Expert Opinion

informa
healthcare

The use of cephalosporins for gonorrhea: the impending problem of resistance

Pennan M Barry† & Jeffrey D Klausner
†*University of California–San Francisco, San Francisco Department of Public Health, San Francisco, California, USA*

Gonorrhea remains an important clinical and public health problem throughout the world. Gonococcal infections have historically been diagnosed by Gram stain and culture but are increasingly diagnosed through nucleic acid tests, thereby eliminating the opportunity for antimicrobial susceptibility testing. Gonococcal infections are typically treated with single-dose therapy with an agent found to cure > 95% of cases. Unfortunately, the gonococcus has repeatedly developed resistance to antimicrobials including sulfonamides, penicillin, tetracyclines and fluoroquinolones. This has now left third-generation cephalosporins as the lone class of antimicrobials recommended as first-line therapy for gonorrhea in some regions. However, resistance to oral third-generation cephalosporins has emerged and spread in Asia, Australia and elsewhere. The mechanism of this resistance seems to be associated with a mosaic penicillin binding protein (*penA*) in addition to other chromosomal mutations previously found to confer resistance to β-lactam antimicrobials (*ponA*, *mtrR*, *penB*, *pilQ*). Few good options exist or are in development for treating cephalosporin-resistant isolates, as most have had multidrug resistance. Preventing the spread of resistant isolates will depend on ambitious antimicrobial management programs, strengthening and expanding surveillance networks, and through effective sexually transmitted disease control and prevention.

Keywords: cephalosporin resistance, *Neisseria gonorrhoeae*

Expert Opin. Pharmacother. (2009) ***10****(4):1-23*

1. Introduction

Urethritis from gonorrhea has probably been affecting humans for thousands of years. Gonorrhea was recognized by ancient physicians such as Galen, and scholars believe that it was mentioned in the bible [1]. The gonococcus was first discovered by Albert Neisser in 1879 and was the second pathogenic bacterium to be isolated in history [2]. Though infections historically were treated with various local and systemic preparations of questionable effectiveness, the first curative treatment came with the introduction of sulfanilamide in 1937 [3] and was followed by the use of penicillin for gonorrhea in 1943 [2]. Resistance to sulfonamides [4], penicillin and each subsequent antimicrobial used to treat gonorrhea has inevitably developed over time [5]. Most recently, the gonococcus has developed resistance to fluoroquinolones [6,7]. As a result, in some regions only third-generation cephalosporins are now recommended as first-line therapy for gonococcal infections [7,8]. However, consistent with the history of the gonococcus, resistance to this class of antimicrobials is now emerging and will almost certainly present

10.1517/14656560902731993 ISSN 1465-6566

significant future challenges to the treatment and control of gonococcal infections and their complications.

1.1 Morbidity of gonococcal infections

Gonococcal infections in males cause predominantly symptomatic urethritis that can be complicated by epididymitis and urethral strictures. In women, gonococcal infections cause cervicitis – only approximately half of which occurs with symptoms, and which can go on to cause pelvic inflammatory disease, ectopic pregnancies and infertility [1]. In addition, in both men and women exposed orally or anally, gonococcal infections can cause a predominantly asymptomatic pharyngitis or proctitis. Especially among gay men and other men who have sex with men (MSM), these nonurethral sites can be the predominant site of infection [9]. Less commonly, *Neisseria gonorrhoeae* can cause conjunctivitis, endocarditis, tenosynovitis, arthritis, meningitis, inflammation of the liver capsule (Fitzhugh-Curtis syndrome) and disseminated blood stream infections [1]. *N. gonorrhoeae* can also cause ophthalmic infections among newborns [10,11].

Like other sexually transmitted infections (STIs), gonococcal infections of the cervix, urethra and rectum have been shown to increase substantially the risk of acquiring and transmitting human immunodeficiency virus (HIV) infection, making gonorrhea control an important part of HIV prevention [12,13].

1.2 Diagnosis of gonococcal infections

Diagnosis of gonococcal infection has historically been a combination of clinical signs and symptoms of cervicitis/urethritis, a Gram stain of urethral or cervical discharge revealing the characteristic Gram-negative intracellular diplococci, and the use of culture on selective media, usually Thayer-Martin media [14,15]. However, over the last 20 years new molecular methods for diagnosing gonococcal infections have been developed and have entered widespread use, mostly in resource-rich settings. These assays are generally much more sensitive than culture and are highly specific for urogenital infections [14,16,17]. However, depending on the assay used (e.g., PCR) some concerns have arisen about the specificity of these tests from other anatomic sites [18,19]. Because these assays can be performed on easily collected specimens such as urine or self-collected vaginal or rectal swabs, in resource-rich settings, especially the USA, they have supplanted culture in many clinical settings and have expanded screening to many nonclinical settings [20-23]. This move away from culture has made routine clinical antimicrobial susceptibility testing impossible in many cases, so nearly all information regarding susceptibility now comes from relatively small surveillance systems set up specifically for this purpose.

In resource-limited settings where diagnostic testing for gonococcal infections is difficult or impossible, persons are typically treated for gonococcal and chlamydial infections using syndrome-based algorithms for urethritis, vaginitis or pelvic inflammatory disease (PID) [24,25]. In these settings the etiologic agent (and the antimicrobial susceptibility) is not known.

1.3 Epidemiology of gonococcal infections

Gonococcal infections are among the most common reportable infections around the world. In the USA, gonorrhea is consistently the second most frequently reported notifiable infection, with more than 350,000 infections reported in 2006 [26]. Many more infections probably go unreported and the actual annual cumulative incidence of gonococcal infections in the USA during 2000 was estimated to be > 700,000 [27]. In the UK during 2007, there were 18,710 uncomplicated gonococcal infections diagnosed in STD (Genito-Urinary Medicine) clinics [28].

In other regions of the world, gonococcal infections are much more common. According to World Health Organization (WHO) estimates for 1999 (updated global estimates are forthcoming), approximately 62.4 million gonococcal infections occur each year worldwide, nearly half (27.2 million) of which occur in South and Southeast Asia, with another 17 million in Sub-Saharan Africa [10].

Gonococcal infection is more common among young persons, particularly those aged 15 – 24 years [26,28]. Rates of disease are also higher among persons with lower socio-economic status, MSM, illicit drug users, commercial sex workers, persons held in correctional facilities, and racial/ethnic minority groups [1,26,29]. In the USA, the disparity in rates between whites and blacks is the highest for gonorrhea than for any other reportable disease, with the rate among blacks more than 24 times the rate among whites in 2002 [30]. In 2006, gonorrhea cases among blacks accounted for 69% of all gonorrhea in the USA, while blacks make up approximately 12% of the population [26].

2. Use of antimicrobials against *Neisseria gonorrhoeae* and the history of development of antimicrobial resistance

2.1 General principles of therapy

Several general principles of the treatment of gonococcal infections are important. Single-dose, directly observed therapy has become the norm in most areas of the world. Single-dose therapy has been effective and assures adequate treatment. WHO recommendations for selecting treatments have stated that cure rates should be > 95% [31]. In the USA, recommendations have further stated that the lower bound of the 95% confidence interval around the estimated treatment efficacy should also be higher than 95% [32]. Additionally, candidate medications should achieve and sustain serum levels of at least 4 times the MIC90 for 10 h [32]. Recently, as a consequence of limited treatment options and few studies, it has been proposed that a slightly less stringent criteria of > 95% cure rate with the lower bound of the 95% confidence interval >90% be used for

alternative regimens in the US Centers for Disease Control and Prevention (CDC) STD Treatment Guidelines [33].

Treatment of sex partners is important to prevent reinfection. Efforts to improve partner treatment have been ongoing in the USA and elsewhere, often through the use of expedited partner therapy, which involves the patient delivering medications or a prescription for medication along with instructions for use to his or her sex partners. This has been shown to lower gonococcal reinfection rates in randomized trials [34-36], but depends on the efficacy and availability of an easily deliverable oral treatment.

Following treatment, in the absence of recurrent symptoms, generally no test of cure is needed for uncomplicated gonorrhea and this is not recommended routinely by the CDC or WHO [8,25]. Retesting 3 months after treatment is recommended because of the high rate of reinfection [8], but this recommendation is difficult to implement in many settings.

Last, because gonococcal and chlamydial coinfection rates are high, persons treated for gonococcal infections are also treated for chlamydia unless chlamydia has already been ruled out. This means that many persons will also receive a macrolide or a tetracycline in addition to treatment for gonorrhea.

2.2 Penicillin

Though sulfonamides were the first antimicrobials used to treat gonococcal infections, resistance quickly developed [3,4]. Alexander Fleming documented the ability of penicillin to inhibit growth of the gonococcus in his 1929 paper describing his monumental discovery [37], and penicillin became the gonorrhea treatment of choice in 1943 [38-40]. Penicillin served as the mainstay of treatment for several decades. However, soon after introduction, *N. gonorrhoeae* began developing low-level resistance to penicillin. Nearly all isolates collected in the pre-penicillin era had MICs of < 0.0125 mg/l (0.02 IU/ml) [5,41]. This gradually climbed so that 22% of isolates had MIC ≥ 0.125 mg/l by 1956 [5,42] and, by 1974, 11 – 23% of isolates in some US cities were resistant (MIC ≥ 0.5 mg/l) [43]. This MIC rise required numerous escalations in the recommended effective dose of penicillin from 50,000 units in 1945 to 4.8 million units by the 1970s [5,44,45]. Increasing low-level penicillin resistance was the additive effect of multiple chromosomal mutations, resulting in altered penicillin binding proteins, increased antibiotic efflux and decreased antimicrobial penetration of the outer membrane [46].

The emergence of *N. gonorrhoeae* with plasmid-mediated β-lactamase (penicillinase) production, which confers high-level penicillin resistance, was first identified in *N. gonorrhoeae* in 1976 [5,47,48]. In Africa and Asia especially, the rates of penicillinase-producing strains rose rapidly, whereas in regions such as North America, Europe and Australia spread was slower and was probably imported from Africa and Asia [5,49,50]. However, by 1989 penicillin was no longer an effective treatment option, and penicillin is no longer recommended in the USA [8]. Penicillin regimens (amoxicillin/probenicid) are recommended in European guidelines for known susceptible isolates, though resistance rates are high (21.3%) [51].

2.3 Tetracyclines

Chromosomally mediated tetracycline resistance emerged in the 1970s along with, and via some of the same mechanisms as, chromosomally mediated penicillin resistance [5]. Plasmid-mediated tetracycline resistance emerged independently in 1985 in the USA and the Netherlands and was the result of the acquisition on a plasmid of a streptococcal *tetM* determinant that restored ribosomal protein synthesis in the presence of tetracycline [46,52].

2.4 Fluoroquinolones

Fluoroquinolones became widely available in the mid-1980s. They were highly effective against *N. gonorrhoeae* infections at all anatomic sites, had few side effects in adults, and required only one oral dose of medication [6,53,54]. Ciprofloxacin became the mainstay of treatment for uncomplicated gonococcal infections, with CDC recommending it as an alternative regimen in 1989 [55] and as a first-line therapy in 1993 [56]. However, resistance was already developing with the first fluoroquinolone-resistant isolates described in the mid-1980s [6,57]. This resistance, through alteration of DNA gyrase (*gyrA*) or topoisomerase IV (*parC*), first became prevalent in Asia; by 1992 ciprofloxacin resistant isolates made up > 40% of isolates in Japan. As had been seen with penicillinase-producing *N. gonorrhoeae*, resistant strains quickly spread from Asia to Australia, Hawaii, North America and Europe [6,58-61], probably via travelers [61,62]. Prevalence of resistant isolates continued to increase in the USA especially in California, Hawaii, and among MSM such that fluoroquinolones were no longer recommended in those populations by the early 2000s [63,64]. Finally, in 2007, the US CDC recommended that no gonococcal infections in the USA be treated with ciprofloxacin as first-line therapy [7]. In Europe, though the last published guideline lists fluoroquinolones as recommended for the treatment of gonococcal infections, recent surveillance shows that quinolone resistance is high (30.9%) and several European countries have removed fluoroquinolones from lists of recommended therapies [51,65].

Other antimicrobials that remain options for the treatment of gonococcal infections, including spectinomycin, are discussed in Section 7.

3. Cephalosporins for the treatment of gonococcal infections

3.1 History and general characteristics of cephalosporins

Cephalosporins were discovered in 1945 by Guiseppe Brotzu when he isolated a mold from sewage effluvium in Sardinia, Italy, that had broad spectrum antibacterial activity [66]. Modern cephalosporins are variations on the prototypic

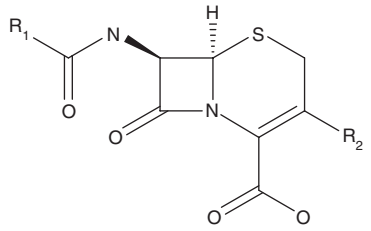

Figure 1. Basic Cephalosporin Nucleus.

molecule produced by *Cephalosporin acremonium*. These variations are achieved by side chain substitutions at R_1 (C7) and R_2 (C3) of the cephalosporin nucleus with R_1 alterations generally being responsible for stability against lactamases and R_2 substitutions affecting elimination half-life (**Figure 1**) [67]. Cephalosporins are classified into 'generations' on the basis of their spectrum of activity. First-generation agents are most active against aerobic Gram-positive cocci including *Staphylococcus aureus* (methicillin sensitive), whereas second-generation agents have more activity against Gram-negatives and less activity against *S. aureus*. Third-generation agents have broader activity against Gram-negatives than second-generation agents. Fourth-generation agents, such as cefipime, have broad activity against both Gram-negative and Gram-positive organisms.

In general, third generation cephalosporins and cephamycins (i.e., cefoxitin) are active against *N. gonorrhoeae*. Some second-generation agents have also been studied; however, ceftriaxone and several oral third-generation agents are the most frequently used for treating gonococcal infections.

Like other β-lactam antimicrobials, cephalosporins work by inhibiting cell wall synthesis through binding and inhibiting enzymes responsible for inserting peptidoglycan cross-linkage structures into the cell wall. These enzymes, including transpeptidases, carboxypeptidases and endopeptidases, are also termed penicillin binding proteins (PBPs) [66]. Cephalosporins are considered bactericidal drugs with time-dependent killing and maximal bacterial killing occurring at 4 times the MIC [67,68]. These characteristics make the peak serum drug level and rate of elimination particularly important in selection of agents for one-time dosing.

3.1.1 *Oral cephalosporins for gonorrhea*

Oral cephalosporins with activity against *N. gonorrhoeae* include cefuroxime axetil [69,70], cefaclor [71], cefixime [72-75], cefpodoxime proxetil [76,77], ceftibuten [78], cefdinir [79], and cefoperozone (see **Table 1**) [80,81]. The WHO recommends cefixime 400 mg and in the USA cefixime 400 mg is the only oral regimen recommended as first-line therapy. This is because it is the only oral option so far that has met the criterion of the lower bound of the 95% confidence interval of the cure rate > 95% (97.5% cure; 95% confidence interval, 95.4 – 98.8%) [33]. Cefixime is also recommended in the UK [65]. Cefixime was not available in the USA from 2002 to 2008 [82], and during that time cefpodoxime 400 mg became more widely used [83]. Other countries have used options including ceftibuten in Hong Kong [84] and cefditoren and cefdinir in Japan.

Table 1 lists the properties of selected oral cephalosporins including the calculated serum level 10 h after peak level. Using this information to apply the theoretical guideline of Moran and Levine that medications used in one-time doses for treatment of gonorrhea should stay 4 times above the MIC90 for 10 h, one can see that there might not be much excess pharmacological capacity in many of these agents to accommodate increases in the MIC.

3.1.2 *Parenteral cephalosporins for gonorrhea*

Among the parenteral cephalosporins, ceftriaxone has been extensively studied and is the parenteral treatment of choice for gonorrhea [85-90]. It is the recommended first-line antimicrobial for treatment of gonorrhea in the USA and the UK, and is recommended by WHO [7,8,31,65]. However, the dose of ceftriaxone is the subject of debate with 125 mg recommended in the USA and by WHO, but many countries recommend 250 mg [8,31,65]. In Japan, 1000 mg IV is recommended [91]. The chemical structure of ceftriaxone, particularly the heterocyclic thiomethyl group at the R_2 (C3) position greatly prolongs the elimination half-life because of extended protein binding [66]. Other parenteral cephalosporins have been studied and recommended as alternative regimens [8]. These include ceftizoxime 500 mg IM [92-94], cefoxitin 2 gm IM with 1 gm of probenecid [95-97], and cefotaxime 500 mg IM [98-100]. Cefuroxime 1.5 gm IM is occasionally used in the UK [70]. Cefodizime has also been studied and used in Japan and has shown activity against recent multidrug resistant Japanese isolates [33,101-103]. However, these agents do not provide any advantage over ceftriaxone (see **Table 2**) and so are not routinely recommended.

4. Epidemiology of cephalosporin resistance

Despite their historic reliability for treating gonococcal infections, resistance to cephalosporins has begun to develop and spread in Asia with possible importation into Australia and Europe.

4.1 Japan

Case reports of treatment failures with the use of third-generation cephalosporins were reported in Japan as early as 2000 [104], though a published report including isolates collected in Japan during 1991 – 1996 also documented elevated MICs to cephalosporins including cefpodoxime and cefdinir (see **Table 3**) [105]. Several subsequent reports from various regions in Japan documented the rapid spread and increase of resistance to oral third-generation cephalosporins during the late 1990s and early 2000s [103-112]. As a result of cephalosporin resistance in Japan, beginning

Table 1. Chemical, pharmacological and microbiological characteristics of selected oral cephalosporins used to treat infections caused by *Neisseria gonorrhoeae*.

Cephalosporin usual dose (alternative dose)	Peak serum level** (mg/l)	Half life** (hrs)	Serum level 10 hours after peak (mg/l)*****	Hypothetical MIC90 limit*** (10 h conc/4) (mg/l)	Breakpoints (CLSI unless indicated otherwise)
Cefixime 400 mg	4.5	3 – 4	0.446 – 0.795	0.112 – 0.199	S: ≤ 0.25 I: ND R: ND
Cefpodoxime (proxetil)**** 400 mg	4.5	2 – 3	0.141 – 0.446	0.035 – 0.112	S: ≤ 0.5 I: ND R: ND
Cefdinir 600 mg	2.87	1.7	0.049	0.012	
Cefuroxime (axetil)**** 1000 mg	13.6	1.3	0.066	0.016	(IV formulation) S: ≤ 1 I: 2 R: ≥ 4
Ceftibuten 400 mg	15	1.5 – 2.5	0.148 – 0.938	0.037 – 0.234	

S: Sensitive; I: Intermediate; R: Resistant; ND: Not determined.

*Source of chemical structures is the Kyoto Encyclopedia of Genes and Genomes Drug database available at: http://www.genome.jp/kegg/drug/ (Accessed August 23, 2008).

**Source of elimination half life and peak concentration is Micromedex DRUGDEX® Evaluations, Thomson Healthcare. http://www.micromedex.com (Accessed September 30, 2008).

***Moran JS, Levine WC. Drugs of choice for the treatment of uncomplicated gonococcal infections. Clin Infect Dis 1995;20(Suppl 1):S47-65 [32].

****Cefuroxime axetil and cefpodoxime proxetil are administered as a prodrug ester and are passively absorbed and hydrolyzed by intestinal epithelial cells to the active cephalosporin form, which is then transferred into the bloodstream.

*****Serum concentration at time $t = \frac{C_{\max}}{e^{0.693t/t_{1/2}}}$.

Table 2. Chemical, pharmacological and microbiological characteristics of selected parenteral cephalosporins used to treat infections caused by *Neisseria gonorrhoeae*.

Cephalosporin usual dose IM (alternative dose IM)	Peak serum level** (mg/l)	Half life** (h)	Serum level 10 h after peak (mg/l)*****	Hypothetical MIC90 limit*** (10 h conc/4) (mg/l)	Breakpoints (CLSI unless indicated otherwise)
Ceftriaxone 125 mg or 250 mg (pk data for 125 mg)	13.5	5.8 – 8.7	4.086 – 6.086	1.022 – 1.521	S: ≤ 0.25**** I: ND R: ND
Cefuroxime 1500 mg	13.6	1.3	0.066	0.016	(IV formulation) S: ≤ 1 I: 2 R: ≥ 4
Ceftizoxime 500 mg	13	1.1 – 2.3	0.024 – 0.638	0.006 – 0.160	S: ≤ 0.5 I: ND R: ND
Cefodizime 1000 mg	75	2.5 – 4	0.141 – 0.446	0.035 – 0.112	
Cefotaxime 1000 mg	20.5	0.8	0.001 – 0.054	0 – 0.013	

S: Sensitive; I: Intermediate; R: Resistant; ND: Not determined.

*Source of chemical structures is the Kyoto Encyclopedia of Genes and Genomes Drug database. available at: http://www.genome.jp/kegg/drug/ (Accessed August 23, 2008).

**Source of elimination half life and peak concentration is Micromedex DRUGDEX® Evaluations, Thomson Healthcare. Available from: http://www.micromedex.com (Accessed September 30, 2008).

***Moran JS, Levine WC. Drugs of choice for the treatment of uncomplicated gonococcal infections. Clin Infect Dis 1995;20(Suppl 1):S47-65 [32].

****Other authors and organizations have picked lower cutpoints to define isolates that are 'less susceptible'. For example, the European Surveillance of Sexually Transmitted Infections (ESSTI) network uses 0.125 as the upper limit of sensitivity [51].

*****Serum concentration at time $t = \frac{C_{\max}}{e^{\frac{t(0.693)}{t_{1/2}}}}$.

Table 3. Reports from Japan of *Neisseria gonorrhoeae* isolates with elevated MICs to third-generation cephalosporins.

Author, publication year	Location	Year of specimen collection	Criteria and number of isolates assessed	Cephalosporin MICs mg/l (range)	Comment
Japan					
Yamaguchi 1998 [105]	Several areas of Japan	1991 and 1996	All isolates: 27	Cefpodoxime $MIC_9 = 4$ Cefditoren $MIC_{90} = 4$	*In vitro* study of investigational antimicrobial
Akasaka 2001 [104]	Kitakyushu	1999	Cefdinir treatment failure: 2	Cefpodoxime MIC = 4 Cefdinir MIC = 1 Ceftriaxone MIC = 0.125	Case report
Muratani 2001 [106]	Kitakyushu	1999	Cefozopran ≥ 8: 17 of 54	For 17 isolates: Ceftriaxone $MIC_{90} = 0.125$ (0.03 – 0.25) Cefpodoxime $MIC_{90} = 4$ (0.5 – 4) Cefixime $MIC_{90} = 0.5$ (0.125 – 0.5)	
Ito 2004 [107]	Central Japan	1999 – 2000 2001 2002	Cefixime ≥ 0.5: 0 of 91 39 of 150 67 of 221	1999: Cefixime $MIC_{90} = 0.06$ (≤ 0.004 – 0.125) Ceftriaxone $MIC_{90} = 0.03$ (≤ 0.004 – 0.06) 2002: Cefixime $MIC_{90} = 0.5$ (≤ 0.004 – 2) Ceftriaxone $MIC_{90} = 0.06$ (≤ 0.004 – 0.5)	Emerging cefixime resistance
Ameyama 2002 [108]	Tokyo	2000 2001	Cefixime ≥ 0.25: 9 of 53 4 of 24	2000 and 2001: Cefixime $MIC_{90} = 0.25$ Ceftriaxone $MIC_{90} = 0.06$	Report also described a mosaic *penA* gene among isolates with cefixime MIC ≥ 0.25
Tanaka 2002 [103]	Fukuoka City	1995 2000	Cefixime ≥ 0.5 0 of 55 5 of 100	1995: Cefixime $MIC_{90} = 0.015$ (0.002 – 0.06) Ceftriaxone $MIC_{90} = 0.015$ (0.001 – 0.03) 2000: Cefixime $MIC_{90} = 0.25$ (0.002 – 0.5) Ceftriaxone $MIC_{90} = 0.06$ (0.002 – 0.5)	Emerging cefixime resistance.
Tanaka 2006 [109]	Fukuoka City	2000 – 2001	Ceftriaxone = 0.5: 1 of 398	Cefixime MIC = 0.5	Analysis of 1 ceftriaxone resistant isolate with mosaic *penA* and *mtrR*, *ponA*, *penB* mutations
Yokoi 2007 [110]	Toyota	2002 – 2003	Cefixime treatment failure: 4	Cefixime (0.5 – 1) Ceftriaxone (0.125 – 0.5)	Case report
Osaka 2006 [111]	Tokyo	2006	Cefixime ≥ 0.125: 17 of 47	Cefixime $MIC_{90} = 0.125$ (0.004 – 0.25) Ceftriaxone $MIC_{90} = 0.06$ (0.002 – 0.125)	MIC values compared with those of Ameyama in 2001
Takahata 2006 [112]	Tokyo	2006	Cefixime ≥ 0.125 28 of 58	For 28 isolates with mosaic *penA* gene: Cefixime $MIC_{90} = 0.5$ (0.12 – 0.5) Ceftriaxone $MIC_{90} = 0.12$ (0.016 – 0.12)	Cefixime MICs correlated with presence of mosaic *penA*

R: Resistant; LS: Less sensitive; NG MAST: *Neisseria gonorrhoeae* multiple antigen sequence typing.

Table 3. Reports from Japan of *Neisseria gonorrhoeae* isolates with elevated MICs to third-generation cephalosporins (continued).

Author, publication year	Location	Year of specimen collection	Criteria and number of isolates assessed	Cephalosporin MICs mg/l (range)	Comment
Europe					
Olsen 2008 [125]	Sweden	2002 – 2005	Cefixime MIC > 0.06 – ≤ 0.5: 6 of 679	All had ceftriaxone MIC < 0.125	
Hoffmann 2005 [126]	Denmark	2004	Ceftriaxone MIC > 0.023 < 0.094 81 of 434		No *PenA* sequencing performed. Serotype, NG-MAST sequence type were related within group of ceftriaxone MIC > 0.023 and < 0.094
Martin 2006 [51]	Europe (ESSTI)	2004	Ceftriaxone > 0.125: 3 of 965	Ceftriaxone MIC = 0.25	Surveillance report. Resistant isolates included 2 from Italy and 1 from Sweden
Vazquez 2007 [127]	Spain	2004 – 2005	204 isolates	Ceftriaxone MIC_{90} = 0.007 (≤ 0.007 – 0.12) Cefditoren MIC_{90} = 0.12 (≤ 0.007–0.25)	
Tzelepi 2008 [128]	Greece	Dec 2006 – Jan 2008	Cefotaxime MIC 0.25 – 1: 17 of 195	Ceftriaxone MIC_{90} = 0.125 (0.064 – 0.125) Cefixime MIC_{90} = 0.25 (0.125 – 0.25)	Isolates were part of a cluster with related serotypes and PFGE patterns in Northern Greece Isolates were multidrug resistant including penicillin, tetracycline, and fluoroquinolones
Gonococcal Resistance to Antimicrobials Surveillance Programme 2008 [28]	UK	2007	Cefixime MIC = 0.25: 2 of 1113	Ceftriaxone MIC = 0.015	Surveillance report

R: Resistant; LS: Less sensitive; NG MAST: *Neisseria gonorrhoeae* multiple antigen sequence typing.

Table 3. Reports from Japan of *Neisseria gonorrhoeae* isolates with elevated MICs to third-generation cephalosporins (continued).

Author, publication year	Location	Year of specimen collection	Criteria and number of isolates assessed	Cephalosporin MICs mg/l (range)	Comment
Australia					
Tapsall 2008 [113]	Australia	1997 – 2006	Ceftriaxone MIC 0.06 – 0.5: 134 of ~ 15,000		Isolates with elevated ceftriaxone MIC mostly from travelers or contacts
Australian Gonococcal Surveillance Program 2008 [114]	Australia	2007	Ceftriaxone MIC 0.06 – 0.25: 25 of 3,042		Surveillance report
Elsewhere in Asia					
Ray 2005 [123]	Chennai, India Hyderabad, India Nagpur, India Pune, India Kolkata, India Bangladesh	2001 2001 2001 2001 2001 1999 – 2000	Ceftriaxone LS (disk diffusion): 4 of 80 9 of 46 10 of 74 4 of 37 4 of 58 2 of 110		Resistant isolates not confirmed at regional reference laboratory
Bala 2007 [124]	New Delhi, India	2002 – 2006	Ceftriaxone MIC ≥ 0.06: 9 of 382	Ceftriaxone MIC 0.064 – 0.094	No treatment failures reported
Ye 2002 [116]	China (various)	1993 – 1998	Ceftriaxone R (not defined): 16 of 2801		Results not confirmed at national reference laboratory
Guoming 2000 [117]	Zhanjiang, China	1998 – 1999	Ceftriaxone MIC ≥ 1: 15 of 98 Ceftriaxone MIC ≥ 0.06: 34 of 98	Ceftriaxone MIC_{90} = 2 (0.016 – 2)	
Wong 2008 [118]	Taipei, Taiwan	Apr 2006 – Aug 2007	Cefixime R (disk diffusion): 24 of 146 Cefpodoxime R (disk diffusion): 31 of 146	All sensitive to ceftriaxone by disk diffusion	NGMAST ST 835 and 2180 associated with cephalosporin resistance

R: Resistant; LS: Less sensitive; NG MAST: *Neisseria gonorrhoeae* multiple antigen sequence typing.

Table 3. Reports from Japan of *Neisseria gonorrhoeae* isolates with elevated MICs to third-generation cephalosporins (continued).

Author, publication year	Location	Year of specimen collection	Criteria and number of isolates assessed	Cephalosporin MICs mg/l (range)	Comment
Lo 2008 [84]	Hong Kong	Oct 2006 – Aug 2007	Ceftibuten treatment failure: 42 of 1228	Ceftibuten MIC_{90} = 1 (0.06 – 8) Ceftriaxone MIC_{90} = 0.06 (< 0.016 – 0.125) Cefixime MIC_{90} = 0.125 (< 0.016 – 0.25)	NG MAST ST 835 and 2469 associated with cephalosporin resistance
Clendennen 1992 [120]	Philippines	Sept 1989	Ceftriaxone ≥ 0.5: 8 of 134 Cefpodoxime ≥ 4: 4 of 134		
Clendennen 1992 [121]	Thailand	May 1990	Ceftriaxone ≥ 0.5: 3 of 333 Cefixime ≥ 4: 1 of 328 Cefpodoxime ≥ 4: 2 of 331		
Cao 2008 [119]	Ho Chi Minh Ville, Vietnam	Mar 2004 – Jun 2006	Ceftriaxone MIC = 0.5: 1 of 121		No other cephalosporins were evaluated
USA					
Wang 2003 [130]	Hawaii	2001	Multidrug resistance: 4 isolates	Cefixime MIC 0.25 – 0.5 Ceftriaxone MIC 0.125	Case report. All 3 patients with links to Asia
Gonococcal Isolate Surveillance Project 2008 [83]	USA	1992 – 2006	Cefixime MIC 0.5 – 2: 48 isolates		Surveillance report
		1988 – 2006	Ceftriaxone MIC = 0.5 4 isolates		

R: Resistant; LS: Less sensitive; NG MAST: *Neisseria gonorrhoeae* multiple antigen sequence typing.

in 2006, cefixime was no longer recommended as first-line therapy for gonorrhea in Japan, with only the parenteral agents ceftriaxone and spectinomycin remaining first-line treatment options [91,110,111].

4.2 Australia

The Australian Gonococcal Surveillance Programme began to identify isolates with ceftriaxone MIC 0.06 – 0.5 mg/l (termed 'less susceptible') in 2001 [113,114]. Isolates were predominately from urban centers and isolated from international travelers and their sex partners, though some domestic transmission was suspected as well [113].

4.3 China, Hong Kong and Taiwan

Cephalosporin resistance might also be emerging in China. The 2006 report of the WHO Western Pacific Region mentions that resistance was 'particularly prominent' in China, though no more information is reported [115]. Other reports from China have reported elevated ceftriaxone MICs among isolates collected from different regions of China during the 1990s; however, some of these results were not confirmed at the national reference laboratory [116,117].

Recently, investigators in Hong Kong reported a rate of ceftibuten (400 mg PO once) treatment failure of 3.7% during October 2006 – August 2007 (n = 1228). Among the 42 persons with clinical ceftibuten failure, 7 had MIC ≥ 1 mg/l. A total of 23 isolates had ceftriaxone MIC of 0.06 or 0.125 mg/l [84]. Other investigators in Taiwan recently reported oral cephalosporin resistance there as well [118].

4.4 Elsewhere in Asia

Reports from Vietnam, Thailand and the Philippines documented sporadic isolates with ceftriaxone MIC ≥ 0.5 [119-121], though further testing on these isolates were not performed and clinical outcomes were not reported. Plans for a more extensive survey of gonococcal antimicrobial resistance patterns in the WHO Western Pacific Regions are underway [122].

A surveillance report from India, Bangladesh, Nepal and Sri Lanka reported significant rates of ceftriaxone less susceptible/intermediate isolates (1.5 – 20%) among 767 total isolates collected and tested in local laboratories during 1999 – 2001. However, these results were not able to be confirmed in the regional reference laboratory [123]. In India, Bala *et al.* recently reported nine isolates with ceftriaxone MIC of 0.064 or 0.094 mg/l among 382 isolates collected in New Delhi during 2002 – 2006. All cases were treated with ceftriaxone 250 mg or cefixime 400 mg and there were no treatment failures [124].

4.5 Europe

Recently, a Europe-wide surveillance system, European Surveillance of Sexually Transmitted Infections (ESSTI), has been implemented to monitor antimicrobial resistance patterns in *N. gonorrhoeae*. This system identified three isolates with ceftriaxone MIC = 0.25 mg/l from Italy and Sweden (ESSTI defined reduced susceptibility to ceftriaxone as ≥ 0.125 mg/l) [51]. The UK gonococcal surveillance system reported their first two isolates with decreased cefixime susceptibility in 2007 (MIC ≥ 0.25 mg/l) [28]. Other reports from Denmark, Spain, Sweden and Greece have documented isolates with increased cephalosporin MICs [125-128].

4.6 USA

Since the start of a national surveillance system in 1986 for gonococcal resistance in the USA (Gonococcal Isolate Surveillance Program; GISP) there have been four sporadic isolates with a ceftriaxone MIC of 0.5 mg/l in San Diego (1987), Cincinnati (1992 and 1993), and Philadelphia (1997) [83,129]. GISP incorporated testing for cefixime in 1992 and through 2006 there have been 48 isolates with cefixime MIC of 0.5 – 2.0 mg/l [83]. However, the percentage of isolates with elevated MIC to cefixime has decreased over time [83]. In 2001, three patients were identified in Hawaii with multidrug-resistant *N. gonorrhoeae* including isolates with cefixime MIC of 0.25 – 0.5 mg/l and ceftriaxone MIC of 0.125 mg/l. Those three persons had epidemiologic links to Asia [130].

4.7 Other global regions including Africa and Latin America

There are very limited recent data from other parts of the world, but there have not been isolates with documented elevated MICs to cephalosporins among recent published reports. These have included reports from Africa (South Africa, Madagascar, Cameroon, Central African Republic) [119,131-133] and Latin America (Argentina, Uruguay, Colombia, Peru and Venezuela) [134].

5. *Neisseria gonorrhoeae* mechanism of resistance to cephalosporins

5.1 *Neisseria* biology review

Gonococci have several features that might be important in the development of antimicrobial resistance. These include surface structures such as a porin protein, Por, encoded by the *porB* gene, and pilQ, another porin coded by the *pilQ* (formerly *penC*) gene through which pili are thought to project [135]. Gonococci are unusual in that they are constitutively competent for exogenous DNA transformation. The gonococcus is able to take up exogenous DNA that has a specific 10-base pair uptake sequence frequently found in the genome of many *Neisseria* species. There are approximately 1900 copies of this uptake sequence in *Neisseria* genomes compared with four copies in *Haemophilus influenza* [136-138]. Gonococci frequently release DNA. This DNA can be taken up and integrated into the recipient gonococcal genome. Some gonococci also do contain a 36-kb conjugal plasmid but are not thought to transfer chromosomal genes via plasmids. There is evidence that gonococci take up genetic information much more efficiently through transformation than through plasmids [138].

5.2 Definitions of resistance

Defining resistance to cephalosporins is difficult because up to now documented clinical treatment failures have been rare. As a result, the Clinical and Laboratory Standards Institute (CLSI) does not define resistance breakpoints for most cephalosporins, including ceftriaxone, but only defines sensitive isolates [139]. This has made terminology and surveillance difficult with programs and authors using varying definitions and terms. Complicating this are inherent differences in laboratory techniques that might render MICs not directly comparable [115,140,141]. Most definitions of cephalosporin resistance are based on ceftriaxone, though there might be important differences in the susceptibility of isolates to ceftriaxone and other oral cephalosporins [106,107,112]. Some authors define *N. gonorrhoeae* with increased ceftriaxone MIC as ≥ 0.06 mg/l [113,124,142], other authors and UK Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP), have used ≥ 0.125 mg/l [28,143], while the ESSTI has chosen > 0.125 mg/l [51], and the CLSI defines isolates ≤ 0.25 mg/l as susceptible, making ≥ 0.5 'nonsusceptible' [139]. In this review, we attempt to report actual MICs and the criteria used for determination of nonsusceptibility.

5.3 Resistance mechanisms

5.3.1 *Altered PBPs*

Neisseria gonorrhoeae has three penicillin-binding proteins (PBPs), designated 1, 2 and 3. PBP2 has a 10-fold higher affinity for penicillin G than PBP1 [144] and is thought to be the major binding site for β-lactam antimicrobials like the cephalosporins. Alterations in PBP2, coded for by the *penA* gene, have been demonstrated to cause decreased binding of penicillin through a single amino acid insertion (Asp-345a) [145,146]. Several additional PBP alterations have been documented to be associated with resistance to β-lactam antimicrobials including cephalosporins (see **Table 4**). However, much is still not known regarding the importance of specific mutations in PBPs, their interactions with each other, and with alterations in other genes.

The most frequently cited PBP alteration related to cephalosporin resistance is the altered PBP2 linked to cefixime resistance in Japanese male urethritis isolates by Ameyama *et al.* in 2002 [108]. In this group of isolates, 13 of 77 (17%) had cefixime MIC ≥ 0.25 mg/l. Sequencing of *penA* revealed a mosaic genotype [108]. This genotype consists of multiple genetic changes in the *penA* transpeptidase domain forming a mosaic *penA* with segments that are nearly identical to the homologous regions of the *penA* genes of related *Neisseria* commensal species such as *N. flavescens*, *N. perflava*, *N. subflava*, *N. cinerea* and *N. meningiditis* [108,109]. Presence of these multiple *penA* alterations are thought to have occurred through transformation of *N. gonorrhoeae penA* genes with genetic sequences from commensal *Neisseria* organisms [108,109]. This has previously been shown to occur in the development of chromosomally mediated penicillin resistance in both *N. gonorrhoeae* and *N. meningiditis* [147,148].

In order to define the role of this mosaic *penA*, Ameyama *et al.* attempted to transform genetically a cefixime-sensitive isolate with cloned copies of a mosaic *penA* gene amplified from an isolate with cefixime MIC of 0.5. The resulting transformant had increased MIC from the initial sensitive transformee isolate, but did not completely replicate the susceptibility profile of the *penA* donor isolate: cefixime MIC increased from 0.001 to 0.06 mg/l; ceftriaxone 0.00025 to 0.002 mg/l [108]. In a recent similar experiment, other investigators showed that the introduction of the mosaic *penA* into a penicillin and cephalosporin susceptible isolate increased the cefixime MIC by 100-fold (to 0.12 mg/l) and the ceftriaxone MIC 20-fold to 0.012 mg/l. When the mosaic *penA* was introduced into a chromosomally mediated penicillin resistant isolate possessing several other mutations (*ponA*, *mtrR*, *penB*) the ceftriaxone MIC increased to 0.25 mg/l and cefixime increased to 0.5 mg/l [149]. Data from Lindberg also suggest that multiple mutations in addition to PBP2 are needed to attain MICs to cephalosporins equivalent to that seen *in vivo* [143].

Within the mosaic *penA*, which specific substitutions are important is not yet clear, but the amino acid substitutions G545S, I312M, V316T, and possibly A501V were demonstrated to be responsible for most of the observed reduced susceptibility to cefixime [112]. Of these substitutions, I312M and V316T occur in the PBP2 of *N. perflava/sicca* and *N. flavescens*, reinforcing the hypothesis that these mosaic sequences might be the result of transformation with commensal *Neisseria* species.

Osaka *et al.* did comparative *penA* sequencing and homology modeling of isolates from Japan with mosaic and nonmosaic *penA* genes with cefixime MIC ≥ 0.125 mg/l. Modeling showed that the β-lactam binding pocket was altered both with the mosaic pattern and with the nonmosaic pattern that included the A501V alteration [111]. Further, direct assays of PBP2 binding using both wild-type and mosaic PBP2 showed that the mosaic PBP2 resisted binding by cefixime and cefdinir, but had no effect on binding of ceftriaxone [150].

Whiley *et al.* published reports questioning the importance of the mosaic *penA* genotype. They sequenced the *penA* gene in 109 *N. gonorrhoeae* isolates collected in Australia during 1997 – 2005 with a range of ceftriaxone MICs. Of the 50 isolates with ceftriaxone MIC ≥ 0.06 mg/l, only 10 had the mosaic *penA* and 10 other *penA* sequences were identified among isolates with ceftriaxone MIC ≥ 0.06 mg/l. Furthermore, one isolate with the mosaic *penA* had a ceftriaxone MIC of 0.03 mg/l and another isolate with a mosaic variant was completely sensitive to ceftriaxone (0.008 mg/l) [142,151]. Those authors report that the PBP2 A501 alteration was present in 22 of the 50 isolates with ceftriaxone MIC ≥ 0.06 (in 5 of the 10 sequence patterns with ceftriaxone MIC ≥ 0.06). However, 3 of the 25 isolates with the A501 alteration had MIC of ≤ 0.008 mg/l raising questions about the specificity of this marker as well [142].

Table 4.Genetic alterations linked to *Neisseria gonorrhoea* reduced susceptibility to β-lactam antimicrobials.

Gene (amino acid alteration)	Gene product	Phenotype	Source
ponA (L421P)	PBP1	Altered PBP1. Requires *penC* for high level resistance. Role in cephalosporin resistance questioned	[150]
penA (Asp-345a)	PBP2	Insertion PBP2 resulting in penicillin resistance	[146]
penA (mosaic PBP2)	PBP2	Oral cephalosporin resistance Possibly increased MIC for parenteral cephalosporins	[108,154]
penA (A501V)	PBP2	Possibly similar effect to mosaic; 2 – 4 fold increase in cephalosporin MIC	[112,142]
penB (*porB1b*)	PorB1b	Altered porin and membrane permeability to hydrophobic antibiotics and tetracycline	[143,152]
pilQ (*penC*)	PilQ outer membrane protein through which pilus projects. Also is a porin. [135]	Increases resistance to penicillin when *penA*, *mtrR*, and *penB* mutations are present; thought to form outer membrane pore through which antimicrobials diffuse into periplasm	[143,185]
MtrR	Transcription repressor	Causes MtrC-D-E efflux pump upregulation resulting in decreased susceptibility to hydrophobic agents such as azithromycin and rifampin. Possible increased *in vivo* fitness.	[186,187]

Tanaka *et al*. reported an *N. gonorrhoeae* isolate with ceftriaxone resistance (MIC = 0.5 mg/L) that possessed the mosaic PBP2, but also had mutations in *ponA* (L421P), *penB* (A120 and A121), and *mtrR* (see **Table 3**). They hypothesized that the L421P substitution in the *ponA* gene coding for PBP1 might also be important in conferring ceftriaxone resistance [109]. However, they did not report isolates with cefixime resistance only (ceftriaxone sensitive) and thus could not compare ceftriaxone phenotypes in regard to these non-*penA* mutations. The possible importance of *ponA* L421P was further supported by data from Takahata in which strains with the L421P substitution were associated with increased cephalosporin MICs compared with laboratory derived transformants possessing only the mosaic PBP2 (all isolates with the mosaic PBP2 also had the L421P substitution in PBP1) [112]. However, Nicholas *et al*. found that neither the presence nor absence of *ponA* affected the cephalosporin MIC [149].

These results seem to indicate that the mosaic *penA* is important but not sufficient to attain a higher level of cefixime resistance and highlights the importance of other chromosomal alterations such as those previously associated with penicillin resistance and perhaps other unknown alterations.

5.3.2 *Reduction of intracellular antimicrobial concentration*

Another basic mechanism of resistance to antimicrobials includes reducing the intracellular concentration of an antimicrobial either by preventing its entry or by actively pumping antimicrobials out. Like other bacteria, *N. gonorrhoeae* has a system of efflux pumps. One of these, the MtrC-D-E system, is repressed by the *mtrR* gene so that mutations in the *mtrR* gene have been shown to increase efflux and induce resistance to penicillin, tetracycline, macrolides and possibly fluoroquinolones. Whether this mutation also confers resistance to cephalosporins is not clear. Tanaka *et al*., however, reported an isolate with resistance to ceftriaxone (MIC = 0.5) that did have an *mtrR* mutation in addition to others [109]. Lindberg *et al*. found that 13 of 18 isolates with ceftriaxone MIC ≥ 0.06 had the *mtrR* mutation along with mutations in *penA*, *penB*, and *ponA* [143].

Other *N. gonorrhoeae* mutations can reduce the permeability of the outer membrane. The *penB* mutation of the porin gene reduces permeability to hydrophilic antimicrobials such as penicillin and tetracycline, but is only apparent when it co-exists with the *mtrR* mutation. It has not been shown to confer meaningful resistance to cephalosporins [152].

Acquisition of β-lactamases is not thought to play a role in resistance to cephalosporins for *N. gonorrhoeae*. Nearly all isolates with decreased susceptibility to cephalosporins have not been found to express β-lactamase [106,108,109,143]. Cephalosporinases like those seen in other resistant gram-negative organisms [153] have not been documented in *N. gonorrhoeae*.

5.4 Is emergence of cephalosporin resistance clonal?

An important question is whether the emerging resistance to cephalosporins is spreading from a common ancestor or whether newly resistant isolates are arising anew as a result of factors such as antimicrobial pressure and transformation from commensal *Neisseria spp*. Muratani *et al*. found rapid emergence of isolates with resistance to some oral cephalosporins (cefixime MIC ≥ 0.125), and, on the basis of RFLP analysis, concluded that this was the result of clonal spread [106]. Further studies in Japan showed that 55% of 47 isolates with the mosaic PBP2 had identical PFGE patterns and 79% had > 90% similarity [154]. In addition, the sequence of the mosaic PBP2 found in different areas of Japan differed by only one base pair [154]. In Hong Kong, 11 isolates with ceftibuten MIC = 8 mg/l had the mosaic *penA* and identical or nearly identical NG-MAST sequence types [84]. In a study of isolates from the UK, Sweden, and the USA, the isolates with decreased susceptibility to cephalosporins were apparently closely related with only two NG-MAST sequence types among 18 isolates [143]. Last, in a cluster of isolates from northern Greece with ceftriaxone MIC 0.06 – 0.125 mg/l (possession of mosaic PBP2 was not determined), the serotypes were unique and PFGE patterns similar [128].

However, casting doubt about clonality, other investigations have found the mosaic PBP2 in a diverse set of isolates typed by porin sequence [112], and Whiley *et al*. found no specific correlation between PBP2 pattern and auxotype, serotype, or NG MAST sequence type among a group of isolates with diverse collection years and locations [142]. Likely multiple mechanisms of resistance including *de novo* development of resistance, selection and clonal spread are involved.

5.5 Methods to detect resistance to cephalosporins

At present, the only reliable method to detect resistance to cephalosporins is through isolation and susceptibility testing. The gold standard culture method for MIC determination is agar dilution, though disk diffusion has also been studied and validated [139]. However, with the declining use of culture for routine diagnosis of gonococcal infections, fewer and fewer isolates are available for susceptibility testing outside of established antimicrobial susceptibility surveillance systems.

This makes the possibility of using molecular assays to identify markers of resistance in specimens collected for nucleic acid-based diagnostic tests very attractive. Molecular tests have been developed to detect ciprofloxacin resistance in *N. gonorrhoeae* [155,156], and azithromycin resistance in *Treponema pallidum* [157] but are not in widespread clinical use. A major limitation of these tests is that they depend on knowing the importance of particular mutations in conferring resistance and how those mutations correlate with *in vitro* MIC and with clinical outcomes, information that is not reliably known for cephalosporin resistance. PCR-based assays for identification of the mosaic *penA* gene have recently been published [158,159]. Such an assay might be useful in identifying organisms with the mosaic *penA* gene

in clinical specimens. However, because the importance of this genotype is not completely understood, the interpretation of the results of the assay is not clear.

6. Treatment options for cephalosporin-resistant infections

The looming question behind this discussion is what treatment options are available when cephalosporins become unreliable? Some possibilities exist and have recently been reviewed [33], but none is likely to be reliable for long. Additionally, in many reports, isolates with increased cephalosporin MICs are resistant to multiple antimicrobials already, further limiting options for treatment [109,113,114,128,143,160,161].

Azithromycin is one possible option since 2 grams is generally effective against *N. gonorrhoeae*. However, isolates with elevated MICs have emerged in multiple locations, including the USA and Europe [83,162,163]. Additionally 2 grams of azithromycin is poorly tolerated because of gastrointestinal upset, though a new timed-release formulation may improve that [44]. However, azithromycin achieves low serum levels, is frequently prescribed for other conditions such as upper respiratory tract infections, and ongoing antimicrobial pressure from azithromycin use might result in the emergence of azithromycin resistance among *N. gonorrhoeae* isolates [129].

Another option is spectinomycin, an injectable aminocyclitol antimicrobial used for gonococcal infections in a dose of 2 gm IM [164]. Spectinomycin is effective for the treatment of anogenital gonococcal infections, but is not effective for treating pharyngeal infections [91,165]. Spectinomycin is one of three first-line antimicrobials for treating gonococcal infections in Japan, where oral cephalosporin resistance is common. It has recently been shown to be effective in this setting as well [91]. However, *N. gonorrhoeae* can develop high-level resistance from a single-step mutation. Resistance has quickly developed with widespread use among American soldiers in the past [8,166], and other reports have documented spectinomycin-resistant isolates in areas where it is frequently used [117,167]. Nevertheless, documented resistance to spectinomycin has been rare and sporadic. It has been identified only five times in the USA during 1986 – 2004 where it is very seldom used [33], and has been infrequently and sporadically identified by surveillance systems in the UK and the WHO Western Pacific Region [115]. Spectinomycin can be difficult to obtain; it is not available at present in the USA, though it is expected to become available in the future [44].

Other antimicrobials might be options but there is currently little clinical evidence of their efficacy. Limited experience exists in treating gonococcal infections with amino-glycosides, though these drugs have been used in Asia and Africa. A number of surveillance studies have not found resistance to kanamycin [168,169]. However, resistance has developed when gentamicin has been used widely in Malawi [44,170]. Rifampin is inexpensive but, like other organisms, *N. gonorrhoeae* has been shown to develop resistance rapidly when rifampin has been used as a single agent [171]. Ertapenem, a parenteral carbapenem, has been studied *in vitro* against stored specimens from UK surveillance isolates, though its activity against cephalosporin nonsusceptible isolates has not been studied [172]. Similarly, tigecycline, a broad spectrum parenteral glycylcycline tetracycline derivative, has shown activity *in vitro* against tetracycline-resistant *N. gonorrhoeae*, but has not been tested clinically or against isolates with known increased cephalosporin MICs [173]. Although new cephalosporins with broader spectrum of activity against antimicrobial-resistant organisms, such as methicillin-resistant *Staphylococcus aureus*, are expected to be approved and become clinically available soon, on the basis of limited *in vitro* data, these might not have additional activity against antimicrobial-resistant *N. gonorrhoeae* [174].

7. Conclusions

Gonorrhea remains among the most common infectious diseases throughout the world and one that has repeatedly proven its ability to develop resistance to antimicrobial agents. Cephalosporins are now the only first-line therapies recommended in many areas worldwide, though resistance has begun to emerge and spread in Asia, Australia and elsewhere. The exact mechanism of this resistance is being studied but might be the result of several different chromosomal alterations, including in PBP2, other alterations that have been important in conferring penicillin resistance in the past, and other unknown alterations. The most widely studied alteration has been the mosaic *penA* gene, which appears to play a role in resistance to oral third-generation cephalosporins. However, this alteration is probably neither necessary nor sufficient to develop high-level cephalosporin resistance and might not play a large role in ceftriaxone resistance.

8. Expert opinion

If history serves as a pattern for future events, then we can expect wide dissemination of cephalosporin resistance among *N. gonorrhoeae* isolates in the future. Many questions remain unanswered such as why and how cephalosporin resistance has developed. However, the question at hand now is what can be done to prevent, delay, or at least prepare for this development.

In making plans to prevent the spread of cephalosporin resistance, it is important to know whether resistance is developing anew or is a result of spread of one (or a few) original resistant isolates. Preventing the development of new strains with cephalosporin resistance must necessarily rely on different prevention strategies (limiting antimicrobial use, assuring complete treatment of all gonococcal infections including pharyngeal infections), whereas prevention of the spread of a resistant clone would rely more on early identification and containment of a resistant isolate through interventions focused on travelers and their partners, such as

contact tracing, directly observed therapy, and possibly tests of cure. Of course, if new resistant mutants are developing anew, strategies of containment will also be useful. They would probably be less effective if the development of new resistant mutants is widespread and could not necessarily focus on travelers or other likely sources of importation.

8.1 Role of pharyngeal infections

There are several reasons to think that pharyngeal gonorrhea might play a role in the development of cephalosporin resistance. Pharyngeal infections have a lower cure rate than anogenital gonococcal infections [77,175,176]. Cephalosporins, particularly oral cephalosporins might not consistently achieve adequate tissue levels in the pharyngeal mucosa. This might mean that many pharyngeal infections, which are predominantly asymptomatic [177], are incompletely treated allowing continued growth of the gonococcus in the pharynx in the presence of declining levels of antimicrobials.

One intriguing hypothesis from the reports of mosaic *penA* genes in Japan highlights this possible role of pharyngeal gonorrhea. Two men with gonococcal urethritis infected with isolates with cefixime MIC of 0.5 mg/L reported exposure only through oral sex. The authors hypothesized that pharyngeal gonorrhea in the source partners allowed *N. gonorrhoeae* and other commensal *Neisseria* to coexist and acquire this mosaic [108], possibly aided by low concentrations of cephalosporins in the pharynx.

If that hypothesis is correct, then the prevention of new cephalosporin resistance arising might require focusing more efforts on diagnosing and properly treating pharyngeal gonorrhea. Some researchers have demonstrated that treatment effectiveness for pharyngeal gonorrhea can be increased with the use of more than one type of antimicrobial [178] or more than one dose of cephalosporin [179]. Prevention and control of cephalosporin resistance might also require modification of current treatment practices making sure that pharyngeal gonorrhea is treated with ceftriaxone or multiple doses of an oral cephalosporin instead of a single dose of oral cephalosporin.

However, controversy exists about the clinical significance of pharyngeal gonococcal infections which are usually asymptomatic and do not result in serious medical sequelae such as infertility or pelvic inflammatory disease. At this point, more research is needed to determine the role of pharyngeal infection in the development of cephalosporin resistance.

8.2 Surveillance programs

Regardless of whether cephalosporin resistance is arising anew or spreading from a few original resistant isolates, surveillance systems are crucial to identify resistant infections for intervention. These systems have already been shown to be critically important in setting treatment guidelines. In the future, these systems should especially focus on cephalosporins and should probably monitor both ceftriaxone and oral third-generation cephalosporin MICs. Unfortunately, most sentinel surveillance systems have important inherent biases such as including only men, usually only those with symptoms who attend STD clinics. Such selection bias might result in the emergence of resistance in other populations being overlooked until resistance has already been established. This has been seen in other sentinel surveillance systems such as for resistant *Streptococcus pneumonia* [180]. This was also observed in GISP; the local prevalence of fluoroquinolone resistance at nonsentinel sites sometimes differed substantially from sentinel sites [129]. As such, these sentinel surveillance systems might need to be augmented with additional testing of nonculture specimens obtained from populations not typically included. The use of molecular assays to monitor molecular markers of resistance will probably be essential in that effort. Because those assays are in development as research tools, their results would necessarily have to be validated and confirmed, but the cost of not developing and using these assays might be that cephalosporin resistance develops and gains a foothold before we know that it is present.

As has been seen in the past, resistant gonorrhea can be spread by international travel [129,130]. As others have pointed out [44,181], this makes international collaboration among regional and national surveillance systems crucial. This might be particularly true in regard to the surveillance of the Western Pacific Region where resistance to cephalosporins has already been seen, and from where resistance to other antimicrobials has spread worldwide in the past.

Response to newly developed antimicrobial resistance in the past has relied chiefly on the development of new antimicrobials. We are now faced with the fact that we are nearly out of options with no new promising alternative on the horizon. Even if there were a new option in development, without other intervention, resistance will no doubt emerge again in the future.

Other pharmaceutical strategies could be considered. The use of more than one agent to treat gonococcal infections in order to prevent emergence and spread of resistance has been suggested on the premise that mutations conferring resistance to both agents would have to develop simultaneously; an unlikely occurrence. There are some data to support the increased efficacy of dual therapy in pharyngeal infections [178]. However, dual therapy is already occurring frequently in order to treat simultaneously for gonorrhea and chlamydia and might be playing a role in the spread of azithromycin resistance. Additionally, critics have pointed out that this approach adds costs and adverse events and is not likely to halt the spread of an imported resistant isolate (the most likely scenario for dissemination of resistance to developed countries) [181,182]. Alternatively single-dose oral regimens could be eliminated in favor of IM ceftriaxone or multiple doses of an oral agent. However, these strategies must be more completely studied and are likely to suffer from increased costs, increased side effects, and would probably adversely affect adherence with partner therapy.

Ultimately, success in preserving cephalosporins as a treatment option for gonorrhea is possible but will probably not be easy

and will require a combination of approaches. More powerful than the gonorrhea-focused options discussed here are broader strategies to control and prevent sexually transmitted infections and to limit antimicrobial use worldwide. Sexually transmitted infection control and prevention is hampered by grossly inadequate global funding and political will, though there is always hope with new attention focused on STI prevention at the 2006 World Health Assembly [183]. A global program focusing on making antimicrobial use more appropriate with the aim of reducing antimicrobial resistance in all pathogenic organisms has been proposed [184]. Over the long term, these programs might take selective pressure off *N. gonorrhoeae*, but significant challenges exist.

Acknowledgments

The authors thank Mark Pandori PhD and Daniel Deck PharmD for reviewing the manuscript.

Declaration of interest

This report was funded in part by US Public Health Service T32 Grant AI007641-06A2 and the Peninsula AIDS Research Center funded by California HIV Research Program Grant CH05-SMCHC-612. In the past 12 months, PMB and JDK have received research support from Forest Laboratories, Inc. JDK has received research support from Gen-Probe, Inc.

Bibliography

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

1. Hook EW III, Handsfield HH. Gonococcal infections in the adult. Fourth edition. In: Holmes KK, Sparling PF, Stamm WE, et al, editors, Sexually Transmitted Diseases. New York: McGraw-Hill Medical, 2008. p. 627-45
2. Brandt AM. No Magic Bullet: A Social History of Venereal Disease in the United States Since 1880. Second edition. New York: Oxford University Press, 1987
3. Dees JE, Colston JAC. The use of sulfanilamide in gonococcic infections. JAMA 1937;108:1855-8
4. Nelson NA. The treatment of syphilis and gonorrhea as of today. Am J Nurs 1944;44:737-41
5. Whittington WL, Knapp JS. Trends in resistance of Neisseria gonorrhoeae to antimicrobial agents in the United States. Sex Transm Dis 1988;15:202-10
6. Dan M. The use of fluoroquinolones in gonorrhoea: the increasing problem of resistance. Expert Opin Pharmacother 2004;5:829-54
   • **Very thorough review of fluoroquinolone resistance in Neisseria gonorrhoeae.**
7. Centers for Disease Control and Prevention. Update to CDC's sexually transmitted diseases treatment guidelines, 2006: fluoroquinolones no longer recommended for treatment of gonococcal infections. MMWR Morb Mortal Wkly Rep 2007;56(14):332-6
8. Centers for Disease Control and Prevention, Workowski KA, Berman SM. Sexually transmitted diseases treatment guidelines, 2006. MMWR Recomm Rep 2006;55(RR-11):1-94
   •• **Crucial resource for clinical treatment recommendations especially for the USA.**
9. Kent CK, Chaw JK, Wong W, et al. Prevalence of rectal, urethral, and pharyngeal chlamydia and gonorrhea detected in 2 clinical settings among men who have sex with men: San Francisco, California, 2003. Clin Infect Dis 2005;41:67-74
10. World Health Organization. Global Prevalence and Incidence of Selected Curable Sexually Transmitted Infections, Overview and Estimates. Geneva: World Health Organization; 2001. Report No.: WHO/HIV_AIDS/2001.02
11. Laga M, Meheus A, Piot P. Epidemiology and control of gonococcal ophthalmia neonatorum. Bull World Health Organ 1989;67:471-7
12. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. Sex Transm Infect 1999;75:3-17
13. Rottingen JA, Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV: how much really is known? Sex Transm Dis 2001;28:579-97
14. Centers for Disease Control and Prevention. Screening tests to detect Chlamydia trachomatis and Neisseria gonorrhoeae infections – 2002. MMWR 2002;51(RR15):1-27
15. Thayer JD, Martin JE Jr. A selective medium for the cultivation of N. gonorrhoeae and N. meningiditis. Public Health Rep 1964;79:49-57
16. Cook RL, Hutchison SL, Ostergaard L, et al. Systematic review: noninvasive testing for Chlamydia trachomatis and Neisseria gonorrhoeae. Ann Intern Med 2005;142:914-25
17. Golden MR, Hughes JP, Cles LE, et al. Positive predictive value of Gen-Probe APTIMA Combo 2 testing for Neisseria gonorrhoeae in a population of women with low prevalence of N. gonorrhoeae infection. Clin Infect Dis 2004;39:1387-90
18. Whiley DM, Garland SM, Harnett G, et al. Exploring 'best practice' for nucleic acid detection of Neisseria gonorrhoeae. Sex Health 2008;5:17-23
19. Tapsall J, Whiley D, Sloots T. Applications of molecular testing in clinical laboratories for the diagnosis and control of gonorrhea. Future Microbiol 2006;1:317-24
20. Dicker LW, Mosure DJ, Steece R, Stone KM. Laboratory tests used in US public health laboratories for sexually transmitted diseases, 2000. Sex Transm Dis 2004;31:259-64
21. Dicker LW, Mosure DJ, Steece R, Stone KM. Testing for sexually transmitted diseases in US. Public health laboratories in 2004. Sex Transm Dis 2007;34:41-6
22. Fredlund H, Falk L, Jurstrand M, Unemo M. Molecular genetic methods for diagnosis and characterisation of Chlamydia trachomatis and Neisseria gonorrhoeae: impact on epidemiological surveillance and interventions. Apmis 2004;112:771-84
23. Gaydos CA, Quinn TC, Willis D, et al. Performance of the APTIMA Combo 2 assay for detection of Chlamydia trachomatis and Neisseria gonorrhoeae in

female urine and endocervical swab specimens. J Clin Microbiol 2003;41:304-9

24. Adler MW. Sexually transmitted diseases control in developing countries. Genitourin Med 1996;72:83-8
25. Department of Reproductive Health and Research WHO. Sexually Transmitted and Other Reproductive Tract Infections: A guide to essential practice. Geneva: World Health Organization, 2005
26. Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance, 2006. Atlanta, GA: US Department of Health and Human Services; 2007. http://www.cdc.gov/std/stats06/pdf/Surv2006.pdf. [Last Accessed 30 Sept 2008]
27. Weinstock H, Berman S, Cates W Jr. Sexually transmitted diseases among American youth: incidence and prevalence estimates, 2000. Perspect Sex Reprod Health 2004;36:6-10
28. GRASP Steering Group. The Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP) Year 2007 report. London: Health Protection Agency; 2008. Available from: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1221117895841 [Last accessed 8 Dec 2008]
29. Stoner BP, Whittington WL, Hughes JP, et al. Comparative epidemiology of heterosexual gonococcal and chlamydial networks: implications for transmission patterns. Sex Transm Dis 2000;27:215-23
30. Centers for Disease Control and Prevention. Racial disparities in nationally notifiable diseases–United States, 2002. MMWR Morb Mortal Wkly Rep 2005;54:9-11
31. World Health Organization. Guidelines for the management of sexually transmitted infections. Geneva, Switzerland; 2003. Available from: http://www.who.int/hiv/pub/sti/en/STIGuidelines2003.pdf. [Last accessed 10 Dec 2008]
32. Moran JS, Levine WC. Drugs of choice for the treatment of uncomplicated gonococcal infections. Clin Infect Dis 1995;20(Suppl 1):S47-65

•• **Classic article stating rationale for selecting antimicrobials for one-time treatment regimens.**

33. Newman LM, Moran JS, Workowski KA. Update on the management of gonorrhea in adults in the United States. Clin Infect Dis 2007;44(Suppl 3):S84-101

•• **Thorough review and explanation of the rationale behind US Centers for Disease Control and Prevention gonorrhea treatment recommendations. Includes review of therapies under investigation.**

34. Centers for Disease Control and Prevention (CDC). Expedited Partner Therapy in the Management of Sexually Transmitted Diseases. Atlanta, GA: US Department of Health and Human Services, 2006. Available from: http://www.cdc.gov/std/treatment/EPTFinalReport2006.pdf. [Last accessed 13 Aug 2008]
35. Golden MR, Whittington WL, Handsfield HH, et al. Effect of expedited treatment of sex partners on recurrent or persistent gonorrhea or chlamydial infection. N Engl J Med 2005;352:676-85
36. Kissinger P, Mohammed H, Richardson-Alston G, et al. Patient-delivered partner treatment for male urethritis: a randomized, controlled trial. Clin Infect Dis 2005;41:623-9
37. Fleming A. On the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of B. influenzae. 1929. Bull World Health Organ 2001;79:780-90
38. Mahoney JF, Ferguson C, Buchholtz M, Van Slyke CJ. The use of penicillin sodium in the treatment of sulfonamide-resistant gonorrhea in men. Am J Syphilis, Gonorrhea, Venereal Dis 1943;27:525-28
39. Herrell WE, Cook EN, Thompson L. Use of penicillin in sulfonamide-resistant gonorrhea infections. JAMA 1943;132:289-92
40. Van Slyke CJ, Arnold RC, Buchholtz M. Penicillin therapy in sulfonamide-resistant gonorrhea in men. Am J Pub Health 1943;33:1392-4
41. Catlin BW, Reyn A. Neisseria gonorrhoeae isolated from disseminated and localised infections in pre-penicillin era. Auxotypes and antibacterial drug resistances. Br J Vener Dis 1982;58:158-65
42. Thayer J, Field F, Magnusos H. The sensitivity of gonococci to penicillin and its relationship to penicillin failures. Antibiot Chemother 1957;7:306-10
43. Jaffe HW, Biddle JW, Thornsberry C, et al. National gonorrhea therapy monitoring study: in vitro antibiotic susceptibility and its correlation with treatment results. N Engl J Med 1976;294:5-9
44. Workowski KA, Berman SM, Douglas JM Jr. Emerging antimicrobial resistance in Neisseria gonorrhoeae: urgent need to strengthen prevention strategies. Ann Intern Med 2008;148:606-13

• **Recent review of antimicrobial resistance from a US public health perspective.**

45. Centers for Disease Control. CDC recommended treatment schedules, 1974. Morb Mortal Wkly Rep 1974;23:341-2
46. Ison CA. Antimicrobial agents and gonorrhoea: therapeutic choice, resistance and susceptibility testing. Genitourin Med 1996;72:253-7
47. Phillips I. Beta-lactamase-producing, penicillin-resistant gonococcus. Lancet 1976;2:656-7
48. Ashford WA, Golash RG, Hemming VG. Penicillinase-producing Neisseria gonorrhoeae. Lancet 1976;2:657-8
49. Lind I. Antimicrobial resistance in Neisseria gonorrhoeae. Clin Infect Dis 1997;24(Suppl 1):S93-7
50. Shigemura K, Shirakawa T, Okada H, et al. Mutations in the gyrA and parC genes and in vitro activities of fluoroquinolones in 91 clinical isolates of Neisseria gonorrhoeae in Japan. Sex Transm Dis 2004;31:180-4
51. Martin IM, Hoffmann S, Ison CA. European Surveillance of Sexually Transmitted Infections (ESSTI): the first combined antimicrobial susceptibility data for Neisseria gonorrhoeae in Western Europe. J Antimicrob Chemother 2006;58:587-93
52. Morse SA, Johnson SR, Biddle JW, Roberts MC. High-level tetracycline resistance in Neisseria gonorrhoeae is result of acquisition of streptococcal tetM determinant. Antimicrob Agents Chemother 1986;30:664-70
53. Scott GR, McMillan A, Young H. Ciprofloxacin versus ampicillin and probenecid in the treatment of uncomplicated gonorrhoea in men. J Antimicrob Chemother 1987;20:117-21
54. Roddy RE, Handsfield HH, Hook EW 3rd. Comparative trial of single-dose ciprofloxacin and ampicillin plus probenecid for treatment of gonococcal urethritis in men. Antimicrob Agents Chemother 1986;30:267-9
55. Centers for Disease Control and Prevention. 1989 Sexually Transmitted Diseases Treatment Guidelines. Morb Mortal Wkly Rep 1989;38(S-8):i-xi, 1-43
56. Centers for Disease Control and Prevention. 1993 sexually transmitted diseases treatment

guidelines. MMWR Recomm Rep 1993;42(RR-14):1-102

57. Tanaka M, Kumazawa J, Matsumoto T, Kobayashi I. High prevalence of Neisseria gonorrhoeae strains with reduced susceptibility to fluoroquinolones in Japan. Genitourin Med 1994;70:90-3
58. Centers for Disease Control and Prevention. Fluoroquinolone resistance in Neisseria gonorrhoeae–Colorado and Washington, 1995. MMWR Morb Mortal Wkly Rep 1995;44:761-4
59. Gorwitz RJ, Nakashima AK, Moran JS, Knapp JS. Sentinel surveillance for antimicrobial resistance in Neisseria gonorrhoeae – United States, 1988–1991. The Gonococcal Isolate Surveillance Project Study Group. MMWR CDC Surveill Summ 1993;42:29-39
60. Turner A, Gough KR, Jephcott AE, McClean AN. Importation into the UK of a strain of Neisseria gonorrhoeae resistant to penicillin, ciprofloxacin and tetracycline. Genitourin Med 1995;71:331-2
61. Tapsall JW, Phillips EA, Shultz TR, Thacker C. Quinolone-resistant Neisseria gonorrhoeae isolated in Sydney, Australia, 1991 to 1995. Sex Transm Dis 1996;23:425-8
62. Knapp JS, Ohye R, Neal SW, et al. Emerging in vitro resistance to quinolones in penicillinase-producing Neisseria gonorrhoeae strains in Hawaii. Antimicrob Agents Chemother 1994;38:2200-3
63. Centers for Disease Control and Prevention. Increases in fluoroquinolone-resistant Neisseria gonorrhoeae among men who have sex with men – United States, 2003, and revised recommendations for gonorrhea treatment, 2004. MMWR Morb Mortal Wkly Rep 2004;53:335-8
64. Centers for Disease Control and Prevention. Increases in fluoroquinolone-resistant Neisseria gonorrhoeae – Hawaii and California, 2001. MMWR Morb Mortal Wkly Rep 2002;51:1041-4
65. BASHH (British Association for Sexual Health and HIV). National Guideline on the Diagnosis and Treatment of Gonorrhoea in Adults 2005
66. Andes DR, Craig WA. Cephalosporins. Sixth edition. In: Mandell GL, Bennett JE, Dolin R, editors, Principles and Practice of Infectious Diseases. Philadelphia, PA: Elsevier, 2005;20:294-310
67. Marshall WF, Blair JE. The cephalosporins. Mayo Clin Proc 1999;74:187-95
68. Craig WA. Interrelationship between pharmacokinetics and pharmacodynamics in determining dosage regimens for broad-spectrum cephalosporins. Diagn Microbiol Infect Dis 1995;22:89-96
69. Thorpe EM, Schwebke JR, Hook EW 3rd, et al. Comparison of single-dose cefuroxime axetil with ciprofloxacin in treatment of uncomplicated gonorrhea caused by penicillinase-producing and non-penicillinase-producing Neisseria gonorrhoeae strains. Antimicrob Agents Chemother 1996;40:2775-80
70. Ison CA, Mouton JW, Jones K, et al. Which cephalosporin for gonorrhoea? Sex Transm Infect 2004;80:386-8
71. Crabbe F, Grobbelaar TM, van Dyck E, et al. Cefaclor, an alternative to third generation cephalosporins for the treatment of gonococcal urethritis in the developing world? Genitourin Med 1997;73:506-9
72. Handsfield HH, McCormack WM, Hook EW 3rd, et al. A comparison of single-dose cefixime with ceftriaxone as treatment for uncomplicated gonorrhea. The Gonorrhea Treatment Study Group. N Engl J Med 1991;325:1337-41
73. Verdon MS, Douglas JM Jr, Wiggins SD, Handsfield HH. Treatment of uncomplicated gonorrhea with single doses of 200 mg cefixime. Sex Transm Dis 1993;20:290-3
74. Plourde PJ, Tyndall M, Agoki E, et al. Single-dose cefixime versus single-dose ceftriaxone in the treatment of antimicrobial-resistant Neisseria gonorrhoeae infection. J Infect Dis 1992;166:919-22
75. Portilla I, Lutz B, Montalvo M, Mogabgab WJ. Oral cefixime versus intramuscular ceftriaxone in patients with uncomplicated gonococcal infections. Sex Transm Dis 1992;19:94-8
76. Novak E, Paxton LM, Tubbs HJ, et al. Orally administered cefpodoxime proxetil for treatment of uncomplicated gonococcal urethritis in males: a dose-response study. Antimicrob Agents Chemother 1992;36:1764-5
77. Hall C, McElroy M, Samuel M, et al. Single-Dose, Oral cefpodoxime proxetil is effective for treatment of uncomplicated urogenital and rectal gonorrhea. 17th Biennial Meeting of the International Society for Sexually Transmitted Disease Research; July 29 - Aug 1 2007; Seattle, WA; 2007
78. Chong LY, Cheung WM, Leung CS, et al. Clinical evaluation of ceftibuten in gonorrhea. A pilot study in Hong Kong. Sex Transm Dis 1998;25:464-7
79. Cohen MA, Joannides ET, Roland GE, et al. In vitro evaluation of cefdinir (FK482), a new oral cephalosporin with enhanced antistaphylococcal activity and beta-lactamase stability. Diagn Microbiol Infect Dis 1994;18:31-9
80. Hook EW 3rd, Judson FN, Verdon MS, et al. Comparative study of cefoperazone and spectinomycin for treatment of uncomplicated gonorrhea in men. Antimicrob Agents Chemother 1986;30:619-21
81. Kim JH, Ro YS, Kim YT. Cefoperazone (Cefobid) for treating men with gonorrhoea caused by penicillinase producing Neisseria gonorrhoeae. Br J Vener Dis 1984;60:238-40
82. Centers for Disease Control and Prevention. Availability of cefixime 400 mg tablets – United States, April 2008. MMWR Morb Mortal Wkly Rep 2008;57:435
83. Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2006 Supplement: Gonococcal Isolate Surveillance Project (GISP) Annual Report – 2006. Atlanta, GA: US Department of Health and Human Services; 2008. Available from: http://www.cdc.gov/STD/gisp2006/GISPSurvSupp2006Complete.pdf. [Last accessed 13 Oct 2008]
84. Lo JY, Ho KM, Leung AO, et al. Ceftibuten resistance and treatment failure of Neisseria gonorrhoeae infection. Antimicrob Agents Chemother 2008;52:3564-7
85. Handsfield HH, Murphy VL. Comparative study of ceftriaxone and spectinomycin for treatment of uncomplicated gonorrhoea in men. Lancet 1983;2:67-70
86. Collier AC, Judson FN, Murphy VL, et al. Comparative study of ceftriaxone and spectinomycin in the treatment of uncomplicated gonorrhea in women. Am J Med 1984;77:68-72
87. Judson FN, Ehret JM, Root CJ. Comparative study of ceftriaxone and aqueous procaine penicillin G in the treatment of uncomplicated gonorrhea in

women. Antimicrob Agents Chemother 1983;23:218-20

88. Rajan VS, Sng EH, Thirumoorthy T, Goh CL. Ceftriaxone in the treatment of ordinary and penicillinase-producing strains of Neisseria gonorrhoeae. Br J Vener Dis 1982;58:314-16
89. Handsfield HH, Murphy VL, Holmes KK. Dose-ranging study of ceftriaxone for uncomplicated gonorrhea in men. Antimicrob Agents Chemother 1981;20:839-40
90. Eichmann A, Weidmann G, Havas L. One-dose treatment of acute uncomplicated gonorrhoea of male patients with ceftriaxone Ro 13-9904, a new parenteral cephalosporin. A dose-range finding pilot study using doses of 500, 250, 125 and 50 mg respectively, in descending order. Chemotherapy 1981;27(Suppl 1):62-9
91. Kojima M, Masuda K, Yada Y, et al. Single-dose treatment of male patients with gonococcal urethritis using 2 g spectinomycin: microbiological and clinical evaluations. Int J Antimicrob Agents 2008;32:50-4
92. Goldstein AM, Clark JH, Wickler MA. Comparison of single-dose ceftizoxime or ceftriaxone in the treatment of uncomplicated urethral gonorrhea. Sex Transm Dis 1991;18:180-2
93. Goldstein AM, Clark JH. Treatment of uncomplicated gonococcal urethritis with single-dose ceftizoxime. Sex Transm Dis 1990;17:181-3
94. Veeravahu M, Clay JC, Mohanty KC, et al. Efficacy of ceftizoxime in the treatment of uncomplicated gonorrhoea: comparison with amoxycillin. Br J Clin Pract 1990;44:216-18
95. Berg SW, Kilpatrick ME, Harrison WO, McCutchan JA. Cefoxitin as a single-dose treatment for urethritis caused by penicillinase-producing Neisseria gonorrhoeae. N Engl J Med 1979;301:509-11
96. Greaves WL, Kraus SJ, McCormack WM, et al. Cefoxitin vs. penicillin in the treatment of uncomplicated gonorrhea. Sex Transm Dis 1983;10:53-5
97. Zajdowicz TR, Sanches PL, Berg SW, et al. Comparison of ceftriaxone with cefoxitin in the treatment of penicillin-resistant gonococcal urethritis. Br J Vener Dis 1983;59:176-8
98. Korting HC, Abeck D. One-shot treatment of uncomplicated gonorrhoea with third-generation cephalosporins with differing serum half-life. Results of a controlled trial with ceftriaxone and cefotaxime. Chemotherapy 1989;35:441-8
99. Mogabgab WJ, Lutz FB. Randomized study of cefotaxime versus ceftriaxone for uncomplicated gonorrhea. South Med J 1994;87:461-4
100. McCormack WM, Mogabgab WJ, Jones RB, et al. Multicenter, comparative study of cefotaxime and ceftriaxone for treatment of uncomplicated gonorrhea. Sex Transm Dis 1993;20:269-73
101. van der Willigen AH, Wagenvoort JH, Schalla WO, et al. Randomized comparative study of 0.5 and 1 g of cefodizime (HR 221) versus 1 g of cefotaxime for acute uncomplicated urogenital gonorrhea. Antimicrob Agents Chemother 1988;32:426-9
102. Matsumoto T, Muratani T, Takahashi K, et al. Single dose of cefodizime completely eradicated multidrug-resistant strain of Neisseria gonorrhoeae in urethritis and uterine cervicitis. J Infect Chemother 2006;12:97-9
103. Tanaka M, Nakayama H, Tunoe H, et al. A remarkable reduction in the susceptibility of Neisseria gonorrhoeae isolates to cephems and the selection of antibiotic regimens for the single-dose treatment of gonococcal infection in Japan. J Infect Chemother 2002;8:81-6
104. Akasaka S, Muratani T, Yamada Y, et al. Emergence of cephem- and aztreonam-high-resistant Neisseria gonorrhoeae that does not produce beta-lactamase. J Infect Chemother 2001;7:49-50

• **Early report of cephalosporin treatment failures in Japan.**

105. Yamaguchi K, Domon H, Miyazaki S, et al. In vitro and in vivo antibacterial activities of CS-834, a new oral carbapenem. Antimicrob Agents Chemother 1998;42:555-63
106. Muratani T, Akasaka S, Kobayashi T, et al. Outbreak of cefozopran (penicillin, oral cephems, and aztreonam)-resistant Neisseria gonorrhoeae in Japan. Antimicrob Agents Chemother 2001;45:3603-6
107. Ito M, Yasuda M, Yokoi S, et al. Remarkable increase in central Japan in 2001–2002 of Neisseria gonorrhoeae isolates with decreased susceptibility to penicillin, tetracycline, oral cephalosporins, and fluoroquinolones. Antimicrob Agents Chemother 2004;48:3185-7
108. Ameyama S, Onodera S, Takahata M, et al. Mosaic-like structure of penicillin-binding protein 2 Gene (penA) in clinical isolates of Neisseria gonorrhoeae with reduced susceptibility to cefixime. Antimicrob Agents Chemother 2002;46:3744-9

• **First discussion of mosaic PBP2.**

109. Tanaka M, Nakayama H, Huruya K, et al. Analysis of mutations within multiple genes associated with resistance in a clinical isolate of Neisseria gonorrhoeae with reduced ceftriaxone susceptibility that shows a multidrug-resistant phenotype. Int J Antimicrob Agents 2006;27:20-6
110. Yokoi S, Deguchi T, Ozawa T, et al. Threat to cefixime treatment for gonorrhea. Emerg Infect Dis 2007;13:1275-7
111. Osaka K, Takakura T, Narukawa K, et al. Analysis of amino acid sequences of penicillin-binding protein 2 in clinical isolates of Neisseria gonorrhoeae with reduced susceptibility to cefixime and ceftriaxone. J Infect Chemother 2008;14:195-203
112. Takahata S, Senju N, Osaki Y, et al. Amino acid substitutions in mosaic penicillin-binding protein 2 associated with reduced susceptibility to cefixime in clinical isolates of Neisseria gonorrhoeae. Antimicrob Agents Chemother 2006;50:3638-45
113. Tapsall JW, Limnios EA, Murphy D. Analysis of trends in antimicrobial resistance in Neisseria gonorrhoeae isolated in Australia, 1997 – 2006. J Antimicrob Chemother 2008;61:150-5
114. Annual report of the Australian Gonococcal Surveillance Programme, 2007. Commun Dis Intell 2008;32:227-31
115. WHO Western Pacific Gonococcal Antimicrobial Surveillance Programme. Surveillance of antibiotic resistance in Neisseria gonorrhoeae in the WHO Western Pacific Region, 2006. Commun Dis Intell 2008;32:48-51
116. Ye S, Su X, Wang Q, et al. Surveillance of antibiotic resistance of Neisseria gonorrhoeae isolates in China, 1993 – 1998. Sex Transm Dis 2002;29:242-5
117. Guoming L, Qun C, Shengchun W. Resistance of Neisseria gonorrhoeae epidemic strains to antibiotics: report of resistant isolates and surveillance in

Zhanjiang, China: 1998 to 1999. Sex Transm Dis 2000;27:115-18

118. Wong WW, Huang CT, Li LH. Molecular epidemiology of gonorrhea identified clonal clusters with distinct susceptibilities associated with specific high-risk groups. J Clin Microbiol 2008; 46(12):3931-4. Epub 2008 Oct 8
119. Cao V, Ratsima E, Tri DV, et al. Antimicrobial susceptibility of Neisseria gonorrhoeae strains isolated in 2004 – 2005 in Bangui, Central African Republic; Yaounde, Cameroon; Antananarivo, Madagascar; and Ho Chi Minh Ville and Nha Trang, Vietnam. Sex Transm Dis 2008; 35(11):941-5
120. Clendennen TE 3rd, Hames CS, Kees ES, et al. In vitro antibiotic susceptibilities of Neisseria gonorrhoeae isolates in the Philippines. Antimicrob Agents Chemother 1992;36:277-82
121. Clendennen TE, Echeverria P, Saengeur S, et al. Antibiotic susceptibility survey of Neisseria gonorrhoeae in Thailand. Antimicrob Agents Chemother 1992;36:1682-7
122. World Health Organization Regional Office for the Western Pacific. Report: Meeting on Controlling Sexually Transmitted Infections – Enhancing HIV Prevention in the Western Pacific Region. Penang, Malaysia: World Health Organization Regional Office for the Western Pacific, 2007 29 October – 1 November 2007. Report No.: (WP)HSI/ICP/HIV/1.4/001 RS/2007/ GE/40(MAA). Available from: http://www.wpro.who.int/NR/rdonlyres/0C9AD220-9EE9-4F2E-9C44-5405BE5B10AE/0/MeetingReport_STIMtg_Penang.pdf [Last accessed 11 Aug 2008]
123. Ray K, Bala M, Kumari S, Narain JP. Antimicrobial resistance of Neisseria gonorrhoeae in selected World Health Organization Southeast Asia Region countries: an overview. Sex Transm Dis 2005;32:178-84
124. Bala M, Ray K, Gupta SM, et al. Changing trends of antimicrobial susceptibility patterns of Neisseria gonorrhoeae in India and the emergence of ceftriaxone less susceptible N. gonorrhoeae strains. J Antimicrob Chemother 2007;60:582-6
125. Olsen B, Hadad R, Fredlund H, Unemo M. The Neisseria gonorrhoeae population in Sweden during 2005-phenotypes, genotypes and antibiotic resistance. Apmis 2008;116:181-9
126. Hoffmann S, Lambertsen L, Berthelsen L, Cowan S. Neisseria gonorrhoeae with increasing ceftriaxone MIC in Denmark in 2004: serotyping, bi-locus sequence typing, and sexual preference, Abstract WP-035. 16th Meeting of the International Society for Sexually Transmitted Diseases Research, 2005; Amsterdam, the Netherlands; 2005. Available from: http://www.parthen-impact.com/pco/6_05STD/public/ [Last accessed April, 4 Dec 2008]
127. Vazquez JA, Martin E, Galarza P, et al. In vitro susceptibility of Spanish isolates of Neisseria gonorrhoeae to cefditoren and five other antimicrobial agents. Int J Antimicrob Agents 2007;29:473-4
128. Tzelepi E, Daniilidou M, Miriagou V, et al. Cluster of multidrug-resistant Neisseria gonorrhoeae with reduced susceptibility to the newer cephalosporins in Northern Greece. J Antimicrob Chemother 2008;62:637-9
129. Wang SA, Harvey AB, Conner SM, et al. Antimicrobial resistance for Neisseria gonorrhoeae in the United States, 1988 to 2003: the spread of fluoroquinolone resistance. Ann Intern Med 2007;147:81-8
130. Wang SA, Lee MV, O'Connor N, et al. Multidrug-resistant Neisseria gonorrhoeae with decreased susceptibility to cefixime-Hawaii, 2001. Clin Infect Dis 2003;37:849-52
131. Lewis DA, Scott L, Slabbert M, et al. Escalation in the relative prevalence of ciprofloxacin-resistant gonorrhoea among men with urethral discharge in two South African cities: association with HIV seropositivity. Sex Transm Infect 2008;84:352-5
132. De Jongh M, Dangor Y, Adam A, Hoosen AA. Gonococcal resistance: evolving from penicillin, tetracycline to the quinolones in South Africa – implications for treatment guidelines. Int J STD AIDS 2007;18:697-9
133. Moodley P, Martin IM, Pillay K, et al. Molecular epidemiology of recently emergent ciprofloxacin-resistant Neisseria gonorrhoeae in South Africa. Sex Transm Dis 2006;33:357-60
134. Dillon JA, Ruben M, Li H, et al. Challenges in the control of gonorrhea in South America and the Caribbean: monitoring the development of resistance to antibiotics. Sex Transm Dis 2006;33:87-95
135. Sparling PF. Biology of Neisseria gonorrhoeae. Fourth edition. In: Holmes KK, Sparling PF, Stamm WE, et al, editors, Sexually Transmitted Diseases. McGraw-Hill Medical, 2008. p. 607-26
136. Chung GT, Yoo JS, Oh HB, et al. The complete genome sequence of Neisseria gonorrhoeae NCCP11945. J Bacteriol 2008;190(17):6035-6. Epub 2008 Jun 27
137. Davidsen T, Rodland EA, Lagesen K, et al. Biased distribution of DNA uptake sequences towards genome maintenance genes. Nucleic Acids Res 2004;32:1050-8
138. Hamilton HL, Dillard JP. Natural transformation of Neisseria gonorrhoeae: from DNA donation to homologous recombination. Mol Microbiol 2006;59:376-85

• **Excellent review of this interesting aspect of Neisseria genetics and biology.**

139. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; Eighteenth Informational Supplement. CLSI document M100-S18. January 2008
140. Tapsall J. Antimicrobial resistance in Neisseria gonorrhoeae. Sydney: WHO Collaborating Centre for STD and HIV, 2001. Report No.: WHO/CDS/CSR/DRS/2001.3

•• **Complete review and guidance for public health programs and laboratories worldwide.**

141. Ison CA, Martin IM, Lowndes CM, Fenton KA. Comparability of laboratory diagnosis and antimicrobial susceptibility testing of Neisseria gonorrhoeae from reference laboratories in Western Europe. J Antimicrob Chemother 2006;58:580-6
142. Whiley DM, Limnios EA, Ray S, et al. Diversity of penA alterations and subtypes in Neisseria gonorrhoeae strains from Sydney, Australia, that are less susceptible to ceftriaxone. Antimicrob Agents Chemother 2007;51:3111-16

• **Very well-carried-out report questioning significance of the mosaic PBP2 in conferring cephalosporin resistance.**

143. Lindberg R, Fredlund H, Nicholas R, Unemo M. Neisseria gonorrhoeae isolates with reduced susceptibility to cefixime and ceftriaxone: association with genetic polymorphisms in penA, mtrR, porB1b, and ponA. Antimicrob Agents Chemother 2007;51:2117-22

- **Complete analysis of multiple mutations among recent cephem-resistant isolates.**

144. Dougherty TJ, Koller AE, Tomasz A. Penicillin-binding proteins of penicillin-susceptible and intrinsically resistant Neisseria gonorrhoeae. Antimicrob Agents Chemother 1980;18:730-7
145. Brannigan JA, Tirodimos IA, Zhang QY, et al. Insertion of an extra amino acid is the main cause of the low affinity of penicillin-binding protein 2 in penicillin-resistant strains of Neisseria gonorrhoeae. Mol Microbiol 1990;4:913-19
146. Dowson CG, Jephcott AE, Gough KR, Spratt BG. Penicillin-binding protein 2 genes of non-beta-lactamase-producing, penicillin-resistant strains of Neisseria gonorrhoeae. Mol Microbiol 1989;3:35-41
147. Spratt BG. Hybrid penicillin-binding proteins in penicillin-resistant strains of Neisseria gonorrhoeae. Nature 1988;332:173-6
148. Spratt BG, Zhang QY, Jones DM, et al. Recruitment of a penicillin-binding protein gene from Neisseria flavescens during the emergence of penicillin resistance in Neisseria meningitidis. Proc Natl Acad Sci USA 1989;86:8988-92
149. Nicholas RA, Zhao S, Tomberg J, et al. Genetics of intermediate resistance to expanded-spectrum cephalosporins in Neisseria gonorrhoeae, [abstract P054]. 16th International Pathogenic Neisseria Conference; 2008 September; Rotterdam, the Netherlands, 2008. p. 133. Available from: http://www.ipnc2008.org/. [Last accessed 2 Oct 2008]
150. Ochiai S, Sekiguchi S, Hayashi A, et al. Decreased affinity of mosaic-structure recombinant penicillin-binding protein 2 for oral cephalosporins in Neisseria gonorrhoeae. J Antimicrob Chemother 2007;60:54-60
151. Whiley DM, Limnios EA, Ray S, et al. Further questions regarding the role of mosaic penA sequences in conferring reduced susceptibility to ceftriaxone in Neisseria gonorrhoeae. Antimicrob Agents Chemother 2007;51:802-3
152. Gill MJ, Simjee S, Al-Hattawi K, et al. Gonococcal resistance to beta-lactams and tetracycline involves mutation in loop 3 of the porin encoded at the penB locus. Antimicrob Agents Chemother 1998;42:2799-803
153. Nordmann P, Mammeri H. Extended-spectrum cephalosporinases: structure, detection and epidemiology. Future Microbiol 2007;2:297-307
154. Ito M, Deguchi T, Mizutani KS, et al. Emergence and spread of Neisseria gonorrhoeae clinical isolates harboring mosaic-like structure of penicillin-binding protein 2 in Central Japan. Antimicrob Agents Chemother 2005;49:137-43
155. Siedner MJ, Pandori M, Castro L, et al. Real-time PCR assay for detection of quinolone-resistant Neisseria gonorrhoeae in urine samples. J Clin Microbiol 2007;45:1250-4
156. Li Z, Yokoi S, Kawamura Y, et al. Rapid detection of quinolone resistance-associated gyrA mutations in Neisseria gonorrhoeae with a LightCycler. J Infect Chemother 2002;8:145-50
157. Lukehart SA, Godornes C, Molini BJ, et al. Macrolide resistance in Treponema pallidum in the United States and Ireland. N Engl J Med 2004;351:154-8
158. Ochiai S, Ishiko H, Yasuda M, Deguchi T. Rapid detection of the mosaic structure of the Neisseria gonorrhoeae penA Gene, which is associated with decreased susceptibilities to oral cephalosporins. J Clin Microbiol 2008;46:1804-10
- **Real time molecular assay for mosaic *penA* gene.**

159. Whiley D, Bates J, Limnios A, et al. Use of a novel screening PCR indicates presence of Neisseria gonorrhoeae isolates with a mosaic penA gene sequence in Australia. Pathology 2007;39:445-6
- **Real-time molecular assay for mosaic *penA* gene.**

160. Deguchi T, Yasuda M, Nakano M, et al. Quinolone-resistant Neisseria gonorrhoeae: correlation of alterations in the GyrA subunit of DNA gyrase and the ParC subunit of topoisomerase IV with antimicrobial susceptibility profiles. Antimicrob Agents Chemother 1996;40:1020-3
161. Roberts MC, DeMaster L, Soge OO, Whittington WLH. Characterization of high-level multidrug resistant Neisseria gonorrhoeae associated with therapy failure. 17th Biennial Meeting of the International Society for Sexually Transmitted Disease Research, Seattle, USA, July 29 - Aug 1, 2007
162. Palmer HM, Young H, Winter A, Dave J. Emergence and spread of azithromycin-resistant Neisseria gonorrhoeae in Scotland. J Antimicrob Chemother 2008;62:490-4
163. Alcala B, Arreaza L, Salcedo C, et al. Molecular characterization of ciprofloxacin resistance of gonococcal strains in Spain. Sex Transm Dis 2003;30:395-8
164. Holloway WJ. Spectinomycin. Med Clin North Am 1982;66:169-73
165. Judson FN, Ehret JM, Handsfield HH. Comparative study of ceftriaxone and spectinomycin for treatment of pharyngeal and anorectal gonorrhea. JAMA 1985;253:1417-19
166. Boslego JW, Tramont EC, Takafuji ET, et al. Effect of spectinomycin use on the prevalence of spectinomycin-resistant and of penicillinase-producing Neisseria gonorrhoeae. N Engl J Med 1987;317:272-8
167. Govender S, Lebani T, Nell R. Antibiotic susceptibility patterns of Neisseria gonorrhoeae isolates in Port Elizabeth. S Afr Med J 2006;96:225-6
168. Su X, Hutapea N, Tapsall JW, Lind I. Plasmid-mediated resistance of Neisseria gonorrhoeae strains isolated from female sex workers in North Sumatra, Indonesia, 1996. Sex Transm Dis 2003;30:178-82
169. Van Dyck E, Karita E, Abdellati S, et al. Antimicrobial susceptibilities of Neisseria gonorrhoeae in Kigali, Rwanda, and trends of resistance between 1986 and 2000. Sex Transm Dis 2001;28:539-45
170. Daly CC, Hoffman I, Hobbs M, et al. Development of an antimicrobial susceptibility surveillance system for Neisseria gonorrhoeae in Malawi: comparison of methods. J Clin Microbiol 1997;35:2985-8
171. Sutrisna A, Soebjakto O, Wignall FS, et al. Increasing resistance to ciprofloxacin and other antibiotics in Neisseria gonorrhoeae from East Java and Papua, Indonesia, in 2004 – implications for treatment. Int J STD AIDS 2006;17:810-12
172. Livermore DM, Alexander S, Marsden B, et al. Activity of ertapenem against Neisseria gonorrhoeae. J Antimicrob Chemother 2004;54:280-1
173. Deshpande LM, Gales AC, Jones RN. GAR-936 (9-t-butylglycylamido-minocycline)

susceptibility test development for streptococci, Haemophilus influenzae and Neisseria gonorrhoeae: preliminary guidelines and interpretive criteria. Int J Antimicrob Agents 2001;18:29-35

174. Barry PM, Lenderman C, Melendez J, et al. In vitro activity of ceftaroline against recent US isolates of Neisseria gonorrhoeae, Poster C1-163. 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and the Infectious Diseases Society of America (IDSA) 46th Annual Meeting. Washington, DC, USA, October 25-28, 2008
175. Moran JS. Treating uncomplicated Neisseria gonorrhoeae infections: is the anatomic site of infection important? Sex Transm Dis 1995;22:39-47
176. Manavi K, Young H, McMillan A. The outcome of oropharyngeal gonorrhoea treatment with different regimens. Int J STD AIDS 2005;16:68-70
177. Morris SR, Klausner JD, Buchbinder SP, et al. Prevalence and incidence of pharyngeal gonorrhea in a longitudinal sample of men who have sex with men: the EXPLORE study. Clin Infect Dis 2006;43:1284-9
178. Sathia L, Ellis B, Phillip S, et al. Pharyngeal gonorrhoea – is dual therapy the way forward? Int J STD AIDS 2007;18:647-8
179. Matsumoto T, Muratani T, Takahashi K, et al. Multiple doses of cefodizime are necessary for the treatment of Neisseria gonorrhoeae pharyngeal infection. J Infect Chemother 2006;12:145-7
180. Schrag SJ, Zell ER, Schuchat A, Whitney CG. Sentinel surveillance: a reliable way to track antibiotic resistance in communities? Emerg Infect Dis 2002;8:496-502
181. Tapsall J. Antibiotic resistance in Neisseria gonorrhoeae is diminishing available treatment options for gonorrhea: some possible remedies. Expert Rev Anti Infect Ther 2006;4:619-28
182. Tapsall JW. What management is there for gonorrhea in the postquinolone era? Sex Transm Dis 2006;33:8-10
183. World Health Organization. Fifty-Ninth World Health Assembly Provisional agenda item 11.6: Prevention and control of sexually transmitted infections: draft global strategy; 2006 May 18. Available from: http://www.who.int/gb/ebwha/pdf_files/WHA59/A59_11-en.pdf
184. Simonsen GS, Tapsall JW, Allegranzi B, et al. The antimicrobial resistance containment and surveillance approach – a public health tool. Bull World Health Organ 2004;82:928-34
185. Ropp PA, Hu M, Olesky M, Nicholas RA. Mutations in ponA, the gene encoding penicillin-binding protein 1, and a novel locus, penC, are required for high-level chromosomally mediated penicillin resistance in Neisseria gonorrhoeae. Antimicrob Agents Chemother 2002;46:769-77
186. Hagman KE, Pan W, Spratt BG, et al. Resistance of Neisseria gonorrhoeae to antimicrobial hydrophobic agents is modulated by the mtrRCDE efflux system. Microbiology 1995;141(Pt 3):611-22
187. Warner DM, Folster JP, Shafer WM, Jerse AE. Regulation of the MtrC-MtrD-MtrE efflux-pump system modulates the in vivo fitness of Neisseria gonorrhoeae. J Infect Dis 2007;196:1804-12.

Affiliation

Pennan M Barry[†1,2] MD MPH &
Jeffrey D Klausner[1,2] MD MPH
[†]Author for correspondence
[†1]San Francisco Department of Public Health, San Francisco, California, USA
[2]University of California–San Francisco, San Francisco, California, USA
1360 Mission Street, Suite 401, San Francisco, CA 94103, USA
Tel: +1 415 355 2000; Fax: +1 415 554 9636;
E-mail: pennanbarry@gmail.com