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

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Abstract

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 left third-generation cephalosporins as the lone class of antimicrobials currently 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 beta-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

Neisseria gonorrhoeae; cephalosporin resistance

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, currently in some regions only third-generation cephalosporins are 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

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emerging and will almost certainly present 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 occur 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 non-urethral sites can be the predominant site of infection.[9] Less commonly, *N. 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 substantially increase the risk of acquiring and transmitting human immunodeficiency virus (HIV) infection,[12, 13] making gonorrhea control an important part of HIV prevention.

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 United States, they have supplanted culture in many clinical settings and have expanded screening to many non-clinical settings.[20-23] This move away from culture has made routine clinical antimicrobial susceptibility testing impossible in many cases so that 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 United States, gonorrhea is consistently the second-most frequently reported notifiable infection with more than 350,000 infections reported in 2006.[26] Many more infections likely go unreported and the actual annual cumulative incidence of gonococcal infections in the United States during 2000 was estimated to be >700,000.[27] In the United Kingdom 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 United States 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 United States while blacks make up approximately 12% of the population.[26]

2. The 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 United States, 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 hours.[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 United States 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 following 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 likely imported from Africa and Asia.[5, 49, 50] However, by 1989 penicillin was no longer an effective treatment option and penicillin is not currently recommended in the United States.[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 United States 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] likely via travelers.[61, 62] Prevalence of resistant isolates continued to increase in the United States 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 United States 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 below 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 molecule produced by *Cephalosporin acremonium*. These variations are achieved by side chain substitutions at R1 (C7) and R2 (C3) of the cephalosporin nucleus with R1 alterations generally being responsible for stability against β-lactamases and R2 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 cefoperazone (see Table 1).[80, 81] The WHO recommends cefixime 400mg and in the United States, cefixime 400mg is the only oral regimen recommended as first line therapy. This is because it is the only oral option to date which 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 United States from 2002 until 2008,[82] and at that time cefpodoxime 400mg 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 hours 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 hours, one can see that there might not be much excess pharmacologic 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 United States and the United Kingdom and is recommended by the WHO.[7, 8, 31, 65] However, the dose of ceftriaxone is the subject of debate with 125mg recommended in the United States and by WHO, but many countries recommend 250mg.[8, 31, 65] In Japan,

1000mg IV is recommended.[91] The chemical structure of ceftriaxone, particularly the heterocyclic thiomethyl group at the R2 (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 1gm of probenecid,[95-97] and cefotaxime 500mg IM.[98-100] Cefuroxime 1.5gm IM is occasionally used in the United Kingdom. [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[105](See Table 3). 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 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 (400mg 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 9 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 250mg or cefixime 400mg 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 3 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 United States

Since the start of a national surveillance system in 1986 for gonococcal resistance in the United States (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 percent 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 3 persons had epidemiologic links to Asia.[130]

4.7 Other global regions including Africa and Latin America

Very limited recent data exist 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 4 copies in *H. influenzae*.[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 "non-susceptible."[139] In this review, we attempt to report actual MICs and the criteria used for determination of non-susceptibility.

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 genetically transform 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 non-mosaic *penA* genes with cefixime MIC ≥0.125 mg/L. Modeling showed that the beta-lactam binding pocket was altered both with the mosaic pattern and with the non-mosaic 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, 1 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]

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 beta-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 United Kingdom, Sweden, and the United States, the isolates with decreased susceptibility to cephalosporins were apparently closely related with only 2 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

Currently, 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 are 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 United States and Europe.[83, 162, 163] Additionally 2 grams of azithromycin is poorly tolerated because of gastrointestinal upset though a new timed release formulation might 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 5 times in the United States during 1986–2004 where it is very seldom used,[33] and has been infrequently and sporadically identified by surveillance systems in the United Kingdom and the WHO Western Pacific Region.[115] Spectinomycin can be difficult to obtain; it is not currently available in the United States 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 aminoglycosides, 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 non-susceptible 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 under study 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 likely 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 likely 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.

9.2 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 likely 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 pneumoniae*.[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 non-culture specimens obtained from populations not typically included. The use of molecular assays to monitor molecular markers of resistance likely will 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 currently 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 is 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 likely adversely affect adherence with partner therapy.

Ultimately, success in preserving cephalosporins as a treatment option for gonorrhea is possible but will likely 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.

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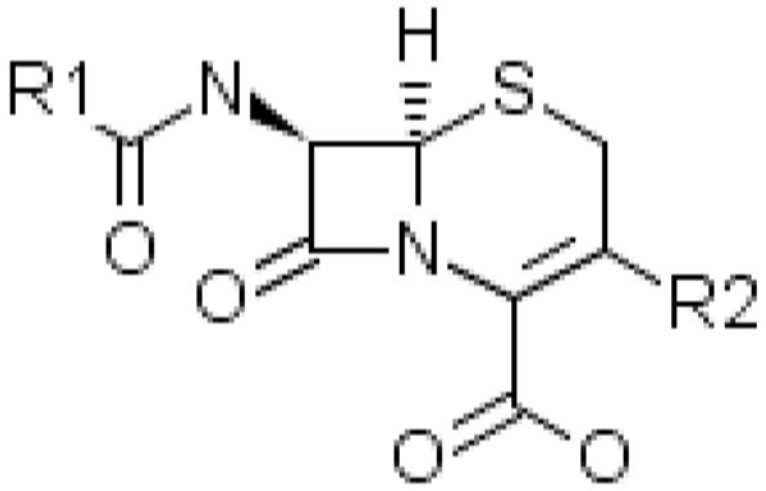
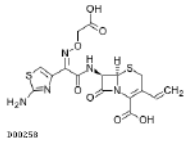
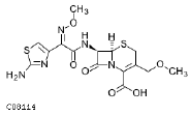
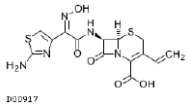
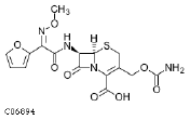
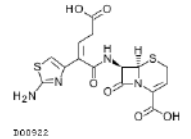


Figure 1.
Basic Cephalosporin Nucleus

Table 1

Chemical, pharmacologic, and microbiologic characteristics of selected oral cephalosporins used to treat infections caused by *Neisseria gonorrhoeae*.

Cephalosporin Usual Dose IM (Alternate Dose IM)	Chemical Structure*	Peak Serum Level** (mg/L)	Half Life** (hrs)	Serum Level 10 hours after peak (mg/L) *****	Hypothetical MIC90 limit*** (10hr conc/4) (mg/L)	Breakpoints (CLSI unless indicated otherwise)
Cefixime 400mg		4.5	3–4	0.446–0.795	0.112–0.199	S: ≤0.25 I: ND R: ND
Cefpodoxime (proxetil)**** 400mg		4.5	2–3	0.141–0.446	0.035–0.112	S: ≤0.5 I: ND R: ND
Cefdinir 600mg		2.87	1.7	0.049	0.012	
Cefuroxime (axetil)**** 1000mg		13.6	1.3	0.066	0.016	(IV formulation) S: ≤1 I: 2 R: ≥4
Ceftibuten 400mg		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)

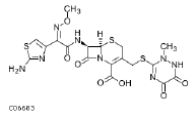
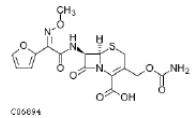
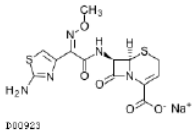
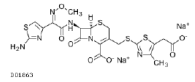
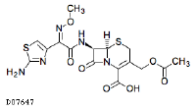
*** Moran JS, Levine WC. Drugs of choice for the treatment of uncomplicated gonococcal infections. Clin Infect Dis 1995 Apr;20 Suppl 1:S47-65.[32]

**** 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 $t = \frac{C_{max}}{e^{0.693\ t/t_{1/2}}}$

Table 2

Chemical, pharmacologic, and microbiologic characteristics of selected parenteral cephalosporins used to treat infections caused by *Neisseria gonorrhoeae*.

Cephalosporin Usual Dose (Alternate Dose)	Chemical Structure*	Peak Serum Level** (mg/L)	Half Life** (hrs)	Serum Level 10 hours after peak (mg/L) *****	Hypothetical MIC90 limit*** (10hr conc/4) (mg/L)	Breakpoints (CLSI unless indicated otherwise)
Ceftriaxone 125mg or 250mg (pk data for 125mg)		13.5	5.8–8.7	4.086–6.086	1.022–1.521	S: ≤0.25**** I: ND R: ND
Cefuroxime 1500mg		13.6	1.3	0.066	0.016	(IV formulation) S: ≤1 I: 2 R: ≥4
Ceftizoxime 500mg		13	1.1–2.3	0.024–0.638	0.006–0.160	S: ≤0.5 1:ND R:ND
Cefodizime 1000mg		75	2.5–4	0.141–0.446	0.035–0.112	
Cefotaxime 1000mg		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. 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 Apr;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_{90}=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.

Author, publication year	Location	Year of Specimen Collection	Criteria and Number of isolates assessed	Cephalosporin MICs mg/L (range)	Comment
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 to 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*.
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]	United Kingdom	2007	Cefixime MIC = 0.25: 2 of 1113	Ceftriaxone MIC = 0.015	Surveillance Report.
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.

Author, publication year	Location	Year of Specimen Collection	Criteria and Number of isolates assessed	Cephalosporin MICs mg/L (range)	Comment
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.
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	September 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.
United States					
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.

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Author, publication year	Location	Year of Specimen Collection	Criteria and Number of isolates assessed	Cephalosporin MICs mg/L (range)	Comment
Gonococcal Isolate Surveillance Project 2008[83]	2006	1992–2006 1988–2006	Cefixime MIC 0.5–2: 48 isolates Ceftriaxone MIC=0.5 4 isolates		Surveillance Report.

R= Resistant; LS= Less Sensitive; NG MAST= Neisseria gonorrhoeae multiple antigen sequence typing

Table 4

Genetic alterations linked to *Neisseria gonorrhoeae* 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 Major 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	Results in MtrC-D-E efflux pump upregulation decreased susceptibility to hydrophobic agents such as azithromycin, rifampin. Possible increased *in vivo* fitness	186, 187