

Review

Antibiotic treatment of gonorrhoea—clinical evidence for choice

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Introduction

The clinician's choice of treatment for gonorrhoea focuses on clinical efficacy, patient acceptability and toxicity. These criteria inevitably encompass consideration of in vitro antimicrobial sensitivities, the pharmacokinetic properties of candidate antimicrobials, anticipated compliance, cost-effectiveness, ease of administration, patient's age, pregnancy and previous adverse drug reactions. Concomitant infection with other sexually transmitted pathogens should be sought and managed appropriately.

General considerations

Effective treatment is defined as the elimination of *Neisseria gonorrhoeae* from all anatomic sites. It also eliminates the potential for continued transmission, minimises complications from the infection, and circumvents the difficulty of ensuring follow-up assessment. An advocated and achievable minimum criterion of clinical efficacy is that treatment for uncomplicated anogenital infection should be demonstrated to eradicate > 95% of infections in sizeable clinical trials.^{1,2} This standard is independent of the prevalence of resistant strains and allows for factors other than resistance that may contribute to treatment failure. Moran and Levine also advocate additional criteria for antimicrobial selection based on the pharmacokinetics of a candidate antimicrobial and its in-vitro sensitivity against prevalent strains of *N gonorrhoeae*.¹ Antimicrobial resistance to *N gonorrhoeae* has shown relentless progression through the acquisition of multiple plasmids and chromosomal mutation. Surveillance data at local, national and international levels are therefore essential to guide the clinician, who often initiates treatment on clinical presentation without prior knowledge of the antimicrobial sensitivity of the *N gonorrhoeae* in the presenting patient.

Many antimicrobials are active against *N gonorrhoeae* and the literature contains an abundance of reports of clinical trials.^{1,3} No single regimen is universally appropriate for all patients and all health care situations. Antimicrobial resistance shows wide geographical variation, some agents have lower efficacy at non-genital sites, some are contraindicated in special circumstances such as pregnancy or in the newborn, and some are unaffordable in some countries. Nearly all clinical trials evaluating antimicrobials in the treatment of gonorrhoea solely recruit adults

with uncomplicated genital infection. These trials offer some data on treatment efficacy for rectal and pharyngeal infection, but leave a dearth of science-based data on treatment outcome for complicated infections. Treatment trials for gonococcal pelvic inflammatory disease are difficult on account of the polymicrobial considerations which dictate therapy at the onset of treatment, and disseminated gonococcal infection is infrequently encountered. Judgement of antimicrobial efficacy should not rely solely on past formal clinical trials, but include ongoing audit of effectiveness in routine clinical practice.

A number of antimicrobials achieve high treatment efficacy with single dose therapy which can be administered under direct supervision, thereby ensuring compliance.¹ Single-dose therapy is the universal practice of choice in the treatment of uncomplicated gonorrhoea and multi-dose regimes have been rendered obsolete.⁴

Antimicrobial options

This paper does not attempt to be exhaustive or to provide a historical review. It focuses on antimicrobials widely used in the United Kingdom or listed in international treatment guidelines.

Penicillins

Penicillin proved highly effective in treating gonorrhoea when introduced in the early 1940s. With escalating dose and in combination with probenecid, penicillin regimens remained the therapy of choice universally until the emergence and spread of penicillinase producing *N gonorrhoeae* (PPNG) in the 1970s. Chromosomally-mediated resistance soon followed and treatment failure matched microbiological expectation.⁵ A switch to alternative therapy became a necessity in many locations in the 1980s.⁶⁻⁸ To maintain effective treatment and control of PPNG, Jaffe and colleagues advocated community-wide use of alternative therapy when the prevalence of PPNG among gonococcal isolates within the community reached a level resulting in less than 95% efficacy for uncomplicated anogenital infection.⁶ Surveillance data in the United States in the late 1980s showed significant and sustained antimicrobial resistance to penicillin.⁹ This guided a revision in national treatment guidelines in the United States in 1989, such that penicillin, ampicillin or amoxycillin were no longer recommended as therapy for gonorrhoea.^{3,10}

Whilst penicillin is inappropriate as a commendable option for gonococcal therapy in many countries, it is still used as a first line treatment in many centres in the United Kingdom, where it is usually given in the form of a single oral dose of amoxicillin or ampicillin, together with probenecid orally at the same time. Such therapy is only reasonable if the gonococcal infection being treated is of known sensitivity to penicillin or the local prevalence of resistance low. Continued use of amoxicillin or ampicillin 2 g plus probenecid 1 g is supported by close monitoring of clinical outcome and penicillin sensitivity to *N gonorrhoeae*.^{11 12} Interestingly, historical reviews of oral penicillin therapy show that many centres were unable to achieve the 95% efficacy criterion prior to the emergence of PPNG.^{5 13} The prevalence of PPNG and chromosomally mediated resistance is not stable and varies in genitourinary clinic populations in the United Kingdom. PPNG prevalence exceeding 10% has been recently reported at Newham General Hospital and Guy's Hospital, London,^{14 15} supporting the use of non-penicillin therapy in these locations. The continued use of penicillin regimens as first line therapy in the United Kingdom in genitourinary medicine clinics demands close monitoring of clinical efficacy, high rates of follow-up for test of cure and selective use of alternative antimicrobials. Infections known to have been acquired overseas demand an alternative therapy, although endemic resistant infection is present at low prevalence and not predictable at the moment of treatment.¹⁴ Penicillin therapy is, however, cheap, easy to administer in oral form, generally well tolerated, safe to give in pregnancy, and safe to use in neonatal infection. Single dose oral penicillin regimens have high failure rates (42–60%) in treating pharyngeal gonorrhoea.¹⁶

Cephalosporins

Cephalosporins, in the form of "third-generation" preparations, have proved highly effective for more than a decade in the treatment of gonorrhoea, including PPNG and chromosomally-mediated penicillin resistance. The efficacy of ceftriaxone, given as a single dose of 250 mg intramuscularly, consistently exceeds 96%.¹⁴ This regime is recommended in North America,¹⁷ and is a standard benchmark regimen in the evaluation of newer agents.^{18–20} Ceftriaxone is favoured in comparison with other cephalosporins for its long serum half-life, and side-effects are infrequent and generally mild. Cefotaxime 500 g IM as a single dose is an alternative preparation of proven efficacy.^{4 17} These cephalosporins regimens have shown good efficacy against rectal and pharyngeal infection,^{18 21 22} and are safe and of proven efficacy in pregnancy²³ and against neonatal infection.²⁴ The drawbacks of these highly effective regimens include expense, the necessity to administer them by injection, and discomfort at the injection site, warranting the practice of using local anaesthetic as diluent. Cefixime is an oral preparation with similar spectrum to that of ceftriaxone. A single oral

dose of cefixime 400 mg has been shown to be of equivalent efficacy to ceftriaxone.^{1 25 26} The treatment of genital infection with *N gonorrhoeae* is, however, not listed on the product licence of cefixime in the United Kingdom. Cephalosporins, in addition to being highly effective for gonorrhoea, are also valuable antimicrobials against a range of other serious infections. Whilst alternative, cheaper, equally effective, oral antimicrobials are available for therapy against gonorrhoea in the United Kingdom, cephalosporins use remains focused on other serious infections, to limit selection pressure for the development of microbial resistance to these agents.

Fluoroquinolones

Fluoroquinolones became popular therapy in the United Kingdom during the mid-1980s and are widely used as effective, oral therapy against penicillin-resistant *N gonorrhoeae*. The most widely used quinolone against uncomplicated gonorrhoea is ciprofloxacin and the efficacy of this agent has been recently reviewed.²⁷ Efficacy reaching 100% is frequently reported, even where the prevalence of resistance to penicillin is high.²⁸ A single oral dose of 500 mg confers no clinical advantage as compared with a 250 mg dose,²⁷ although use of 500 mg is advocated to delay the development of resistance.²⁹ Ofloxacin, 400 mg orally in a single dose, compares well with ciprofloxacin,^{1 30} as does norfloxacin given as a single oral dose of 800 mg.^{1 31} Newer quinolones, such as fleroxacin, also show good clinical efficacy.²⁰ Routine use of ciprofloxacin since 1987 in one clinic has not resulted in the development of clinically significant resistance,¹⁴ although treatment failure has been documented in association with in-vitro resistance.^{32 33} Use of ofloxacin for the treatment of gonorrhoea in Hong Kong since 1985 has resulted in a significant prevalence of quinolone resistance.³⁴ Side-effects of a single dose of quinolone are rare and patient acceptability is high. Quinolones are effective in eradicating rectal and pharyngeal infection.^{27 29} They are, however, contraindicated for use in pregnancy, and in children and growing adults.

Azithromycin

Azithromycin is a newer antibiotic belonging to a class of compounds known as azalides, which resemble macrolides. It achieves a high, prolonged, intracellular concentration and is effective in single dose therapy against genital infection with *Chlamydia trachomatis*.^{35 36} It is active in-vitro against *N gonorrhoeae* and recent studies show promising efficacy in-vivo using a single oral dose. Single-dose treatment with 2 g orally gave a 98.9% (95% CI: 97.9–100%) efficacy in uncomplicated gonococcal infection,¹⁸ whereas smaller studies using a single-dose of 1 g showed marginally lower efficacy.^{37 38} The 2 g dose was associated with a high frequency (35%) of gastrointestinal side effects, which were generally mild.¹⁸ Azithromycin proved highly effective (100%) against pharyngeal infection and against penicillin-resistant strains.¹⁸ All co-infections with

C trachomatis were cured. Azithromycin has potential as an alternative, effective, oral therapy for gonorrhoea. It is, however, relatively expensive and there are more commendable alternatives with substantial records of proven efficacy and safety. The treatment of genital infection with *N gonorrhoeae* is not a listed indication on the product licence for azithromycin in the United Kingdom.

Spectinomycin

Spectinomycin played a central role in the control of gonococcal infection following the emergence of PPNG and higher-level chromosomal resistance.⁷ Adoption of spectinomycin as the routinely used drug of choice was soon followed by reports of spectinomycin resistance,³⁹ although spectinomycin resistance is unstable and reverts once its use is discontinued. It is highly effective as a single intramuscular dose of 2 g for urethral and cervical infection and is safe in pregnancy.¹ It is, however, expensive, has poor efficacy against pharyngeal infection, and is generally reserved for situations where cheaper alternatives are contraindicated, for example in a pregnant woman who is allergic to β -lactams. It remains a useful reserve option for gonococcal therapy. A new analogue of spectinomycin, trospectomycin, failed to achieve a sufficiently high cure rate to be recommended agent for treating anogenital gonococcal infection.¹⁹

Tetracyclines

Tetracyclines cannot contend as a recommended therapy for gonorrhoea in the 1990s. Although cheap and widely used in some developing countries, they only offer acceptable efficacy using a multi-dose regime⁴⁰ and compliance with multi-day regimens is unsatisfactory in some populations.⁴¹ Tetracycline resistance, both chromosomal and plasmid mediated, is increasing and has attained a high prevalence in some countries.⁹ Tetracyclines remain important and effective agents in the treatment of other sexually transmitted infections, notably *C trachomatis*.

Combined therapy for possible co-infection with chlamydia

Co-infection with *C trachomatis* is not uncommon in men and women with acute urogenital gonococcal infection. A recent report in east London cited a co-infection rate of 16% in men and 31% in women.¹⁴ The co-infection rate for women was 41% for women in Nottingham in 1995 (unpublished data). The sensitivity of current routine tests for chlamydia probably underestimates the prevalence of co-infection.⁴² The physician treating a patient for gonococcal infection has, therefore, an obligation to routinely give treatment for this possible co-infection or undertake testing that reliably excludes it. Combined therapy at the time of initial treatment for gonorrhoea may reduce morbidity, although there is no evidence of increased complications when treatment for chlamydia is delayed. Combined therapy certainly facilitates a more rapid

resumption of "infection-free" intercourse and circumvents the problem of sub-optimal follow-up after initial treatment. In most treatment trials, the rate of non-returners for evaluation after single-dose therapy exceeds 20%. Since 1985, the Centers for Disease Control in the United States have recommended a 7 day therapy with an antimicrobial effective against *C trachomatis* following single-dose therapy for the eradication of gonorrhoea.¹⁷ Untreated genital infection with *C trachomatis* can give rise to the damaging complications of pelvic inflammatory disease, ectopic pregnancy and infertility. Combined treatment has been assessed as highly cost-effective.⁴³

Therapy in special situations

Pharyngeal infection

The natural history of untreated pharyngeal gonorrhoea appears to be spontaneous elimination within a matter of weeks.^{44 45} Pharyngeal gonococcal infection can, however, cause symptomatic pharyngitis, be transmitted from the oropharynx and be the source of disseminated infection. The clinical importance of pharyngeal gonorrhoea has not been fully defined, but is generally considered of less significance than anogenital infection on the grounds that infection in the pharynx is relatively uncommon, mainly asymptomatic, self-limited and not very infectious.^{2 29} Nonetheless, from a public health perspective, individuals with or at risk of pharyngeal infection should be offered therapy known to eliminate *N gonorrhoeae* at this site.

The efficacy of some antimicrobials against pharyngeal infection with *N gonorrhoeae* has been shown to be significantly lower than their efficacy against anogenital infection, when administered as a single dose. The reduced efficacy is not a consequence of reduced antimicrobial susceptibility to pharyngeal isolates. In a systematic review of published therapeutic trials of various antimicrobial regimens, aggregation of treatment outcome by site showed cure rates of 79.2% (95% CI: 73.3–85.2%) for infection in the male pharynx and 83.7% (95% CI: 79.0–88.4%) for infection in the female pharynx.²⁹ However, the more recently introduced antimicrobials for treatment of uncomplicated anogenital gonorrhoea, namely third generation cephalosporins, quinolones and azithromycin, offer much improved efficacy as single dose therapy compared with penicillins or spectinomycin.²⁹

Large comparative trials of therapy against pharyngeal infection with *N gonorrhoeae* have not been performed, although treatment outcome at this site has been reviewed.^{3 45} Failure rates of 43–60% are reported in studies involving more than 20 patients receiving single-dose orally administered penicillin (ampicillin, amoxycillin, or pivampicillin).¹⁶ Historically, aqueous procaine penicillin G, 4.8 million units intramuscularly, together with probenecid 1 g, produced failure rates of less than 11%.^{16 45} The table lists selected studies of

Antimicrobial therapy for pharyngeal gonorrhoea—selected studies involving more than ten patients

<i>Antimicrobial</i>	<i>Patients followed-up</i>	<i>Cured</i>	<i>Population</i>	<i>Year of study</i>	<i>Reference</i>
Ampicillin 2 g +probenecid 1 g, orally	37	20 (54%)	GUM clinic, Edinburgh	1978–1981	60
	94	50 (53%)	STD clinic, Oslo	1972	61
	78	36 (46%)	2 STD clinics, Sweden	1971–1974	62
Ampicillin 3.5 g plus probenecid 1 g orally	35	24 (69%)	STD clinic, Denver, USA	1982–1984	44
Ampicillin 3.5 g two doses 8–16 hours apart, with probenecid 1g	25	21 (92%)	STD clinic, Denver, USA	1982–1984	44
Spectinomycin 2 m, im	14	6 (43%)	STD clinics, USA	1983	21
	17	5 (29%)	STD clinics, USA		15
Ceftriaxone 125 mg, im	32	30 (94%)	STD clinics USA	1983	21
Ceftriaxone 250 mg im	32	32 (100%)	STD clinic, Copenhagen	1986–1987	20
	15	15 (100%)	STD clinics, USA	1991–1992	17
Cefuroxime 1.5 g im, plus probenecid 1 g oral	13	7 (54%)	STD clinic, Copenhagen		63
Ciprofloxacin 250 mg, oral	25	24 (96%)	GUM clinic, London	1988–1989	45
Azithromycin 2 g oral	19	19 (100%)	STD clinics, USA	1991–1992	17

therapy against pharyngeal gonorrhoea involving more than ten cases. The efficacy of spectinomycin as a single intramuscular dose of 2 or 4 g is less than 50%.^{16 22} Studies reporting more than ten patients treated for pharyngeal gonorrhoea with ceftriaxone,^{18 21 22} ciprofloxacin^{27 46} or azithromycin,¹⁸ and aggregate treatment reviews of these agents, all report efficacies exceeding 90%.²⁹ Multi-dose therapy with oral tetracyclines has shown good efficacy against pharyngeal gonorrhoea, but this class of antimicrobial has not been reassessed following the recent emergence of significant levels of tetracycline resistance.

Pregnant women

Therapeutic studies usually exclude pregnant women by design, and quinolones and tetracyclines are contraindicated in pregnancy. A recent study compared the efficacy of three recommended regimens in pregnancy.²³ Ceftriaxone 250 mg IM achieved cure in 95% of cervical infections, 100% of pharyngeal infections, and 95% of rectal infections. In comparison, amoxicillin 3.0 g orally with probenecid 1 g cured 91%, 80%, and 85% respectively of infections at these sites, whereas spectinomycin 2 g IM achieved cure rates of 95%, 83% and 100% respectively. The authors conclude that in their location, the results could not support the use of amoxicillin with probenecid for the treatment of gonorrhoea in pregnancy, in accordance with the earlier defined criterion of efficacy.^{1 2} Clinical experience with other regimens has accumulated without apparent formal study. Two doses of amoxicillin 3 g, given 24 hours apart, are cited as routine treatment in pregnancy in an east London clinic.¹⁴

Allergy, Intolerance, or Adverse Reactions

Quinolones offer a very effective alternative to individuals who report allergy to β -lactams. If quinolones are contraindicated in such individuals, spectinomycin could then be used, although this agent is sub-optimal for pharyngeal infection.

Disseminated gonococcal infection

Disseminated infection is rare and treatment recommendations are not based on the results of formal clinical trials, but on collated clinical experience, general principles for treating systemic infection, and results from treating uncomplicated infection.⁴⁷ DGI can be caused by PPNG strains.⁴⁸ General principles in the treatment of the arthritis-dermatitis syndrome and septic arthritis with an effective antimicrobial would appear to be: (i) short duration of therapy appears effective. Parenteral therapy for 3 days produced cure in all cases,⁴⁹ although therapy for 5–7 days seems prudent; (ii) oral therapy appears of equal efficacy to parenteral therapy⁵⁰; (iii) initiation of antimicrobial therapy intravenously would seem prudent in a bacteraemic individual, then change to oral administration after 24–48 hours; (iv) the choice of antimicrobial will follow local efficacy in uncomplicated infection; (v) intra-articular instillation of antimicrobials is unnecessary. Recent case reports in the UK reveal the successful use of oral amoxicillin and of augmentin in a case of penicillin resistance.^{48 51}

Neo-natal infection

Gonococcal infection among neonates results from peripartum transmission of *N gonorrhoeae* from cervical infection in the mother. Conjunctival infection is the commonest clinical form of neo-natal gonorrhoea, but the mucous membranes of the pharynx, rectum or vagina may also be colonised,⁵² and infection may occur at sites of intrauterine fetal monitoring. Disseminated infection occurs rarely.

There appears to be consensus on the following treatment principles^{17 53 54}: (i) antimicrobial therapy should be administered systemically rather than topically. Infection may involve mucosal sites in addition to the conjunctivae⁵² and there are case reports of unsatisfactory clinical response to topical therapy alone⁵⁵; (ii) topical antimicrobial therapy is unnecessary when systemic therapy is administered; (iii) penicillin resistance should be considered in choosing appropriate antimicro-

bial therapy; (iv) the conjunctivae should be irrigated with saline to clear the purulent discharge; (v) the mother and her partner(s) should be tested and treated for gonorrhoea and other STDs including chlamydia.

Formal trials evaluating antimicrobial treatment for gonococcal ophthalmia neonatorum are few and treatment recommendations are often based on accumulated clinical experience. Penicillin has been widely used in the treatment of gonococcal ophthalmia neonatorum and systemic therapy for one to 21 days resulted in favourable clinical responses prior to the emergence of penicillin resistance.⁵⁶ There have been no formal studies to determine the optimum dose or duration of penicillin therapy. One advocated regimen is benzylpenicillin 50 000 units (30 mg) per kg per day in 2 divided doses either intramuscularly or intravenously for 7 days.⁵⁴ Procaine penicillin 50 000 units/kg as a single intramuscular dose daily for three days has also been found to be effective in clinical practice (treatment guidelines, Royal London Hospital). Ceftriaxone, 25–50 mg/kg IV or IM in a single dose not to exceed 125 mg, is the regime recommended by the CDC.¹⁷ Its efficacy has been established.^{24–27} In the United Kingdom, the Committee on Safety of Medicines imposed a contraindication to the use of ceftriaxone in premature infants and during the first six weeks of life. This restriction relates to concern about the theoretical possibility of bilirubin displacement and the consequent risk of kernicterus. This restriction only applies to the United Kingdom. Use elsewhere is cautioned if the neonate is jaundiced. Cefotaxime 100 mg/kg as a single intramuscular injection has been reported in a small series as an effective treatment, including against penicillin-resistant *N. gonorrhoeae*.⁵⁸ Kanamycin 100 mg as a single IM injection achieved an efficacy of 98.6% in Zimbabwe,⁵⁹ but effective alternatives and concerns relating to possible ototoxicity must limit its recommendation in the UK. There are no data to support the use of spectinomycin in infants. There are insufficient data to form a judgement on whether anti-chlamydial therapy should be added to gonococcal therapy in cases of gonococcal ophthalmia neonatorum.

Using data from the studies and case reports already mentioned, and suggestions in current clinical guidelines, a protocol for the management of a case of gonococcal ophthalmia in the United Kingdom might include: (a) admission of the neonate to hospital if there are complications, concerns about compliance with close monitoring, or if intravenous therapy is used; (b) antimicrobial treatment with cefotaxime 100 mg/kg as a single intramuscular dose, or benzylpenicillin 50 000 units (30 mg) per kg per day in 2 divided doses by IM or slow IV injection for 3–7 days, or procaine penicillin 50 000 units/kg intramuscularly daily for three days; (c) conjunctival irrigation with saline, up to hourly at first; (d) close monitoring of the neonate to ensure clinical cure; (e) counselling, investigation and treatment of the

mother and her sexual partner(s). Cefotaxime should be used for treating gonococcal ophthalmia caused by penicillin-resistant strains or where resistance is suspected. Concomitant therapy for *C. trachomatis* would comprise erythromycin ethylsuccinate suspension 12 mg/kg four times a day for 14 days.

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