Antibiotic-resistant gonorrhoea

The gonococcus has become either relatively or completely resistant to many antibiotics. However, knowledge of prevailing local resistance patterns and region in the world of acquisition of infection means that effective treatment is always possible.

BACKGROUND

Before the advent of sulphonamides in 1937, urethritis of all types was treated by urethral irrigation with antiseptic solutions. By 1944, however, infection persisted in about one third of those treated with sulphanilamide. Fortunately, the efficacy of penicillin for treating gonorrhoea was established in 1943 and it rapidly became the treatment of choice, being virtually 100% effective initially. Sadly, that is no longer the case: the development of gonococcal antibiotic resistance is now described.

RESISTANCE TO PENICILLIN

Isolates in the 1940s were usually inhibited by 0.01μ/ml penicillin G or less. Soon the sensitivity to penicillin decreased and larger doses began to be required. This was the result of mutations at a series of loci on the chromosome that affect the cell surface structure resulting in isolates, chromosomally-mediated penicillin-resistant *Neisseria gonorrhoeae* (CMRNG), with penicillin minimum inhibitory concentrations (MICs) of 1 mg/litre or greater.

There is geographical variation in the proportion of strains showing significant levels of resistance to penicillin; high-level regions include south-east Asia and parts of Africa. Antibiotic availability is not controlled in some of these areas and treatment resulting in suboptimal penicillin levels may contribute to the selection of resistant strains.

A new type of gonococcal resistance to penicillin was first described in 1976 at St Thomas' Hospital in London (Phillips, 1976) and simultaneously in the USA (Ashford et al, 1976). This was the result of a plasmid coding for a TEM-type of β-lactamase (penicillinase) — plasmid-mediated resistance. This possibility had been predicted the previous year (Falkow et al, 1976) when it was postulated that transfer of such plasmids might occur from enteric bacteria. Now it is suspected that gonococci acquired the penicillinase-producing plasmid from *Haemophilus ducreyi* (common in parts of the Far East and West Africa) or from *H. influenzae*. Thus single-step plasmid acquisition created penicillinase-producing *N. gonorrhoeae* (PPNG), which were unresponsive to clinically useful doses of penicillin.

RESISTANCE TO TETRACYCLINE

Resistance to tetracycline is caused either by the additive effects of several chromosomal mutations producing low-level resistance, or by the acquisition of a tetracycline-resistance plasmid, first described in 1985 (Centers for Disease Control (CDC), 1985), resulting in high-level tetracycline-resistant *N. gonorrhoeae* (TRNG).

RESISTANCE TO OTHER ANTIBIOTICS

Resistance to macrolides (erythromycin) has also been seen, and sporadic cases of single-step chromosomally mediated high-level resistance to spectinomycin have been detected. Unfortunately, chromosomally-mediated resistance to the quinolone ciprofloxacin (CRNG), the most frequently used alternative to penicillin in the UK, is becoming increasingly widespread, having first been detected in 1989 (Gransden et al, 1990). Once chromosome resistance develops to one fluoroquinolone, cross resistance is seen to other fluoroquinolones, but at varied MICs (Ross, 1998).

SURVEILLANCE FOR *N. GONORRHOEAE* RESISTANCE

Selection of the correct antibiotic regimen to provide effective treatment and prevent transmission of resistant isolates requires information on antimicrobial susceptibility patterns. Some industrialized countries have programmes which monitor gonococcal susceptibility. In the UK, many laboratories submit antibiotic-resistant isolates to the gonococcus reference unit of the PHLS genitourinary infections reference laboratory at Bristol Royal Infirmary, and data from this source are published regularly, matched with epidemiological data.

The Centre for Disease Surveillance and Control (CDSC) (1999) reported an increase in PPNG/TRNG strains as well as a 93% increase in CRNG strains, 48% of which were also PPNG. Region of acquisition was also reported. There was a decrease (44%) in CMRNG between 1997 and 1998. (*Table 1* lists a glossary of terms.) The London Gonococcal Working Group, a London surveillance programme, has been established since such a high proportion of gonococcal infections in the UK occur in the Greater London area.

In the developing world, where the burden of infection and resistance is greatest, there are some sentinel studies from individual laboratories but no continuous surveillance data are available. The World Health Organization coordinates the global antimicrobial susceptibility programme which is collecting data from the Americas, Caribbean, western Pacific and south-east Asia. This has been useful in monitoring the emergence and continued increase in quinolone-resistant *N. gonorrhoeae*.

CHOICE OF ANTIBIOTIC REGIMEN

Treatment of uncomplicated gonorrhoea will be determined by local patterns of antibiotic sensitivity; discussion with

TABLE 1.
Antibiotic-resistant *Neisseria gonorrhoeae*: glossary of terms

Abbreviation	Description/site of resistance (gene)
CMRNG	Chromosomally-mediated penicillin-resistant *N. gonorrhoeae* — MIC>1mg/l (chromosome)
PPNG*	Penicillinase-producing *N. gonorrhoeae* (plasmid)
TRNG*	High-level tetracycline resistant *N. gonorrhoeae* — MIC≥16mg/l (plasmid)
CRNG*	Decreased susceptibility to ciprofloxacin — MIC≥0.05mg/l (chromosome)

From Centre for Disease Surveillance and Control (1999). MIC = minimum inhibitory concentration.
*PPNG/TRNG and PPNG/CRNG combinations can occur

the hospital microbiologist or genitourinary physician is advised. Single dose, directly observed therapy is preferred. Use of newer antibiotics is advocated when more than 5% of incident strains are resistant to penicillin but it should be possible to predict (from travel or contact history) the likelihood of, say, PPNG (Sherrard and Barlow, 1993).

In our clinics in South London, our routine single dose of oral treatment with amoxycillin 2g and probenecid 1g gives a failure rate of less than 5% as long as infections acquired outside the UK are recognized. This contrasts with the 3.5g amoxycillin recommended by the CDC. In our department, at present, the overall PPNG rate is running in the region of 10%. Ison (1996) has produced a good overview of gonococcal resistance and antibiotic choice.

Many physicians advocate the addition of azithromycin 1g, or doxycycline 100 mg twice daily for 1 week for possible coincidental chlamydial infection. Spectinomycin intramuscularly is useful in penicillin allergy.

Uncomplicated infection acquired overseas is treated with ciprofloxacin 500 mg unless it has originated in the Phillipines when a cephalosporin (cefotaxime 500 mg intramuscularly in our case) is used. Treatment guidelines have been produced for the UK and USA (CDC, 1998; Bignell, 1999) (www.mssvd.org.uk). However, in the UK, most laboratories will provide sensitivity results with a positive culture report, so a patient who has been given inappropriate therapy can be recalled. It is usual to attempt at least one test of cure on patients with gonorrhoea.

Disseminated gonococcal infection does not usually present to a genitourinary medicine clinic because of the frequent absence of genital signs or symptoms, the arthralgia/arthritis and characteristic skin lesions pointing the patient or referring doctor to other specialties. Organisms responsible for disseminated gonococcal infection are almost universally fully sensitive to penicillin. Treatment of other complications also takes account of the infection's provenance and antigonococcal therapy is always supplemented with an antichlamydial antibiotic, a tetracycline or macrolide. In pelvic infection metronidazole is often added to treat any anaerobic component.

PARTNER NOTIFICATION

The incidence of gonorrhoea in England increased by 26% in males and 30% in females between 1998 and 1999 (CDSC, 2000). Partner notification (contact tracing) should always be attempted to limit the spread of infection, particularly in cases of antibiotic-resistant gonorrhoea.

Patients diagnosed with gonorrhoea in genitourinary medicine clinics in the UK are often given contact slips which their partners should produce when attending for screening and treatment. Since clinics often share information (where a partner attends another clinic), confidentially, if the antibiotic sensitivities are known this information is useful in selecting appropriate medication for the partner(s). Individuals presenting as a contact of someone with gonorrhoea should be seen urgently and not given an appointment for a later date, in order to minimize the risk of spread of infection and of complications. With the significant rise in workload seen in many clinics recently, this is not always easy.

The National Sexual Health Strategy presently being developed may recommend that more sexually transmitted infections are managed in the primary care setting. If this is the case, vigilance for antibiotic-resistant gonorrhoea must be maintained and effective contact tracing, meeting national standards, carried out. HM

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KEY POINTS

- The gonococcus may be partially or completely resistant to some antibiotics.
- The incidence of penicillinase-producing *Neisseria gonorrhoeae* is higher in Africa, the Far East and in the USA than in the UK.
- Gonorrhoea acquired in these regions should not be treated with penicillin.
- A geographic sexual history is valuable in predicting the risk of antibiotic resistance.
- Antibiotic sensitivity testing should be carried out on all isolates of *N. gonorrhoeae*.
- Partner notification (contact tracing) should always be attempted in order to control the spread of antibiotic-resistant gonorrhoea.