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Editorial

The best of times, the worst of times, and emerging gonococcal multidrug resistance

In most modern cities, including Hong Kong, we have at our disposal the latest technologies that allow real-time diagnostics to be performed for a wide range of viruses, bacteria and fungi. We are also able to perform bloodless organ transplantations, cell imaging at the molecular level, and have hand-held, high speed, wireless devices that could readily set up teleconference with the World Health Organization (WHO) and National Health Authorities on any public health crisis. In June this year, as Scarlet fever broke out in Hong Kong, the causative organism, Group A streptococcus type 12 was completely sequenced and assembled in three days. Surely, we are in "*the best of times and the age of wisdom*." And yet, this year the WHO has devoted World Health Day to antimicrobial resistance and warned the world that many common infections will no longer have a cure. Antimicrobial resistance is a serious problem. To underline the importance of growing antimicrobial resistance, the Center for Disease Control in the United States estimated that methicillin-resistant *Staphylococcus aureus* (MRSA) infections alone are causing more deaths than HIV, AIDS and road traffic accidents. Last year, the United Kingdom was on red alert as researchers observed that NDM-1 "superbugs" resistant to the most powerful antibiotics may be spreading to the country via medical tourism.[1,2] In this issue of the *Journal*, Siu *et al* reviewed the challenge from a common bacterium, *Neisseria gonorrhoeae* that is emerging as one of the potentially untreatable pathogens

Gonorrhoea is the second most common bacterial sexually transmitted infections. Globally, the WHO estimated that 88 million new cases of gonococcal infections occur every year. The causative bacterium can grow easily in the reproductive tracts in women and in the urethra in both women and men. It can also multiply in the throat, eye and anus. If left untreated, it can adversely affect reproductive, maternal and newborn health through complications including pelvic inflammatory diseases, infertility, ectopic pregnancy, first trimester abortion, and severe neonatal eye infections that may lead to blindness. Gonorrhoea also increases the transmission of HIV infection by fivefold.[3] In the absence of a vaccine, appropriate and effective antimicrobial therapy is one of the key elements of gonococcal control. However, treatment options for gonorrhoea have dwindled because of the emergence and global spread of resistance. Consequently, antibiotics, previously considered as first-line options, including penicillins, tetracyclines, azithromycin and fluoroquinolones are becoming obsolete in many countries. It is widely accepted that the clinical efficacy of first-line regimens for treatment of gonorrhoea should be at least 95%, meaning that the resistance rates for first-line empirical agent should be less than 5%. As the correlation between *in vitro* data (i.e. MIC or inhibition zone diameters) and cure rates are imperfect, the breakpoints should be considered tentative and not surprisingly, there are variations between the major guidelines (Table 1).

In April 2011, the World Health Organization warned that gonorrhoea may soon become untreatable.[4] Not only is there continued increasing resistance to the older antibiotics, but the WHO is concerned that the extended-spectrum cephalosporins (ESCs) are also threatened. The warning was made following verified reports of reduced susceptibility to ESCs and treatment

failures with single dose regimen of oral cefixime and ceftibuten in Japan, Hong Kong, Australia, Norway and the United Kingdom.[4-8] These isolates were found to have decreased susceptibility to the ESCs with cefixime MIC of 0.125-2 mg/L as compared with a wild type mode of 0.008-0.03 mg/L. The major surveillance programs demonstrated that these gonococci with decreased susceptibility to cefixime often have multiple co-resistance to other antibiotics, notably penicillin, tetracyclines and fluoroquinolones (Table 2). In addition, several countries have observed a progressive rise in the number of gonococcal isolates with cefixime MICs of 0.125-0.25 mg/L; the tentative breakpoints for treatment failures with oral ESCs. In the UK, the GRASP (Gonococcal Resistance Antimicrobials Surveillance Programme) which examined thousands of

Table 1. MIC interpretive standards for *Neisseria gonorrhoea*

	MIC breakpoints, mg/L		
	CLSI, 2011	**EUCAST, 2011**	**ECDC, 2009**
Ceftriaxone	S: ≤0.25	S: ≤0.125, R: ≥0.25	R: ≥0.25
Cefixime	S: ≤0.25	S: ≤0.125, R: ≥0.25	R: ≥0.25[a]
Ceftibuten	None	None	None
Spectinomycin	S: ≤32, R: ≥128	S: ≤64, R: ≥128	S: ≤64, R: ≥128
Azithromycin	None	S: ≤0.25, R: ≥1	S: ≤0.5, R: ≥1
Ciprofloxacin	S: ≤0.06, R: ≥1	S: ≤0.03, R: ≥0.12	S: ≤0.06, R: ≥1

CLSI, Clinical Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; ECDC, European Centre for Disease Prevention and Control; S, sensitive; R, resistant
[a] Decreased susceptibility

Table 2. Prevalence of antimicrobial resistance to ciprofloxacin, azithromycin and penicillin and decreased susceptibility to cephalosporins, 2009

Year	**No of isolates tested**	**% Resistant[a]**			**% with DS to cefixime**
		Ciprofloxacin	**Azithromycin**	**Penicillin**	
2009, Europe	1366	62.7	13.2	12.6 (PPNG only)	5.1 (>0.125 mg/L)
2009, United States	>5000	12.4	6.1	15.2	0.8
2009, WPR	7677	50.8	–	23.5	–[b]
2009, SEAR	1027	81.7	–	82.9	–[b]
2009, Hong Kong	1366	97.6	–	50.9 (PPNG 32.4)	Sporadic cases[c]

DS, decreased susceptibility; PPNG, penicillinase-producing *Neiserria gonorrhoeae*; SEAR, South East Asia Region; WHO, World Health Organization; WPR, Western-Pacific Region
The information was compiled from data published at the websites of the Centers for Diseases Control in the United States, Europe and Australia.[10,12,20]
[a] Given the variations in the testing and interpretation criteria, the figures may not be directly compared between programmes.
[b] Very few centres tested susceptibility to the oral cephalosporins. Centre in most countries (Australia, Bhutan, Brunei, Fiji, Hong Kong, India, Japan, New Caledonia, New Zealand, Papua New Guinea, the Philippines, Sri Lanka, Singapore, Thailand, Vietnam) reported very low proportions of strains with decreased susceptibility to ceftriaxone. Centres in several countries (Brunei, China, Korea and Mongolia) reported gonococci with decreased susceptibility to ceftriaxone but the exact proportions were not given.[12]
[c] Five patients were found to be infected with *Neisseria gonorrhoeae* strains harbouring the mosaic *penA* gene associated with decreased susceptibility to oral extended-spectrum cephalosporins such as cefixime and ceftibuten.

isolates annually, showed that decreased susceptibility (cefixime MIC ≥0.125 mg/L) first emerged in 2005 (0.1%) and has since increased from 2.8% in 2008 to 10.6% in 2009.[9] At a higher cut-off, decreased susceptibility to cefixime MIC ≥0.25 mg/L was 1.2% in 2009.[9] According to the Euro-GASP data for 2009, isolates displaying decreased susceptibility to cefixime (MIC ≥0.25 mg/L) was detected in ten of 17 participating countries.[10] In five countries, the decreased susceptibility rate for cefixime was above the 5% threshold; including Austria (21.2%), Italy (18.6%), Denmark (15.1%), Slovenia (8.3%) and Belgium (6.4%).[10] Most of the isolates with decreased susceptibility to cefixime were from men (79%) and involved both MSM (in Italy) and heterosexual (in Austria and Denmark) individuals.[10] In the United States, national surveillance found that gonococci with decreased susceptibility to cefixime (MIC ≥0.25 mg/L) had increased from 0.1-0.2% in 2000-2006 to 0.8% in 2009 and 1.4% in 2010.[11] The highest rates were observed in Honolulu (7.7% in 2010) and California (4.5% in 2010).[11] The picture is less clear for the WHO Western Pacific and South East Asian Regions because most centres do not test oral cephalosporins. Decreased susceptibility to ceftriaxone have been observed in isolates from Brunei, China, Korea and Mongolia but the prevalence is unclear.[12] In Japan, decreased susceptibility to cefixime are increasingly prevalent and treatment failures have been observed for several years.[13] Data submitted to the WHO indicated that over 35% of the gonococcal isolates from the Kanagawa (神奈) Prefecture in 2007-2008 had cefixime MIC ≥0.25 mg/L. Hence, cefixime had been excluded from treatment guidelines in Japan since 2006 and intravenous ceftriaxone or cefodizime at high doses (1 gram) is recommended as first-line treatment.[13]

Decreased susceptibility to ESCs has been associated with a variety of genetic mutations, including multiple mosaic *penA* (PBP2) patterns, critical *penA* substitutions (A501V or T), adenine deletion in the *mtrR* efflux pump promoter and certain alteration of amino acids in the PorB (*penB* gene) porin. While mosaic *penA*, especially the X pattern is believed to be the major resistance determinant, multiple other resistance determinants were often observed in strains with elevated MIC to ESCs.[13-16] Typing of the gonococci with decreased susceptibility to cefixime has provided additional insights on the bacterial population genetics. With increasing access to sequencing technology, NG-MAST (*N. gonorrhoeae*-multiantigen sequence typing) and MLST (multilocus sequencing typing) have been widely applied in gonococcal epidemiology studies. In general, the emergence of gonococci with decreased susceptibility to ESCs involved diverse bacterial lineages with multiple MLST and NG-MAST sequence types.[5,17,18] However, there was also evidence of clonal dissemination. For instance, NG-MAST strains previously described in Australia have been reported in Hong Kong (sequence type [ST] 835), Sweden (ST326) and the United States (ST925).[7,17,18] In Hong Kong, ten of 11 strains with decreased susceptibility to ESCs in 2006 were found to belong to ST835.[7] In the UK, 74% of 96 gonococcal isolates with cefixime MIC ≥0.125 mg/L collected through the GRASP between 2005 and 2008 were genetically indistinguishable (NG-MAST, ST1407) indicating a transmissible clone may be emerging.[14]

While the prevalence of decreased susceptibility to ESCs remains uncommon in Hong Kong, the evolution of gonococcal resistance for the previously first-line antibiotics should remind us that widespread resistance could occur explosively. As in the past, drug-resistant *N. gonorrhoea* including the successful clones can be imported from regions where cephalosporin resistance is common, most likely through international travelers and sex tourists. Worldwide, decreased susceptibility to cephalosporins is clearly emerging and the first strain, designated H041 with high-level resistance to ceftriaxone (Etest MIC 4 mg/L and agar dilution MIC 2 mg/L) has been verified in Kyoto (京都), Japan.[13] The strain is resistant to multiple other antibiotics, including penicillin (MIC 4 mg/L), tetracycline (4 mg/L), ciprofloxacin (MIC

>32 mg/L) and azithromycin (MIC 1 mg/L). Of note, strain H041 represents a subclone of the previously described MLST ST7363 that has been shown to circulate worldwide.[13] These findings indicate that a future era of untreatable gonorrhoea may be approaching.

Gonococcal multidrug resistance is clearly in the "*worst of times*." It is crucial that we maximize the use of all available tools, including preventative interventions, screening and appropriate laboratory testing to reduce the burden of gonorrhoea. As antimicrobial resistance is closely associated with overuse of antibiotics, inappropriate dosing and suboptimal quality of antibiotics, gonococcal control should be part of a wider strategy for control of antimicrobial resistance. Most importantly, the government should encourage pharmaceutical research for newer treatments to reverse the dwindling choice of antimicrobial agents.[19] Short of this, gonococcus or the other superbugs are going to take the last straw from us.

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