitro*, are

being assessed in clinical studies. However, more evidence is required before recommending these over the tried and tested therapies.

Neisseria gonorrhoeae and *Chlamydia trachomatis* serovars D-K are the major sexually transmitted bacteria globally, which both individually and concurrently cause genital and ocular disease in men, women, and infants. These organisms can be carried asymptomatically or cause diseases ranging from uncomplicated infections such as urethritis in men or mucopurulent cervicitis in women to sequelae such as epididymitis, sexually acquired reactive arthritis, and pelvic infection with complications of tubal pathology leading to infertility, ectopic pregnancy and chronic pelvic pain.[1,2] Other bacteria have been implicated as causes of nonspecific genital infection, either nongonococcal urethritis or mucopurulent cervicitis. These organisms are potentially transmitted concurrently with *C. trachomatis* and *N. gonorrhoeae*. The role of genital mycoplasmas is controversial but the activity of drug regimens against these organisms should be considered in order to provide optimal treatment to patients.[3]

1. Treatment Rationale

The aims of treatment are to achieve microbiological cure for both infections of greater than 95% and to achieve clinical cure, that is absence of symptoms. The 1998 Centers for Disease Control and Prevention (CDC) recommended regimens for *N. gonorrhoeae* are shown in table I and for *C. trachomatis* in table II.[4]

Patients diagnosed with gonococcal infection should also receive treatment with a regimen effective against uncomplicated chlamydial genital infection. Between 20 to 60% of patients infected with gonorrhoea also have *C. trachomatis* infection. The cost of therapy for *C. trachomatis* is less than the cost of testing. Therefore, in some populations where some tests have low sensitivity, this approach is more cost-effective. In geographical areas where co-infection rates are low, and sensitive tests are available, the CDC suggest that clinicians might prefer to test for *C. trachomatis* rather than to treat presumptively. Compliance of the patient in returning for follow-up should also be considered when choosing such a management strategy.

The CDC recommendations are based on studies of the efficacy of antibiotic therapy. However, many of these studies are methodologically flawed; they have often involved small numbers of patients, a short duration of follow-up, no details on treatment of sexual partners, and no distinction between persistence or re-infection at follow-up. In particular, the methodologies for testing for *C. trachomatis* vary from study to study. The sensitivity of culture for *C. trachomatis* is only 60 to 80% which affects the accuracy of evaluations performed after therapy.[5] As some treatments may induce the latent state, follow-up of less than 1 month may be insufficient for the organisms to have reverted to the normal infectious state.[6]

There are particular problems in assessing clinical efficacy in men because of the persistence of urethritis. There is evidence that inflammation may occur following eradication of the original infecting organism which is immunologically mediated.[7] There is no precise definition of persistent urethritis and the presence of polymorphonuclear leucocytes (PMNs) in the absence of symptoms is of uncertain significance. Most studies have not defined clinical cure in a systematic way, and there is a

Table I. Recommended treatment regimens for uncomplicated gonococcal and chlamydial infections of the cervix, urethra and rectum[4]

Drug	Dosage
One of the following agents:	
Cefixime	400mg orally single dose
Ceftriaxone	125mg intramuscularly single dose
Ciprofloxacin	500mg orally single dose
Ofloxacin	400mg orally single dose
Plus one of the following agents:	
Azithromycin	1g orally single dose
Doxycycline	100mg orally twice daily for 7 days

Table II. Regimens for the treatment of uncomplicated chlamydial infection of the cervix, urethra and rectum[4]

Drug	Dosage
Recommended regimens	
Azithromycin	1g orally, single dose
Doxycycline	100mg orally twice daily for 7 days
Alternative regimens	
Erythromycin base	500mg orally 4 times daily for 7 days
Erythromycin ethylsuccinate	800mg orally 4 times daily for 7 days
Ofloxacin	300mg orally twice daily for 7 days

subjective element to the diagnosis of persistent urethritis. The discrepancies between some studies may be because of different follow-up periods between the completion of antibiotic therapy and when patients are re-assessed.

2. *In Vivo* Activity Against *Neisseria gonorrhoeae* and *Chlamydia trachomatis*

Four classes of antibacterials are considered for the treatment of infections by these organisms, the β lactams, tetracyclines, macrolides and fluoroquinolones.

2.1 β Lactams (Cephalosporins and Penicillins)

The choice of treatment for *N. gonorrhoeae* depends upon the epidemiology of antibiotic resistance in the geographical area being considered. Penicillinase-producing *N. gonorrhoeae* (PPNG) are common in many parts of the world. Hence, the CDC recommends that a third generation cephalosporin is given initially pending results of sensitivity testing.[4] The prevalence of PPNG in the UK is relatively low. Therefore, the national guidelines produced by specialists in genitourinary medicine suggest that amoxycillin and probenecid can be used provided that the infection was not contracted from an area where PPNG is common.[8]

Ceftriaxone 125mg as a single intramuscular injection provides sustained high bactericidal serum concentrations and a bacteriological cure rate of 99.1% for uncomplicated urogenital and anorectal infections in published clinical trials.[9,10] Cefixime has a similar antimicrobial spectrum but a single 400mg oral dose does not provide as high nor as sustained bactericidal concentrations as the intramuscular ceftriaxone dose. However, the bacteriological cure rate is 97.1% on published evidence and the advantage of cefixime is oral administration.[10,11]

Penicillins and cephalosporins are not satisfactory for treatment of *C. trachomatis* infections. They are at best bacteriostatic and relapse is likely on cessation of therapy. The exception for recommending their use may be chlamydial infection in pregnancy.[12]

2.2 Tetracyclines

Some geographical areas worldwide have a high level of tetracycline-resistant gonococci. Hence this antibiotic class is not recommended by CDC for treatment for *N. gonorrhoeae* infections.

Microbiologically, there is little to choose between the various tetracyclines for treating chlamydial infections, as failure rates are within the range 0 to 8%.[13] Minocycline and doxycycline have longer half-lives than tetracycline allowing for less frequent administration. Absorption of tetracyclines, apart from doxycycline and minocycline, is decreased by various substances including milk and antacids. Tetracyclines may exacerbate renal failure and all are known to cause gastrointestinal adverse effects of nausea, vomiting and diarrhoea. Some, particularly the triple tetracycline preparation (chlortetracycline/demeclocycline/tetracycline), are more likely to result in light sensitive skin reactions.

Doxycycline 100mg twice daily for 7 days is the regimen against which the majority of new treatments for *C. trachomatis* infections have been compared for the past 10 years. There is considerable literature available on the use of this regimen. Failure rates defined as '*C. trachomatis* positive' on follow-up range from 0 to 7% in men with urethritis and 0 to 8% in women with cervicitis.[14-16]

Horner et al.[7] evaluated a single initial dose of doxycycline 200mg followed by 100mg twice daily for 13 days, with evaluation between 13 to 29 days using direct fluorescent-antibody (DFA) and polymerase chain reaction (PCR) assays. The microbiological efficacy was 96%. Other doxycycline-containing regimens have been assessed including an initial single 200mg dose followed by 100 mg/day for 6 days. Using this regimen, Hay et al.[17] studied 112 patients with non-gonococcal urethritis, of whom 55 had chlamydial urethritis. Patients were evaluated using DFA, enzyme immunoassay (EIA) and PCR assays. Urethritis was defined as greater than 5 PMN/high power field on Gram stain of urethral smear. At follow-up of patients with chlamydial infection, initially 65% had persistent urethritis. Two of these patients had persistent chlamydial infection, 1 by all 3 methods and 1 by EIA only. This regimen has not been evaluated in women.

Tetracycline 500mg 4 times daily for 7 days has been shown to have a failure rate of between 0 to 8% in men and women.[18-20] Tetracycline 250mg 3 times daily for 7 days had a similar failure rate.[19] Minocycline 100mg twice daily for 7 days has a similar efficacy to doxycycline 100mg twice daily or minocycline 100 mg/day.[21,22] Minocycline was associated with fewer adverse effects. Triple tetracycline (chlortetracycline/demeclocycline/tetracycline) 300mg twice daily for 7 days has an efficacy of 100% bacteriological cure at 2 weeks in women.[23] However, a study by Munday et al.[24] following 43 women for up to 2 years found that 3 had chlamydial infection 3 months after treatment, although 2 were probably re-infections. Oxytetracycline (250mg 4 times daily) when given for more than 2 weeks in women had a bacteriological cure rate of more than 90%.[24]

No studies answer the questions as to whether lower doses or dose intervals of the various tetracyclines are as effective as those described above.

2.3 Macrolides

The activity of various macrolides against *N. gonorrhoeae, C. trachomatis* and the genital mycoplasmas is shown in table III.[25] The pharmacokinetics of an antibiotic *in vivo* influence the extracellular concentration for a given administered dose. The new azalide/macrolide, azithromycin, has a long half-life and is concentrated intracellularly, giving concentrations sufficient to be effective as single-dose treatment for *N. gonorrhoeae* and *C. trachomatis*.[26] The bioavailability of antibiotics also depends on the formulation used and how and when it is taken. For example, greater absorption of erythromycin is seen with the enteric-coated pellets than tablets.[27] Irrespective of formulation, the same oral dose may give different plasma concentrations of erythromycin base in different people because of variations in rate of gastric emptying, neutralising and diluting effects of food and liquids on gastric acid, and the pH at which enteric coatings are dissolved.[27] Studies of erythromycin are complicated by the variety of preparations available including erythromycin base, erythromycin stearate and erythromycin ethylsuccinate. The clinical significance of bioavailability in the treatment of infected patients is unknown.

Resistance of *N. gonorrhoeae* to macrolides is poorly understood but cross-resistance is to be ex-

Table III. Antibiotic susceptibility of *N. gonorrhoeae*, *C. trachomatis* and genital mycoplasmas to macrolides, reported as minimum inhibitory concentrations (mg/L) [reproduced from Ridgway,[25] with permission]

Drug	*N. gonorrhoeae*	*C. trachomatis*	*U. urealyticum*	*M. hominis*
Clarithromycin	1.0–2.0	0.007	0.025–1.0	8–64
Josamycin	0.25–1.0	0.03	0.02–0.5	
Roxithromycin	0.25–1.0	0.03	0.06–1.0	8–64
Midecamycin acetate	1.0	0.06	0.03–0.25	0.008–0.12
Erythromycin	0.6–2.0	0.06	0.12–2.0	>32
Azithromycin	0.12–0.25	0.125	0.12–1.0	2–16

pected. Erythromycin is not a satisfactory treatment for gonorrhoea *in vivo* in a single oral dose although it is highly active against the gonococcus *in vitro*.

In a multicentre study, Handsfield[28] found that a single oral dose of azithromycin 1g provided a bacteriological cure rate of 85 to 95% in patients with uncomplicated gonorrhoea. A study in the UK found that this dose was effective against gonorrhoea in 95% of men with gonococcal urethritis, and 100% of patients with cervicitis, rectal and pharyngeal infection.[29]

A further study by Handsfield et al.,[30] using a single oral dose of azithromycin 2g showed similar efficacy to an intramuscular injection of ceftriaxone 250mg and a better bacteriological cure rate than the 1g dose of azithromycin. The incidence of gastrointestinal adverse effects was much higher with azithromycin 2g (35% compared with 2.5% with ceftriaxone). It would appear that azithromycin is very effective as a 1g oral dose providing macrolide resistance is not a significant epidemiological problem.

The most active available macrolide against *C. trachomatis* is clarithromycin. Twice daily administration of clarithromycin 250mg for 5 to 7 days should be satisfactory in treating chlamydial infection.[31] Azithromycin has a higher minimum inhibitory concentration (MIC) than clarithromycin (0.125 mg/L *vs* 0.007 mg/L, respectively) [table III] but because of much higher intracellular levels and a longer half-life, it can be used as single-dose therapy even though chlamydiae have a >48-hour asynchronous life cycle.[25] An early dose-ranging study demonstrated the efficacy of a single oral dose of azithromycin 1g, with eradication of the organisms in 43 out of 44 infected individuals.[32] In a double-blinded, placebo-controlled study, a single dose of azithromycin 1g was compared with a 7-day course of doxycycline 100mg twice daily.[33] Both groups were clear of chlamydial infection at first follow-up (6 to 12 days). Clinical cure rates did not differ significantly at 3 weeks follow-up (89 *vs* 94%, respectively). In a small study of chlamydial infection in women,[34] 14 women with cervical infection treated with a standard course of doxycycline and 17 women treated with a single dose of azithromycin 1g were clear of infection on follow-up at 1 to 4 weeks after the start of treatment.

A larger multicentre study demonstrated that a single dose of azithromycin 1g was as effective as standard doxycycline therapy for chlamydial urethritis and cervicitis.[35] In the azithromycin group, 41/43 men (95%) and 95/98 women (97%), and 37/39 men (97%) and 185/187 women (99%) in the doxycycline group were free of infection on follow-up. Assessments of clinical cure varied between 91 to 98% and were not standardised between centres. There were no statistical differences between treatment arms.

In a study of chlamydial infection in adolescents, bacteriological cure rates of 91% (42/46) were obtained in the azithromycin 1g single-dose group and 85% (23/27) in the doxycycline 100mg twice daily group.[36] Patients in each group not achieving cure at follow-up were probably re-infected.

Some studies have addressed the problem of nonspecific genital infection, where neither *C. trachomatis* nor *N. gonorrhoeae* are isolated and microbiological cure can not be used as an end-point. These studies rely on clinical response which give less favourable cure rates of 80 to 90%.[37,38] Length of follow-up varies and criteria for clinical cure are subjective. Stamm et al.[39] reported a multicentre sexually transmitted disease clinic-based study of urethritis in men where there was a 2 to 1 randomisation of single-dose azithromycin 1g with doxycycline standard dose regimens. *C. trachomatis* was cultured in 60% of the azithromycin group and 24% of the doxycycline group. *Ureaplasma urealyticum* was cultured from 38 and 28%, respectively. The overall microbiological cure rates for these organisms were similar with either regimen (83 *vs* 90% for *C. trachomatis* and 45 *vs* 47% for *U. urealyticum*, respectively). Clinical cure rates were not dissimilar, irrespective of the presence or absence of either organism. Cumulative clinical cure rates were 81% in the azithromycin group and 77% in the doxycycline group. Reported adverse effects (23 *vs* 29%) were mild.

A multicentre study looking at treatment of chlamydial urethritis and cervicitis in community-based practices, compared azithromycin with doxycycline.[40] Bacteriological cure was achieved in 338/347 (97%) patients treated with single-dose azithromycin 1g compared with 61/63 (99%) treated with doxycycline 100mg twice daily for 7 days. Clinical cure rates were comparable at 61 versus 65% at week 1 follow-up and 86 versus 83% at week 2, respectively. Adverse effects recorded were predominantly gastrointestinal and were relatively high in this study (41 and 47%, respectively).

A few studies have reported data for patients with concurrent chlamydial and gonococcal infections. In an open comparative study of single-dose azithromycin 1g for treatment of *N. gonorrhoeae* infection, 13 patients who were identified as culture positive for *C. trachomatis* on urethral or cervical swabs and who returned for follow-up, were cured.[29] All 17 patients in a randomised, controlled trial who received oral azithromycin 2g for gonococcal infection but also had *C. trachomatis* were cured compared with 2 out of 7 patients who received ceftriaxone 125mg.[30]

A randomised controlled trial compared azithromycin administered as a single 1g dose or 500mg on day 1 followed by 250mg on days 2 and 3 with doxycycline 100mg twice daily for 7 days. Both organisms were eradicated from 20 patients identified with mixed infection irrespective of antibiotic regimen.[41] Of 183 male patients participating in a randomised, controlled trial comparing a single dose of azithromycin 1g with doxycycline 100mg twice daily, 28 had concurrent infection. Although the results are not detailed for bacterial outcome in patients with mixed infection, the overall cure rate for *C. trachomatis* was 92.4% in the azithromycin arm compared with 98.5% in the doxycycline arm, and 96.4 and 100% for *N. gonorrhoeae*, respectively. There was clear evidence of re-exposure to infected partners accounting for those patients not cured on re-assessment.[42]

2.4 Fluoroquinolones

The activity of various quinolones against *N. gonorrhoeae*, *C. trachomatis* and genital mycoplasmas is shown in table IV.[43] Fluoroquinolones such as norfloxacin, ciprofloxacin and ofloxacin have a broad antimicrobial spectrum, including high activity against *N. gonorrhoeae*. Resistance, which is not plasmid mediated, is slow to develop. These agents are commonly recommended in the treatment of gonococcal infection. Other fluoroquinolones such as fleroxacin, lomefloxacin, moxifloxacin, trovafloxacin[1] and grepafloxacin[1] also have excellent *in vitro* activity against *N. gonorrhoeae*.

Ciprofloxacin achieves high concentrations in urethral and prostatic secretions. In a study with a high prevalence of PPNG strains and strains with chromosomally mediated resistance to tetracycline and penicillin, the efficacy of oral ciprofloxacin 250mg was similar to a single intramuscular injection of ceftriaxone 125mg.[9] Adverse effects to ciprofloxacin are rare and patient acceptability is high. Ofloxacin 400mg has very good activity against *N. gonorrhoeae* with cure rates up to 100%.[44]

N. gonorrhoeae develops quinolone resistance through mutations of the genes *gyrA* (Ser-91 to Phe) and *parC* (Ser-87 to Ile).[45-47] Resistant isolates show reduced uptake of quinolones and cross-resistance to other strains. Fluoroquinolone resistance is increasingly common, especially in parts of Asia and in North America.[48-50] In an epidemiological survey in the US, approximately 1.3% of all reported gonococcal infections from 26 cities were quinolone resistant. In Sydney, Tapsall et al.[51] reported that 3.1% of isolates were resistant in 1995 and 12.4% in 1997. In the Far East, the increase of resistance from 1994 to 1997 was 12 to 72%.[52] Cross-resistance between ciprofloxacin and newer agents such as levofloxacin and sparfloxacin was demonstrated.[51,52]

Reports on clinical trials with new quinolones are few. A single oral dose of sparfloxacin 200mg

1 Trovafloxacin and grepafloxacin have been withdrawn from use.

Table IV. Antibiotic susceptibility of *N. gonorrhoeae*, *C. trachomatis* and mycoplasmas to fluoroquinolones, reported as minimum inhibitory concentrations (MICs)[43]

Drug	*N. gonorrhoeae*	*C. trachomatis*	*U. urealyticum*	*M. hominis*
Clinafloxacin	0.002	0.06	0.06–2.0	0.015–0.06
Grepafloxacin	0.004	0.06	0.12–1.0	0.015–0.06
Sitafloxacin (DU-6859a)	0.008	0.06	0.12	0.06
Ciprofloxacin	0.008	1.0	0.25–1.0	0.25–0.5
Levofloxacin	0.008	0.5		
Gatifloxacin (AM-1155)	0.015	0.12		
Trovafloxacin	0.015	0.06	0.12–0.5	0.015–0.03
Ofloxacin	0.015	0.5	1.0–4.0	0.25–1.0
Moxifloxacin	0.03	0.06	0.12	0.06
Sparfloxacin	0.03	0.06	0.06–0.5	0.008–0.015

has been shown to be effective against gonococcal urethritis in men.[53] Grepafloxacin 400mg is effective when compared with cefixime 400mg in uncomplicated gonococcal infection in men and women.[54,55] However, the single dose failed to eradicate concurrent chlamydial infection in the grepafloxacin group. Trovafloxacin as a 100mg dose was as effective as ofloxacin 400mg orally in both men and women.[56]

Dessus-Babus et al.[57] describe the development of quinolone resistance in the laboratory-manipulated L2 strain of *C. trachomatis*. Cross-resistance was found against other fluoroquinolones. The resistance is characterised as resulting from a point mutation *gyrA* of ser83 to ile. Salman and Ridgway also produced laboratory manipulated L2 isolates with ciprofloxacin and ofloxacin MICs of 256 and 512 mg/L, respectively, and complete cross-resistance (Ridgway, unpublished observations). The clinical significance of these findings is unknown.

Quinolones are generally bactericidal against *C. trachomatis* and do not appear to induce latency. Older quinolones, including norfloxacin, fleroxacin and ciprofloxacin have no place in the therapy of non-gonococcal genital infection as they are unreliable against *C. trachomatis*. Clinical studies with ofloxacin have demonstrated high eradication rates with a dose of 200mg twice daily or 400mg once daily for 7 days. 354/356 patients treated with ofloxacin for 9 days had a microbiological cure at the end of therapy.[58] An American study reporting use of ofloxacin 300mg twice daily for 7 days for chlamydial cervicitis had a greater than 95% bacteriological cure rate. One of the two patients not cured on re-assessment had unprotected intercourse.[59] An 100% cure rate was reported in a study of men and women receiving ofloxacin 400 mg/day for 7 days with follow-up for 15 days.[60] It is unclear which regimen should be used for therapy to cover co-existent chlamydial infection. In the US, the recommended dosage of ofloxacin is 300mg twice daily for 7 days.[4] This recommendation is impractical in a situation where 400mg is given initially for gonococcal infection followed by 300mg twice daily especially when the only tablets available in the UK are 200 or 400mg. Other recommendations are 400 mg/day either as a single daily dose or in divided doses.[61]

Reports of ofloxacin for treatment of concurrent gonococcal and chlamydial infection are contained within studies which have been designed to look at outcomes of treatment for single organisms. Single dose ofloxacin is ineffective in treating chlamydial infection.[58,62] In a randomised study of 7-days treatment with twice daily ofloxacin 300mg or doxycycline 100mg, 3/40 patients had concurrent infection, of whom 1 received ofloxacin and 2 received doxycycline. All 3 were successfully treated.[63] In an open study of 149 patients, in which patients with gonorrhoea received single dose of ofloxacin 400mg and patients with chlamydial infection received ofloxacin 200mg twice daily for 7 days, 16 men and 19 women with dual infection were included.[64] Results for patients with concurrent in-

fection are not reported separately but the authors conclude that ofloxacin treatment is appropriate for both gonococcal and chlamydial infections.

There are few reports of clinical studies using newer fluoroquinolones. A single dose of sparfloxacin 200mg followed by 100 mg/day for 6 days, was as effective as standard doxycycline therapy for non-gonococcal urethritis in men.[65] Grepafloxacin 400 mg/day for 7 days and trovafloxacin 200 mg/day for 5 days also compare favourably with doxycycline in the treatment of endocervical chlamydial infection.[66,67]

In nongonococcal, nonchlamydial urethritis (nonspecific urethritis) the activity of fluoroquinolones in trials is unknown. *In vitro*, the compounds show greater activity against *M. hominis* than *U. urealyticum*.[68]

3. Special Situations

3.1 Pelvic Inflammatory Disease

C. trachomatis and *N. gonorrhoeae* are the commonest pathogens identified in pelvic inflammatory disease (PID) although other organisms such as *M. hominis*, coliforms and nonsporing anaerobes have been implicated.[69] There have been few quality, controlled studies of antibiotic therapy for PID. Studies have lacked strict standardised protocols, and the accuracy of diagnosis of PID on clinical criteria is less than 65%. The CDC recommends therapy according to whether patients are managed as in- or outpatients, reflecting the severity of disease.[4] The recommended regimens follow.

- Intravenous regimen A: intravenous cefotetan 2g every 12 hours or intravenous cefoxitin 2g every 6 hours, plus doxycycline 100mg intravenously or orally every 12 hours.
- Intravenous regimen B: intravenous clindamycin 900mg every 8 hours; plus an intravenous or intramuscular loading dose of gentamicin 2 mg/kg bodyweight followed by a maintenance dose of 1.5 mg/kg bodyweight every 8 hours (daily administration may be substituted at a dose of 7 mg/kg).

Parenteral therapy may be changed to oral therapy 24 hours after clinical improvement, and oral doxycycline or clindamycin should be continued for a total of 14 days. Parenteral doxycycline is not available in the UK.

- Oral regimen A: oral ofloxacin 400mg, twice daily for 14 days, plus oral metronidazole 500mg twice daily for 14 days.
- Oral regimen B: a single intramuscular dose of ceftriaxone 250mg, or cefoxitin 2g plus a concurrent single oral dose of probenecid 1g, or another parenteral third generation cephalosporin (e.g. ceftizoxime or cefotaxime), plus oral doxycycline 100mg twice a day for 14 days (included with the above).

Any regimen used to treat PID must have antichlamydial activity. In areas where *N. gonorrhoeae* is also identified as a common cause of PID, the regimen must also have good activity against this organism, depending on its likely sensitivity. Preliminary clinical studies indicate that a course of azithromycin (500mg intravenously on day 1 then 250 mg/day orally on days 2 to 7) with or without the addition of metronidazole is an effective therapy for this disease.[70] Results of more extensive studies are awaited.

Studies on the efficacy of ofloxacin confirm that this drug has a role in the treatment of PID. In a study of women with laparoscopically confirmed PID, 36 were given parenteral ofloxacin 400mg twice daily for at least 3 days then oral 400 mg/day for 10 to 14 days.[71] *N. gonorrhoeae* was identified in 25 (69.4%) and *C. trachomatis* in 6 (16.7%) women. Of 34 patients returning for follow-up, all were negative for *N. gonorrhoeae.* One woman initially negative for *C. trachomatis* and positive at follow-up was probably re-infected. All patients responded clinically. Ofloxacin does not have activity against anaerobes, but for outpatient therapy Faro[72] suggested that organisms and anaerobic bacteria, other than *N. gonorrhoeae* and *C. trachomatis*, were usually not involved in early salpingitis. However, he indicated additional oral therapy with clindamycin or metronidazole might be necessary. Hence the CDC recommendations.

A multicentre, randomised study of oral ofloxacin versus cefoxitin/doxycycline in 249 women with PID treated in an outpatient setting identified *N. gonorrhoeae* in 16% and *C. trachomatis* in 12% of patients.[73] These organisms were eradicated from all patients treated with ofloxacin. All patients were clinically improved on follow-up. Out of 17 patients with *C. trachomatis*, 15 in the cefoxitin/doxycycline group were cured. Most women in this study had nonspecific PID. The authors considered that the need for activity against anaerobes when choosing antibiotics for treatment of outpatient PID was questionable.

Newer quinolones with greater activity against anaerobic organisms need to be studied to see whether they are clinically superior. One study of trovafloxacin alone (200 mg/day for 14 days) compared favourably with ofloxacin 400mg twice daily plus clindamycin 450mg four times daily for 14 days. Clinical and microbiological cure was 100 and 92%, respectively.[74]

Although from research published over the last 15 years it is clear that *C. trachomatis* plays a major role in PID, some clinicians still use regimens that do not have antichlamydial activity. The use of penicillins, cephalosporins and older quinolones such as ciprofloxacin with or without metronidazole to treat pelvic PID is inappropriate unless an antichlamydial drug is also prescribed.

3.2 Pregnancy

Tetracyclines and fluoroquinolones are contraindicated in pregnancy. Women infected with *N. gonorrhoeae* should be treated with either a cephalosporin or a single intramuscular dose of spectinomycin 2g. In a clinical trial of the treatment of gonorrhoea in pregnancy,[75] spectinomycin bacteriologically cured 95% of uncomplicated urogenital and anorectal gonococcal infections, its disadvantage being parenteral administration.

Erythromycin or amoxycillin have been used in pregnancy. There are concerns about the latter agent causing suppression rather than eradication of chlamydial infection but a meta-analysis has supported its use.[12] Although not yet licensed for use in pregnancy, azithromycin appears not to be teratogenic. A study involving 146 pregnant women with proven chlamydial infection demonstrated a 95% bacteriological cure rate with no adverse sequelae on the fetus.[76]

3.3 Treatment in Children

Gonococcal infection usually results from exposure to maternal cervical infection at birth. The most serious manifestations are ophthalmia neonatorum and sepsis including arthritis and meningitis. The recommended treatment regimen is a single intravenous or intramuscular dose of ceftriaxone 25 to 50 mg/kg bodyweight to a maximum of 125mg. Topical antibiotic therapy is inadequate and unnecessary if systemic treatment is given. Disseminated infection requires 7 day course.

In older children who weigh more than 45kg, one of the regimens recommended for adults can be used. Quinolones are not approved for use in children because of concerns about toxicity based on animal studies. However, their use in children with cystic fibrosis has not demonstrated adverse effects. For children under 45kg, a single intramuscular dose of ceftriaxone 125mg or spectinomycin 40 mg/kg bodyweight may be used.

Chlamydial infection in children often accompanies gonococcal infection. Ophthalmia neonatorum and infant pneumonia are the commonest manifestations. Recommended treatment is erythromycin 50 mg/kg divided into 4 oral doses daily for at least 10 to 14 days. Topical antibiotic therapy alone is inadequate for treatment, and unnecessary with systemic therapy. The eyes should be kept clean.

Chlamydial infection in older children is uncommon and sexual abuse must be considered as a cause. Erythromycin base 50 mg/kg/day is recommended for children weighing less than 45kg. A single oral dose of azithromycin 1g may be used in children who are less than 8 years of age but weigh more than 45kg. The adult regimen of azithromycin or doxycycline can be used in older children.

4. Compliance

Many drug regimens fail not because the drugs are inappropriate, but because patients do not take them according to instructions. Therefore, in choosing antibiotic regimens, consideration should be given to the likelihood that the patient will comply. Noncompliance is overcome with single-dose therapy, however, azithromycin is more expensive than therapy with doxycycline. In most studies, at least 30% of patients do not follow advice on administration.[77] However, in one study, despite the fact that doxycycline may not have been taken appropriately, there were still few treatment failures.[78]

Consideration should be given to factors which can be modified to influence whether a patient adheres to their antibiotic regimen. Nonmodifiable factors include characteristics of patient, practitioner or illness. Evaluation of antibiotic compliance for *C. trachomatis* and *N. gonorrhoeae* did not find an association with race or gender.[79] However, those who were younger were less likely to comply with treatment.

Modifiable factors include aspects of doctor/patient interaction and dosage regimen. Increased adherence to treatment may result from tailoring regimens to a patient's daily routine, giving clear written treatment instruction, using reminders, utilising family support, providing information about missed doses and adverse effects, and checking the patient's health beliefs and understanding of the instructions.[77,80] This is extremely important when patients who have asymptomatic infection with these organisms are asked to take a course of antibiotics. There may be a difference in compliance between sexual contacts of infected patients and patients experiencing disease symptoms.[79]

The occurrence of gastrointestinal adverse effects is associated with noncompliance. Adequately informing patients of possible adverse effects during the consultation may reduce failure to take or complete the course of medication.

The complexity of the regimen, as indicated by frequency of administration, number of tablets to be taken daily and length of treatment, is related to adherence.[77,81] Therefore, once daily or twice daily regimens are recommended, although there are no worthwhile or significant differences in level of compliance between these two administration intervals. In some circumstances, missing a dose may be more serious with once daily than twice daily dosage. It may be more sensible to choose medicines whose efficacy is unlikely to be affected by occasional missed doses.[82]

The role of azithromycin as a single dose treatment of both uncomplicated gonorrhoea and chlamydial infection has much to commend it. A few studies have reported the successful treatment of concurrent infection with single dose azithromycin 2g having greater efficacy but more adverse effects than the 1g regimen. The majority of treatment failures have been attributed to re-exposure to untreated partners. Although the acquisition cost of azithromycin is considerably more than doxycycline, it may be more cost effective when all factors are considered.[83] However, there is a presumption that nonadherence leads to reduced efficacy which is not based on hard data.[26,84] Any recommendation to use single-dose azithromycin 1g should include the necessity to follow-up patients to ensure eradication of both organisms. The recommended use of azithromycin in cervical chlamydial infection is based on relatively few studies, including some with small sample size, compared with the considerable published evidence to support the use of doxycycline.

5. Conclusion

There are an array of drugs, usually used in combination, which will satisfactorily cure concurrent gonococcal and chlamydial infection. The choice of regimen will be influenced by factors which may affect compliance. In suspected poorly compliant patients, a group which includes adolescents in particular, single-dose therapy with azithromycin should be considered despite its higher cost. In areas where gonococcal resistance to macrolides is low, azithromycin would be satisfactory although it remains unlicensed for treatment of *N. gonorrhoeae*. If compliance is not such an issue, regi-

mens which result in the lowest incidence of adverse effects should be considered. Doxycycline and ofloxacin tend to be favoured by clinicians over erythromycin, but the acquisition cost of ofloxacin is higher. In patients with uncomplicated infections who are likely to return for follow-up, single-agent antibiotic regimens may be sufficient given the data reported for concurrent infection.

Newer fluoroquinolones may have better clinical outcomes in nonspecific urethritis because of their activity against mycoplasmas. The validation of this hypothesis depends upon what the role mycoplasmas have in the aetiology of nonspecific urethritis, and the results of clinical trials are awaited.

With the known ability for *N. gonorrhoeae* to rapidly develop resistance and concern at the ease with which *C. trachomatis* L2 strains can be manipulated to develop fluoroquinolone resistance in the laboratory, the search for new oral therapies for these conditions continues. The efficacy of antibiotic regimens for concurrent infection is rarely addressed in clinical trials. Although specific studies may not be feasible, results from studies of activity against single organisms should include explicit data about cure rates for concurrent infections. Physicians will then have evidence rather than opinions on which to base decisions about what treatment is best for patients with concurrent infections.

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