The role of antimicrobial resistance monitoring in Neisseria gonorrhoeae

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Treatment regimens for most sexually transmitted diseases of bacterial origin are well established. For example, treatment of infections with Chlamydia trachomatis is usually now with macrolides, and Treponema pallidum is still reliably susceptible to penicillins. However, antibiotic treatment for gonorrhoea is more complicated because of the propensity of the gonococcus to develop antimicrobial resistance (AMR), so that standard treatment protocols for gonorrhoea require regular review. Additionally, treatment for gonorrhoea is usually by means of a single dose regimen (for better compliance with treatment) and is best given at first presentation/diagnosis (to reduce the potential for disease spread). Testing of individual isolates on an emerging basis is not a practical means of guiding treatment for this situation. Thus, standardised treatments are determined from an epidemiologically-based assessment of the susceptibility of gonococci prevalent in a region or community. Another complicating factor for treatment of gonococcal infection is the frequency of gene recombination in Neisseria gonorrhoeae that results in continuing rearrangement of and within gonococcal populations. AMR patterns within different sexual networks are also affected and, in addition to changes over time, patterns of resistance also differ substantially in different parts of Australia.

Role of effective treatment in disease control

Because of the potential for spread of gonococcal infection and of the morbidity associated with gonorrhoea, control of the disease is an important public health issue. Disease control strategies in place for gonorrhoea emphasise the importance of early and rapid diagnosis coupled with the use of effective antibiotic treatment. The need for optimal treatment within this public health context imposes additional requirements for the monitoring of AMR in N. gonorrhoeae. The World Health Organisation (WHO) stipulates that any standardised treatment regimen should be effective in a minimum of 95% of cases, and in the circumstance of ‘high frequency transmitters’ of the disease, such as commercial sex workers, any treatment used should cure all infections to curtail disease spread.

The Australian Gonococcal Surveillance Programme

This need for definition and continuing re-definition of optimal treatments for both the treatment of gonorrhoea in individuals and for public health control of the disease, has been approached in Australia through the Australian Gonococcal Surveillance Programme (AGSP). This is a component of the National Neisseria Network of public health reference laboratories in each state and territory that deals with laboratory issues surrounding the diagnosis, typing and AMR monitoring of the pathogenic Neisseria. These reference laboratories monitor AMR in gonococci contributed by both public and private sector laboratories in their jurisdiction. Standardised protocols are used in each AGSP centre to test susceptibility to antibiotics relevant to the treatment of gonorrhoea and a set of international control strains and a programme-specific EQAS ensures comparability of data. Results are published quarterly and distributed to relevant bodies. An annual report is also prepared and circulated. The AGSP thus conforms to the WHO description of a comprehensive, integrated, active and continuous AMR surveillance system.

One factor of great importance in the use and interpretation of minimal inhibitory concentration (MIC) data is the very close correlation between the likely outcome of antibiotic treatment used for gonorrhoea and the MICs of the infecting organism. For example, penicillinase-producing gonococci (PPNG), will almost invariably fail treatments with the penicillin group of antibiotics, and spectinomycin resistance is usually manifested at a very high in vitro MIC level and is also strongly associated with treatment failure. The ‘breakpoint’ MICs for penicillin, non-PPNG and for quinolones are set conservatively, but the MIC range for these antibiotics may be quite wide as different resistance mechanisms take effect. Treatment outcome also depends on the doses of antibiotics used and the site of infection. Thus, the outcome of treatment with an infection with N. gonorrhoeae having an MIC in the ‘intermediate’ range may not be as predictable as those that are more obviously fully sensitive or resistant. For example, treatment with currently recommended doses of 500 mg of ciprofloxacin is effective in more than 90% of cases in the MIC range 0.06–0.5 mg/L, but lower (e.g. 250 mg) doses of the antibiotic will result more often in treatment failure. The ‘breakpoint’ MICs for penicillin, non-PPNG and for quinolones are set conservatively, but the MIC range for these antibiotics may be quite wide as different resistance mechanisms take effect. Treatment outcome also depends on the doses of antibiotics used and the site of infection. Thus, the outcome of treatment with an infection with N. gonorrhoeae having an MIC in the ‘intermediate’ range may not be as predictable as those that are more obviously fully sensitive or resistant. For example, treatment with currently recommended doses of 500 mg of ciprofloxacin is effective in more than 90% of cases in the MIC range 0.06–0.5 mg/L, but lower (e.g. 250 mg) doses of the antibiotic will result more often in treatment failure. The ‘breakpoint’ MICs for penicillin, non-PPNG and for quinolones are set conservatively, but the MIC range for these antibiotics may be quite wide as different resistance mechanisms take effect. Treatment outcome also depends on the doses of antibiotics used and the site of infection. Thus, the outcome of treatment with an infection with N. gonorrhoeae having an MIC in the ‘intermediate’ range may not be as predictable as those that are more obviously fully sensitive or resistant. For example, treatment with currently recommended doses of 500 mg of ciprofloxacin is effective in more than 90% of cases in the MIC range 0.06–0.5 mg/L, but lower (e.g. 250 mg) doses of the antibiotic will result more often in treatment failure. The ‘breakpoint’ MICs for penicillin, non-PPNG and for quinolones are set conservatively, but the MIC range for these antibiotics may be quite wide as different resistance mechanisms take effect. Treatment outcome also depends on the doses of antibiotics used and the site of infection. Thus, the outcome of treatment with an infection with N. gonorrhoeae having an MIC in the ‘intermediate’ range may not be as predictable as those that are more obviously fully sensitive or resistant. For example, treatment with currently recommended doses of 500 mg of ciprofloxacin is effective in more than 90% of cases in the MIC range 0.06–0.5 mg/L, but lower (e.g. 250 mg) doses of the antibiotic will result more often in treatment failure. The ‘breakpoint’ MICs for penicillin, non-PPNG and for quinolones are set conservatively, but the MIC range for these antibiotics may be quite wide as different resistance mechanisms take effect. Treatment outcome also depends on the doses of antibiotics used and the site of infection. Thus, the outcome of treatment with an infection with N. gonorrhoeae having an MIC in the ‘intermediate’ range may not be as predictable as those that are more obviously fully sensitive or resistant. For example, treatment with currently recommended doses of 500 mg of ciprofloxacin is effective in more than 90% of cases in the MIC range 0.06–0.5 mg/L, but lower (e.g. 250 mg) doses of the antibiotic will result more often in treatment failure.
recommendations are in harmony with the Australian approach. Taken from the most recent annual report of the AGSP, data on resistance rates for jurisdictions within Australia for the penicillins and quinolone antibiotics, are shown in Figures 1 and 2, with some interpretive criteria included.

The AGSP has reported data on AMR in gonococci in Australia continuously for twenty-five years, making it one of the longer-running programmes of this type. Australia’s near neighbours have a particular problem with AMR in gonococci. This has meant that multi-resistant gonococci have been repeatedly introduced into Australia by infected travellers. Over time these resistant N. gonorrhoeae have become established as micro-epidemics in sexual networks in some jurisdictions at different times, and on occasion have appeared suddenly and spread rapidly. It is for these reasons that a comprehensive and continuous monitoring programme is in place. The AGSP also contributes to regional programmes of surveillance of AMR in gonococci conducted by the WHO. Data from these programmes provide an ‘early warning’ of changes in AMR that may be expected to appear in Australia.

**Emergence and spread of AMR in gonococci and impact on treatment**

For many years the standard treatment for gonorrhoea was with an oral penicillin such as ampicillin. Oral antibiotics are much more acceptable to patients than painful injections. From the 1970s onwards, gonococci became increasingly resistant to penicillins by a number of mechanisms. The most dramatic example was the appearance and rapid spread of PPNG. The spread of the PPNG genes was enhanced by their location on gonococcal plasmids that also carried conjugative elements. Perhaps less well recognised was the emergence of chromosomally mediated or ‘intrinsic’ penicillin resistance (CMPR) through the aggregation of multiple chromosomal changes, each of which contributed incremental increases in penicillin MICs. Penicillin-resistant gonococci harbouring one or both of these resistant mechanisms soon appeared and spread in Australia, compromising this treatment option.

Ciprofloxacin was introduced in urban Australia as an oral treatment for gonorrhoea following the decline in efficacy of penicillins. Figures 1 and 2 show the percentage of penicillin resistance of gonococcal isolates in Australia in 2005 by region.

**Category of susceptibility, MIC values and interpretation for treatment**

- **FS**: fully sensitive to penicillin, MIC \( < 0.03 \) mg/L. A cure is expected with standard doses.
- **LS**: less sensitive to penicillin, MIC 0.06 – 0.5 mg/L. A cure would be expected with standard regimens (eg. single dose oral 3 g amoxicillin) used to treat male urethral gonorrhoeae, but treatment failures may sometimes occur at other infected sites eg. endocervix, pharynx, rectum.
- **CMPR**: chromosomally mediated penicillin resistance, MIC \( \geq 1 \) mg/L.
- **PPNG**: penicillinase-producing N. gonorrhoeae (plasmid mediated) penicillin resistance, due either to chromosomal (CMPR) or plasmid mediated (PPNG) forms, has a high probability of treatment failure.
In Focus

the penicillins. It was a well-tolerated and effective treatment but over time quinolone resistant gonococci also appeared in increasing numbers in more and more centres in Australia and the MICs in quinolone resistant gonococci also continued to increase. (Quinolone resistance in gonococci is thus far mediated entirely by chromosomal mechanisms\(^7\).)

The susceptibility of two other antibiotics is also monitored routinely by the AGSP, namely spectinomycin and ceftriaxone\(^2\), both of which are administered intramuscularly. Ceftriaxone, a third generation cephalosporin, is now the treatment most used for treating gonorrhoea in urban settings and remains highly efficacious. Some concerns have appeared following the appearance of gonococci with decreased susceptibility to third generation cephalosporins, notably in Japan, but now also in Australia\(^2\) (Figure 3). Spectinomycin resistance is rare, but the drug is little used because of failure to eradicate infections from some sites and reduced availability of the drug.

From time-to-time other antibiotics have been proposed for the treatment of gonorrhoea, but these have either been multi-dose regimens or were beset with other problems. This diminishing lack of options for the treatment of gonorrhoea as a result of continuing problems of AMR emergence and spread shows little prospect of reversal. Consequently, there is an important need to optimise use of those treatments available and to redouble broader approaches to disease control efforts\(^9\).

The rural/urban divide

Australia has some unusual circumstances with respect to the distribution of gonococcal disease\(^7\). As is the case in most western-style industrialised economies, high numbers of cases of gonorrhoea and moderately high disease rates in urban centres are found in Australia, especially amongst men who have sex with men (MSM). For instance, the Eastern Sydney area, which referred the highest number of \textit{N. gonorrhoeae} strains to the NSW AGSP reference laboratory, has disease rates of almost 80/100,000\(^9\). In contrast, in rural centres lower numbers of cases are reported, but disease rates in these less-populated centres may be exceptionally high with an incidence of over 1000/100,000 population reported in some communities\(^10\). Another major contrast between rural and urban gonorrhoea is in the suitability of antibiotic treatments for use in these different circumstances.

Quite unusual, and fortunate, in those rural groups with high disease rates, was the lack of resistance to the penicillins. This has meant that almost uniquely, many parts of Australia with exceptionally high disease rates have been able to retain use of penicillin-based treatments as a standard treatment. Figure 3 shows a comparison of the proportions of penicillin-resistant (by all mechanisms) gonococci in the Northern Territory of Australia determined by the AGSP in 2005 and contrasts these with those seen in an urban population – in this example in Sydney\(^1\). Although there has been some increase in rates

### Figure 2. Percentage of gonococci with altered quinolone susceptibility in Australia in 2005 by region.

<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>LS QRNG</th>
<th>R QRNG</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSW</td>
<td>0.2%</td>
<td>0.8%</td>
</tr>
<tr>
<td>NT</td>
<td>0.5%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Qld</td>
<td>1.1%</td>
<td>3.2%</td>
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<tr>
<td>SA</td>
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<tr>
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<tr>
<td>WA</td>
<td>6.5%</td>
<td>15.0%</td>
</tr>
<tr>
<td>Australia</td>
<td>7.2%</td>
<td>18.0%</td>
</tr>
</tbody>
</table>

### Category of susceptibility, MIC values and interpretation for treatment

- **LS QRNG**: less sensitive to ciprofloxacin; MIC 0.06 – 0.5 mg/L  
  A cure would be expected with > 90% of cases treated with a high dose oral regimen, eg 500mg ciprofloxacin, but treatment failure occurs more often with lower doses\(^4\).

- **R QRNG**: resistant to ciprofloxacin; MIC \text{\geq} 1 mg/L  
  High probability of treatment failure with currently recommended doses.
of penicillin resistance over time, (and also continuing drift upwards in MICs of susceptible isolates), the current level of penicillin resistance in the Northern Territory is still below the suggested 5% rate that is the threshold for change suggested by the WHO. Penicillin-based treatments continue to be used there, and enhanced AMR surveillance is maintained.

Also shown in Figure 3, and again by way of illustration, is a comparison of the rates of resistance to the other widely used oral treatment, ciprofloxacin, a member of the quinolone group of antibiotics, in the Northern Territory and New South Wales in 2005. Again, the ‘rural/urban divide’ evident in differential rates of penicillin resistance, can also be seen in the geographical resistance rates for the quinolones. These very high rates of quinolone resistance seen in urban Australia then saw a need for the replacement of quinolones as the standard treatment in many centres.

The future of AMR surveillance for gonococci

Surveillance of gonococcal AMR is an integral component of these approaches, but here too there are problems. The increasing use of molecular-based approaches to the diagnosis of gonorrhoea has provided many advantages and contributed significantly to disease control efforts. However, paradoxically, because molecular methods are unlikely to be suitable for AMR surveillance in gonococci, this advance in one segment of laboratory analysis potentially compromises AMR monitoring as reduced numbers of isolates are available for this purpose. The WHO requirements for valid and reliable data for AMR surveillance for public health purposes can be quite onerous in terms of the needs for adequate sample size and the ‘representativeness’ of any such sample. Currently the AGSP approaches exceed these requirements, but it may be increasingly difficult to meet them in view of this decreasing availability of isolates - unless the recommendations for their continuance are heeded.

Acknowledgements

The members of the AGSP are thanked for their contributions over a quarter of a century; public and private laboratories throughout Australia isolate and refer gonococci to AGSP reference laboratories; the Commonwealth Department of Health and Ageing provides funding for the AGSP.

References


Figure 3. A comparison of the percentage of penicillin, quinolone and ceftriaxone resistant Neisseria gonorrhoeae found in ‘rural’ and ‘urban’ Australia in 2005.