Annual report of the Australian Gonococcal Surveillance Programme, 2006

The Australian Gonococcal Surveillance Programme

Abstract

The Australian Gonococcal Surveillance Programme (AGSP) monitors the antibiotic susceptibility of *Neisseria gonorrhoeae* isolated in all states and territories. In 2006 the *in vitro* susceptibility of 3,850 isolates of gonococci from public and private sector sources was determined by standardised methods. Different antibiotic susceptibility patterns were again seen in the various jurisdictions and regions. Resistance to the penicillins nationally was at 34% and, with the exception of the Northern Territory, ranged between 17% and 51%. Quinolone resistance in gonococci increased, especially in Queensland, with resistance to this agent found in all jurisdictions. Nationally, 38% of all isolates were ciprofloxacin-resistant, and most of this resistance was at high minimum inhibitory concentration (MIC) levels. With the exception of the Northern Territory excepted, proportions of quinolone resistant gonococci ranged between 16% and 54%. All isolates remained sensitive to spectinomycin. Less than 1% of isolates showed some decreased susceptibility to ceftriaxone. A high proportion of gonococci examined in larger urban centres were from male patients and rectal and pharyngeal isolates were common. In other centres and in rural Australia the male to female ratio of cases was lower, and most isolates were from the genital tract. *Commun Dis Intell* 2007;31:180–184.

Keywords: antimicrobial resistance; disease surveillance; gonococcal infection; *Neisseria gonorrhoeae*

Introduction

Antimicrobial resistance (AMR) is a major problem in *Neisseria gonorrhoeae* and treatment options have been severely limited by the increasing lack of efficacy of several major antibiotic groups. Strategies for treating and controlling gonorrhoea are based on use of single dose treatments that cure a minimum of 95% of cases.[1] Information on the most reliable treatment options are based on data derived from continuous monitoring of the susceptibility of gonococci to recommended antibiotics. This task has been undertaken by the Australian Gonococcal Surveillance Programme (AGSP) continuously since 1981.[2,3] The emergence and spread of penicillin and quinolone resistant gonococci has been closely followed. There are concerns about gonococcal isolates showing resistance to multiple antibiotics including decreased susceptibility to the third generation cephalosporin ceftriaxone, which is used extensively in Australia.[4] This analysis of AMR in *N. gonorrhoeae* in Australia is derived from data generated by the AGSP during the 2006 calendar year.

Methods

Ongoing monitoring of AMR in gonococci in Australia is performed by the AGSP through a collaborative program conducted by reference laboratories in each state and territory. The AGSP is a component of the National Neisseria Network of Australia and comprises participating laboratories in each state and territory (see acknowledgements). This collaborative network of laboratories obtains isolates for examination from as wide a section of the community as possible and both public and private sector laboratories refer isolates to regional testing centres. The increasing use of non-culture based methods of diagnosis has the potential to reduce the size of the sample of isolates available for testing. Details of the numbers of organisms examined are thus provided in order to indicate the AGSP sample size.

Gonococci, isolated in and referred to the participating laboratories, were examined for antibiotic susceptibility to the penicillins, quinolones, spectinomycin and third generation cephalosporins and for high-level resistance to the tetracyclines by a standardised methodology.[2,5] The AGSP also conducted a program-specific quality assurance (QA) program.[6] Antibiotic sensitivity data were submitted quarterly to a coordinating laboratory which collated the results and also conducted the QA program. Additionally, the AGSP received data on the sex of the patient and site of isolation of gonococcal strains. Where available, data on the geographic source of acquisition of antibiotic-resistant isolates were included in the analyses.

Results

Numbers of isolates

There were 3,937 gonococcal isolates referred to or isolated in AGSP laboratories in 2006, little different from the 3,980 examined in 2005. The source and site

of infection with these isolates are shown in the Table. One thousand one hundred and ninety-eight gonococci (30.4% of the Australian total) were isolated in New South Wales, 951 (24%) in Victoria, 565 (14.3%) in Queensland, 549 (13.9%) in the Northern Territory, 397 (10%) in Western Australia, and 244 (6.2%) in South Australia with small numbers in Tasmania (14) and the Australian Capital Territory (19). Three thousand eight hundred and fifty isolates remained viable for susceptibility testing.

Source of isolates

There were 3,315 strains of gonococci from men and 621 from women, with a male to female (M:F) ratio of 5.3:1, slightly higher than the 4.7:1 ratio for 2005. The number of strains from men increased by 27 and there was a corresponding decrease in the number of isolates from women. The M:F ratio was again high in New South Wales (12.6:1) and Victoria (11.3:1) where strains were more often obtained from urban populations. The lower ratios in Queensland (3.9:1) Western Australia (3.6:1), South Australia (2.5:1) and the Northern Territory (2:1) reflected the large non-urban component of gonococcal disease in those regions. Male rectal and pharyngeal isolates were most frequently found in Victoria (30% of isolates from men), and New South Wales (36%). About 1.5% of isolates are shown as being isolated from 'other' (46) or unknown (16) sites. These included 9 cases of disseminated gonococcal infection in men (0.3%) and 12 (1.9%) in women. There were 13 pharyngeal and 6 rectal isolates from women. Although not all infected sites were identified, isolates from urine samples were regarded as genital tract isolates. Most of the other unidentified isolates were probably from this source, although they were not so specified. There were small numbers of isolates from the eyes of both newborn and older infants and also adults, and from Bartholin's abscesses and infections ascending from the endocervix in women to pelvic organs.

Antibiotic susceptibility patterns

In 2006 the AGSP reference laboratories examined 3,850 gonococcal isolates for sensitivity to penicillin (representing this group of antibiotics), ceftriaxone (representing later generation cephalosporins), ciprofloxacin (representing quinolone antibiotics) and spectinomycin and for high level resistance to tetracycline (TRNG). As in past years the patterns of gonococcal antibiotic susceptibility differed between the various states and territories. For this reason data are presented by region as well as aggregated for Australia as a whole.

Penicillins

The categorisation of gonococci isolated in Australia in 2006 by penicillin minimum inhibitory concentration (MIC) is shown in Figure 1. Infections unlikely to respond to the penicillin group of antibiotics (penicillin, ampicillin, amoxycillin, with or without clavulanic acid) are those caused by gonococci shown as 'penicillinase-producing' *N. gonorrhoeae* (PPNG) and 'RR – relatively resistant'. Resistance in the PPNG group results from the production of beta-lactamase and in those 'relatively resistant' by the aggregation of chromosomally-controlled resistance mechanisms[1] – so-called CMRNG. Chromosomal resistance is defined by an MIC to penicillin of 1 mg/L or more.[1,5] (The minimal inhibitory concentration in mg/L is the least amount of antibiotic that inhibits *in vitro* growth under defined conditions.) Infections with gonococci classified as fully sensitive (FS, MIC ≤0.03 mg/L),

Source and number of gonococcal isolates, Australia, 2006, by sex, site and state or territory

Gender	Site	State or territory						
		NSW	NT	Qld	SA	Vic	WA	Aust*
Male	Urethra	698	360	370	145	601	289	2,482
	Rectal	255	1	53	10	159	10	495
	Pharynx	149	0	16	18	107	8	303
	Other/NS	8	4	11	2	7	3	35
	Total	1,110	365	450	175	874	310	3,315
Female	Cervix	79	175	110	65	64	80	575
	Other/NS	9	8	5	4	13	7	46
	Total	88	183	115	69	77	87	621
Unknown	Total	0	1	0	0	0	0	1
Total*		1,198	549	565	244	951	397	3,937

* Includes isolates from Tasmania (14) and the Australian Capital Territory (19).

NS Not stated.

The site of isolation and sex of some infected patients was not known.

less sensitive (LS, MIC 0.06–0.5 mg/L) would be expected to respond to standard penicillin treatments, although response to treatment may vary at different anatomical sites.

Figure 1. Penicillin resistance of gonococcal isolates, Australia, 2006, by state or territory

FS Fully sensitive to penicillin, MIC ≤0.03 mg/L.

LS Less sensitive to penicillin, MIC 0.06–0.5 mg/L.

RR Relatively resistant to penicillin, MIC ≤1 mg/L.

PPNG Penicillinase-producing *Neisseria gonorrhoeae.*

Nationally, 1,306 (34%) gonococci were penicillin resistant by one or more mechanisms in 2006, a further increase on the 1,148 (29.5%) resistant to this group of antibiotics in 2005 and the 770 (21.7%) resistant by any mechanism in 2004. Of these, 964 (25% of all isolates) were CMRNG and 342 (9%) PPNG. The proportion of penicillin-resistant gonococci of all gonococcal isolates in New South Wales was 51.4% (PPNG 8.6%, CMRNG 42.8%), Victoria 41.6% (PPNG 9.6%, CMRNG 32%), Queensland 27.6% (PPNG 13%, CMRNG 14.6%), Western Australia 19.2% (PPNG 11.2%, CMRNG 8%), and South Australia 17.3% (4.8% PPNG and 12.5% CMRNG). Two PPNG and 5 CMRMG were identified in the Australian Capital Territory, and in Tasmania there were 3 PPNG and 7 CMRNG. In the Northern Territory there were 21 PPNG and 4 CMRNG showing that 4.6% of strains were penicillin resistant (3.4% in 2005). Data on acquisition were available in 80 (23%) infections with PPNG. Thirty-four infections with PPNG were acquired locally and 46 by overseas contact. These contacts were principally in Western Pacific or South East Asian countries including China, India, Indonesia (Bali), Korea, the Philippines, Singapore and Thailand.

Ceftriaxone

From 2001 onwards, low numbers of isolates with slightly raised ceftriaxone MICs have been found in Australia. In 2002, there were 21 gonococci with ceftriaxone MICs more than 0.03 mg/L isolated nationally, 10 in 2003, 24 (0.7%) in 2004 and 48 (1.2%) in 2005. In 2006, there were 23 (0.6%) gonococci with ceftriaxone MICs in the range 0.06–0.25 mg/L. Fifteen of these were present in New South Wales (1.3% of New South Wales isolates) 1 (0.4%) in South Australia, 6 (1.1%) in Queensland and 1 (0.3%) in Western Australia. These isolates were generally also penicillin and quinolone resistant.

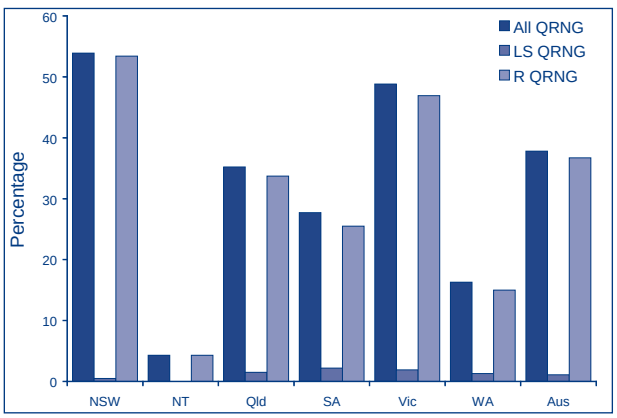
Spectinomycin

All isolates were again susceptible to this injectable antibiotic.

Quinolone antibiotics

Figure 2 shows the distribution of gonococci with altered susceptibility to quinolones nationally and by state or territory. Thus far, resistance to the quinolone antibiotics in *N. gonorrhoeae* is mediated only by chromosomal mechanisms so that incremental increases in MICs are observed. The AGSP uses ciprofloxacin as the representative quinolone and defines altered susceptibility as an MIC of 0.06 mg/L or more.[5] Treatment with currently recommended doses of 500 mg of ciprofloxacin is effective for strains with a lower level of resistance, viz. 0.06–0.5 mg/L, in about 90% of cases, but lower doses of the antibiotic will result in treatment failure more often. At higher levels of resistance i.e. an MIC of 1 mg/L or more, rates of failed treatment rise rapidly. Currently, gonococci with MICs up to 16 and 32 mg/L are being seen in Australia. At MIC levels of 4 mg/L or more, treatment failure, even with higher ciprofloxacin doses, approaches 100%.

Figure 2. Percentage of gonococcal isolates which were less sensitive to ciprofloxacin or with higher level ciprofloxacin resistance and all strains with altered quinolone susceptibility, Australia, 2006, by state or territory



LS QRNG MIC 0.06–0.5 mg/L.

R QRNG MIC 1 mg/L or more.

Nationally in 2006, 1,455 (37.8%) gonococci had some level of resistance to quinolones (QRNG), an increase over the 1,190 (30.6%) detected in 2005 and the 825 (23.3%) in 2004. Most of the QRNG (1,413 or 97%) had resistance at a higher level i.e. MICs ≥ 1mg/L and many of these had MIC levels of the order of 8–32 mg/L. A similar proportion had higher level resistance in 2005. The highest proportion of QRNG was seen in New South Wales where 635 QRNG were 53.9% of all isolates examined. In Victoria, there were 463 QRNG (48.8%), 193 (35.2%) in Queensland (double the number and proportion seen in 2005), 64 (27.8%) in South Australia, and 61 (16.3%) in Western Australia. In other jurisdictions the numbers of QRNG remained low (Northern Territory, 23; Tasmania, 7; the Australian Capital Territory, 9)

Information on acquisition of QRNG was available in 321 of the 1,455 cases (22%). Two hundred and sixty of these (81%) were acquired locally and 59 (19%) overseas from sources referred to under PPNG acquisition with contacts also reported in Brazil, Hong Kong, Korea, the Netherlands, Pakistan, Vietnam, the United Kingdom and the United States of America.

High-level tetracycline resistance

The spread of high-level tetracycline resistance in *N. gonorrhoeae* (TRNG) is examined as an epidemiological marker even though tetracyclines are not a recommended treatment for gonorrhoea. There was an upsurge in TRNG isolation in 2002 when 11.4% of strains of this type were detected nationally with little further change in 2003. A further increase in TRNG numbers to 490 in 2004 saw them represent 13.8% of all gonococci. This proportion was unchanged in 2005 when 534 TRNG, were detected. In 2006, there were slightly fewer TRNG (12%).

TRNG were present in all states and territories with the highest proportions in Western Australia (105 TRNG, 28%) and Queensland (92, 16.8%). Lower proportions of TRNG were present in New South Wales (125, 10.6%), Victoria (97 TRNG, 10.2%) and South Australia (15, 6.5%). There were 24 (4.3% TRNG, found in the Northern Territory and 2 each in Tasmania and the Australian Capital Territory.

Discussion

The number and proportion of gonococci resistant to antibiotics used for treating gonorrhoea increased still further in 2006. A surge in resistant strains was noted in 2005,[4] but the increase in 2006 was relatively small. Resistance to both the penicillin and quinolone groups of antibiotics reached historical highs. Nationally, one third of gonococci were penicillin resistant by at least one mechanism and a slightly higher proportion was quinolone resistant. Figures 1 and 2 illustrate the need for disaggregated information rather than pooled national data in that significant differences in the rates of resistance can be seen in the various jurisdictions. Remote areas in some jurisdictions with high disease rates continue to be able to use penicillin-based treatments, but effective use of this cheap and acceptable treatment requires close monitoring of resistance patterns. In contrast, more than half the isolates from New South Wales and nearly half the isolates from Victoria were both penicillin and/or quinolone resistant. Significant increments in the proportion of quinolone resistant gonococci occurred in all jurisdictions and the MICs of these QRNG were also generally higher.

The presence of a number of gonococci with decreased susceptibility to ceftriaxone was again a concern. Although the numbers of these isolates still remains low at about 1% of all isolates tested, they are almost always also resistant to quinolones and penicillins. Data from regional surveys has confirmed the spread to countries in close proximity to Australia, of gonococci with decreased ceftriaxone susceptibility. Annual National Neisseria Network reports[4] have consistently emphasised that the local recommendation for a minimum dose of 250 mg of ceftriaxone is prudent given the presence of these isolates and the propensity for resistance to develop in *N. gonorrhoeae*. The mechanism of resistance to ceftriaxone in these isolates is not fully elucidated. Although alterations in the *penA* gene, including the presence of mosaic *penA* genes,[7] have been implicated, it is likely that other mechanisms may also be involved.[8] All gonococci tested in Australia in 2006, including those with altered cephalosporin susceptibility, were susceptible to spectinomycin. A low proportion of gonococci was also found to be resistant to azithromycin in 2006 and treatment failures have been recorded in Australia with 1 g doses of this antibiotic.[9] Although susceptibility to azithromycin is assessed in some jurisdictions, there are no firm parameters defined for this purpose.[9] Overseas, increasing resistance to azithromycin, widely used as an anti-chlamydial agent in conjunction with gonococcal treatment, has been reported.

These increasing and multiple problems with antimicrobial resistance in *N. gonorrhoeae* suggest a continuing need for surveillance of antimicrobial resistance in this organism. Standard treatment guidelines can be reliably based on the results of properly-conducted surveillance of antimicrobial resistance. This surveillance is still based on testing of gonococcal isolates. Despite challenges posed by the increasing use of non-culture based methods for the diagnosis of gonorrhoea, the number of gonococcal isolates available for testing in Australia

under the AGSP remains satisfactory for surveillance purposes. As a guide to interpretation of AGSP data, the WHO currently recommends that once resistance to an antibiotic has reached a level of 5% in a population, continuing use of that agent should be reconsidered.[1] A continuing commitment to maintenance of culture-based systems is still required to examine gonococci in sufficient numbers to detect resistance rates at the 5% level.[10]

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