Cephalosporin MIC creep among gonococci: time for a pharmacodynamic rethink?

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Background: Gonorrhoea has been among the easiest infections to cure with antibiotics. Nevertheless, emerging resistance has driven repeated treatment shifts. Decreased cephalosporin susceptibility is now being reported. We examined cephalosporin MIC trends for Neisseria gonorrhoeae in the UK and undertook pharmacodynamic analyses to predict efficacy against strains with raised MICs.

Methods: Neisseria gonorrhoeae isolates were collected annually in a structured surveillance from 26 genitourinary medicine clinics in England and Wales. MICs were determined by agar dilution and confirmed by Etests. Pharmacodynamic modelling was performed for cefixime and ceftriaxone with Monte Carlo simulations.

Results: There was a progressive emergence of small numbers of gonococci with cephalosporin MICs of 0.125–0.25 mg/L; these were not seen before 2005 but, for ceftriaxone and cefixime, respectively, accounted for 0.4% (95% confidence interval 0.2%–1.1%) and 2.8% (1.6%–4.8%) of the 1253 isolates collected in 2008; such MICs are 16–64 times the modal values for the species. Pharmacodynamic analysis was complicated by evidence that cephalosporins need a longer period with the free drug level above MIC than the 7–10 h required for penicillin G; nevertheless, pharmacodynamic analyses predict that failures with the standard 400 mg cefixime po and 250 mg ceftriaxone im regimens become likely around the present MIC maxima.

Conclusions: Gonococci with ceftriaxone and cefixime MICs of 0.125–0.25 mg/L are accumulating in the UK. These MICs lie on the edge of likely responsiveness to current regimens, which need review. Possible responses include: (i) higher cephalosporin doses; (ii) multidose cephalosporin regimens; (iii) multidrug regimens; (iv) microbiologically directed treatment; or, in the future, (v) drug cycling. The practicalities of these approaches are discussed.

Keywords: Neisseria gonorrhoeae, gonorrhoea, cefixime, ceftriaxone

Introduction

From the start of the antibiotic era, gonorrhoea was among the easiest infections to treat. Just 72 mg penicillin was reliably curative in 1942–43, given as six divided doses 3 h apart,1 and there are persistent rumours that much early penicillin production was diverted to gonorrhoea treatment because so little of the precious drug was needed to effect a cure, allowing an infected soldier swiftly to be returned to active service. The treatment of wound infections required more penicillin and had less certain outcomes. Whatever the general truth of this story, Howie recounts a particular situation when wartime gonorrhoea cases were prioritized for available penicillin,2 and it is striking that, among 500 early penicillin-treated patients in the USA, 129 had gonorrhoea.3

Unfortunately, the vulnerability of gonococci to penicillin gradually eroded in the decades following the 1940s, owing to the selection of (i) mutants with penicillin-binding proteins (PBPs) that had reduced affinity for penicillin, and (ii) other mutants with reduced permeability or up-regulated efflux. In 1955, 99% of gonococci in the USA were susceptible to penicillin at a concentration of 0.03 mg/L but, by 1965, 37% of MICs lay between 0.06 and 0.3 mg/L and 5% exceeded 0.3 mg/L. By 1968–9, these latter proportions had risen to 51% and 14%, respectively,4 and the recommended dose of penicillin had been increased 40-fold to 3 g (5 MU), given with probenecid to extend...
the serum half-life. This regimen proved effective up to MICs of 1–2 mg/L, but penicillin was later ‘lost’ through the emergence of β-lactamase-producing gonococci in the mid-1970s\textsuperscript{5,6} with a few failures also seen, somewhat later, for strains with the highest levels of chromosomal-type resistance determined by changes to PBPs and uptake.\textsuperscript{7} Penicillin was replaced as therapy by spectinomycin, then, in the 1980s, by ciprofloxacin, which proved extremely effective at 250 mg or, later, 500 mg po.

Again, however, resistance accumulated, this time via multiple DNA gyrase and topoisomerase mutations. In England and Wales, the proportion of gonococci resistant to ciprofloxacin rose from 2% in 2000\textsuperscript{8} to 28% in 2008\textsuperscript{9} with similar, if later, rises in the USA.\textsuperscript{10} Over 90% of gonococci are now fluoroquinolone-resistant in parts of the Far East.\textsuperscript{11} Another wholesale switch in therapy resulted, with fluoroquinolones abandoned in favour of cephalosporins, which were prescribed to 92% of gonorrhoea patients attending genitourinary medicine (GUM) clinics in England and Wales in 2008\textsuperscript{9} compared with 6% in 2001.\textsuperscript{8} This replacement reflected a change in national guidelines to recommend cefixime (400 mg po) or ceftriaxone (250 mg im) as first-line therapy.\textsuperscript{12}

There is now concern that the activity of the cephalosporins is being eroded by mutations and PBP gene recombination\textsuperscript{13} akin to those that undermined penicillin. These fears are being realized most strongly in Japan, with cefixime MICs of 1–2 mg/L reported\textsuperscript{14} compared with a wild-type mode of 0.008–0.03 mg/L.\textsuperscript{13} Worryingly, there are no good, single-dose oral regimens in reserve behind the cephalosporins, and the treatment of gonorrhoea has the potential to become more problematic than for the past 70 years. Against this background we aimed to (i) ascertain whether cefixime MICs for gonococci are increasing in the UK; (ii) analyse how treatment regimens might be altered to overcome resistance and to slow its accumulation; and (iii) open debate on the clinical practicability of altered regimens.

Materials and methods

GRASP surveillance

The Gonococcal Resistance to Antimicrobials Programme (GRASP) is an ongoing sentinel surveillance that has monitored Neisseria gonorrhoeae isolates in England and Wales since 2000.\textsuperscript{5,9} It comprises a network of 26 GUM clinics supported by 24 microbiology laboratories that refer all gonococcal isolates recovered from June to August each year to the HPA’s Sexually Transmitted Bacteria Reference Laboratory (STBRL) for susceptibility testing. Ceftriaxone has been tested against all isolates since 2003 and cefixime since 2004, with a total of 10022 episodes of gonococcal infection sampled since the former year. Based on the 2008 surveillance, 29% of the isolates were from women and (based on the 92% of male patients whose sexual orientation was recorded) 39% were from heterosexual men with 32% from men who have sex with men.\textsuperscript{9} In the UK, 91% of gonorrhoea cases in males and 78% of cases in females are diagnosed at National Health Service GUM clinics,\textsuperscript{14} with an even greater proportion referred there for treatment. The GRASP collection sites comprise a sample of these clinics, though the patient group is believed to over-represent infections among men who have sex with men.\textsuperscript{9}

MICs were determined on Diagnostic Sensitivity Test agar (Oxoid, Basingstoke, UK) supplemented with 5% (v/v) lysed equine blood (Sigma, Gillingham, UK), 1% IsoVitaleX (Becton Dickinson, Oxford, UK) and doubling antimicrobial concentrations from 0.002 to 0.125 mg/L for ceftriaxone (Sigma) and 0.002 to 0.25 mg/L for cefixime (Astellas, Staines, UK). MICs were recorded after 48 h incubation at 36°C in 5% CO\textsubscript{2}. Any gonococcus with a ceftriaxone MIC ≥0.125 mg/mL or cefixime MIC ≥0.25 mg/L was re-examined by Etest (Bio-Stat, Stockport, UK), used according to the manufacturer’s instructions; briefly, a gonococcal suspension of ~10\textsuperscript{8} cfu/mL (McFarland Standard 0.5) was inoculated on GC agar supplemented with 1% IsoVitaleX, Etests were applied and MICs recorded following incubation at 36°C in 5% CO\textsubscript{2} for 18–20 h.

The WHO control strains A, D, E and J were tested on every batch of media, along with seven in-house control strains, to ensure the consistency of the MIC data generated by agar dilution. These controls included a strain with raised ceftriaxone and cefixime MICs (0.03 and 0.06 mg/L respectively). The WHO control strains K and L with decreased susceptibility to cefixime and ceftriaxone have only recently become available and were not included in the surveillance period reviewed; they were, however, included in 2010 and gave MICs within one doubling dilution of the expected levels (cefixime and ceftriaxone 0.25 and 0.06 mg/L respectively for K and 0.125 mg/L for both drugs for WHO L).\textsuperscript{15}

Trends were analysed in Stata (StataCorp, TX, USA). The analyses used weights to allow for the fact that, depending on the source laboratory and year, a variable proportion of the collected isolates could not be recovered by the reference laboratory; in addition standard errors were inflated to allow for the clustering of the sample within the 26 GUM clinics. For ceftriaxone, the percentage increase in the geometric mean MIC between 2003 and 2008 was estimated from a linear regression model of the log-transformed MIC values. Cefixime MICs showed greater variability between years, so instead our analysis was based on the percentage with decreased susceptibility, as confirmed by Etest. Significance tests for differences between 2008 and prior years came from a generalized linear model of the binomial family which estimated percentage point differences between years.\textsuperscript{16}

Pharmacodynamic analyses

The periods for which free drug concentrations of cefixime and ceftriaxone exceeded MIC (\(\text{MIC} \times \text{MIC}
\text{T}) after various single-dose regimens were estimated from the published pharmacokinetic parameters listed in Table 1,\textsuperscript{17–22} using MICLAB version 3.07 (Mediware, Maastricht, The Netherlands) assuming a one-compartment model. Monte Carlo simulation\textsuperscript{23,24} was performed for the single-dose regimens of cefixime (400 mg po) and ceftriaxone (250 mg im) routinely used in most of Europe and North America and for a high-dose 1 g im ceftriaxone regimen now used in parts of the Far East (see Results). A 2×200 mg cefixime regimen, with the doses 6 h apart, as previously used in Japan,\textsuperscript{25} was also simulated, as was a similar regimen with 2×400 mg dosages.

Results

Trends in cephalosporin MICs

Throughout the surveillance, the great majority (99.3%) of the gonococci isolated in England and Wales were susceptible to ceftriaxone, with no significant change in the proportion of gonococci with MICs >0.25 mg/L. This is reflected in the constant percentage of gonococci with MICs >0.25 mg/L, with a mode of 0.06–0.125 mg/L. A similar trend was seen with cefixime. There was no significant change in the proportion of gonococci with MICs >0.06 mg/L, with a mode of 0.008–0.015 mg/L.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cefixime po\textsuperscript{17,18}</th>
<th>Ceftriaxone im\textsuperscript{19–22}</th>
</tr>
</thead>
<tbody>
<tr>
<td>VI, volume of distribution (L)</td>
<td>19.0 ± 3.0</td>
<td>14.7 ± 4.9</td>
</tr>
<tr>
<td>k10, elimination rate (h\textsuperscript{−1})</td>
<td>0.204 ± 0.020</td>
<td>0.082 ± 0.029</td>
</tr>
<tr>
<td>Fu, unbound fraction</td>
<td>0.35</td>
<td>0.05</td>
</tr>
<tr>
<td>F, bioavailability</td>
<td>0.45 ± 0.045</td>
<td>1.00</td>
</tr>
<tr>
<td>Ka, absorption constant (h\textsuperscript{−1})</td>
<td>0.55</td>
<td>1.00</td>
</tr>
<tr>
<td>t\textsubscript{1/2}, half-life (h)</td>
<td>3.40</td>
<td>8.45</td>
</tr>
</tbody>
</table>
cefixime at \( \leq 0.06 \text{ mg/L} \) and to ceftriaxone at \( \leq 0.03 \text{ mg/L} \) (Table 2). Nevertheless small and growing numbers of isolates with higher MICs progressively appeared. Gonococci with cefixime MICs of 0.125 mg/L were first seen in 2005, and were followed by those with MICs of 0.25 mg/L in 2006. Isolates with ceftriaxone MICs of 0.06 and 0.125 mg/L appeared in 2005 followed, in 2008, by those with MICs of 0.25 mg/L. The increase in the percentage of isolates with cefixime MICs \( \geq 0.25 \text{ mg/L} \) from 2004 (0%) to 2008 (1.5%) was significant (\( P=0.002 \)), as was that between 2006 (0.1%) and 2008 (1.5%) (\( P=0.005 \)). Ceftriaxone MICs increased significantly from 2003 to 2008, with an estimated 33% [95% confidence interval (CI) 22–45%] rise in the geometric mean MIC over these 6 years (\( P<0.001 \)). There is strong evidence that the ratio of geometric means between successive years increased over the period, suggesting that the rate of MIC increase is accelerating (\( P<0.001 \)).

### Pharmacodynamic analyses

Simulated \( f_{\text{T}\geq\text{MIC}} \) periods based on mean pharmacokinetic parameters for standard and potential single- and double-dose cefixime and ceftriaxone regimens are shown in Table 3. Intramuscular ceftriaxone has complete bioavailability and an 8.45 h serum half-life, whereas cefixime has 50% bioavailability and a 3.40 h half life. These advantages for ceftriaxone translated into a longer \( f_{\text{T}\geq\text{MIC}} \) than for cefixime at low MIC values, but were offset by the greater protein binding of ceftriaxone, which reduced the free ceftriaxone concentration and led to similar values of \( f_{\text{T}\geq\text{MIC}} \) for both cephalosporins at higher MICs.

For isolates with cefixime and ceftriaxone MICs \( \leq 0.06 \) and \( \leq 0.03 \text{ mg/L} \), respectively (i.e. the vast majority), the \( f_{\text{T}\geq\text{MIC}} \) periods for 400 mg cefixime po or 250 mg ceftriaxone im were \( \geq 22.2 \) h and \( \geq 41.4 \) h, respectively. Even the 125 mg ceftriaxone im regimen (as used until recently in the USA) gave an \( f_{\text{T}\geq\text{MIC}} \) of 32.9 h at a ceftriaxone MIC of 0.03 mg/L. \( f_{\text{T}\geq\text{MIC}} \) durations became markedly shorter at higher MICs, falling to 18.8 h, 15.3 h and 11.7 h for cefixime 400 mg po and to 24.3 h, 15.6 h and 6.6 h for ceftriaxone 250 mg im at MICs of 0.125, 0.25 and 0.5 mg/L, respectively. High-dose (1 g im) ceftriaxone achieved an \( f_{\text{T}\geq\text{MIC}} \) of 24.3 h at an MIC of 0.5 mg/L—considerably longer than for any other regimen for MICs at this level. This 1 g im regimen is used in China whereas in Japan the same dosage is given by the intravenous route. Modelling here was for im administration as being more convenient for GUM clinics, but the difference in mode of injection has little impact on \( f_{\text{T}\geq\text{MIC}} \) because serum clearance is slow compared with absorption and distribution.

Two-dose regimens were modelled only for cefixime, being impracticable for parenteral antibiotics in GUM clinics. Dividing

#### Table 2. Weighted MIC distributions for gonococci by year

<table>
<thead>
<tr>
<th>MIC (mg/L)</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefixime</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.002</td>
<td>NT</td>
<td>412.6</td>
<td>232.2</td>
<td>1056.8</td>
<td>278.7</td>
<td>263.9</td>
<td>2244.2</td>
</tr>
<tr>
<td>0.004</td>
<td>NT</td>
<td>332.3</td>
<td>165</td>
<td>215.6</td>
<td>347.8</td>
<td>295.4</td>
<td>1356.1</td>
</tr>
<tr>
<td>0.008</td>
<td>NT</td>
<td>524.4</td>
<td>322.3</td>
<td>198.8</td>
<td>387.8</td>
<td>400.5</td>
<td>1833.7</td>
</tr>
<tr>
<td>0.015</td>
<td>NT</td>
<td>365.6</td>
<td>546.6</td>
<td>64.6</td>
<td>232.7</td>
<td>213.5</td>
<td>1422.9</td>
</tr>
<tr>
<td>0.03</td>
<td>NT</td>
<td>350.8</td>
<td>228</td>
<td>43.7</td>
<td>23.3</td>
<td>29.7</td>
<td>675.5</td>
</tr>
<tr>
<td>0.06</td>
<td>NT</td>
<td>59.3</td>
<td>184.8</td>
<td>17.3</td>
<td>19.8</td>
<td>14.7</td>
<td>295.8</td>
</tr>
<tr>
<td>0.125</td>
<td>NT</td>
<td>0</td>
<td>1.1</td>
<td>1.2</td>
<td>16.8</td>
<td>16.3</td>
<td>35.4</td>
</tr>
<tr>
<td>0.25</td>
<td>NT</td>
<td>0</td>
<td>0</td>
<td>1.2</td>
<td>2.1</td>
<td>19</td>
<td>22.3</td>
</tr>
<tr>
<td>Total</td>
<td>2045</td>
<td>1680</td>
<td>1599</td>
<td>1309</td>
<td>1253</td>
<td>7886</td>
<td></td>
</tr>
</tbody>
</table>

| Ceftriaxone |      |      |      |      |      |      |       |
| 0.002       | 1633.2| 1743.1| 1252.8| 1281.3| 673.6| 678.3| 7262.4|
| 0.004       | 293.3 | 188.7 | 201.7 | 160.5 | 289.7| 310.2| 1444.3|
| 0.008       | 139   | 87.5  | 116.3 | 116.2 | 157.3| 146.5| 762.7 |
| 0.015       | 59.3  | 22.2  | 62.2  | 29.7  | 166.5| 102.3| 442.4 |
| 0.03        | 10.9  | 3.6   | 35.9  | 7.6   | 14.9 | 3.1  | 76.0  |
| 0.06        | 0     | 0     | 9.9   | 2.5   | 7    | 7.3  | 26.8  |
| 0.125       | 0     | 0     | 1.1   | 1.2   | 0    | 4.2  | 6.4   |
| 0.25        | 0     | 0     | 0     | 1     | 0    | 1.1  | 1.1   |
| Total       | 2136  | 2045  | 1680  | 1599  | 1309 | 1253 | 10022 |

*Weighted to compensate for variable proportions of isolates being recoverable among submission from different contributing laboratories.

#### Table 3. Simulation of \( f_{\text{T}\geq\text{MIC}} \) values (h) for various cefixime and ceftriaxone regimens based on mean pharmacokinetic parameter values

<table>
<thead>
<tr>
<th>MIC mg/L</th>
<th>200 mg</th>
<th>400 mg</th>
<th>2×200 mg, 6 h apart</th>
<th>2×400 mg 6 h apart</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefixime po</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.008</td>
<td>29.2</td>
<td>32.6</td>
<td>36.5</td>
<td>39.9</td>
</tr>
<tr>
<td>0.015</td>
<td>25.8</td>
<td>29.2</td>
<td>33.1</td>
<td>36.5</td>
</tr>
<tr>
<td>0.03</td>
<td>22.3</td>
<td>25.7</td>
<td>29.5</td>
<td>32.9</td>
</tr>
<tr>
<td>0.06</td>
<td>18.8</td>
<td>22.2</td>
<td>26.1</td>
<td>29.5</td>
</tr>
<tr>
<td>0.125</td>
<td>15.3</td>
<td>18.8</td>
<td>22.6</td>
<td>26.1</td>
</tr>
<tr>
<td>0.25</td>
<td>11.7</td>
<td>15.3</td>
<td>19.0</td>
<td>22.6</td>
</tr>
<tr>
<td>0.5</td>
<td>7.8</td>
<td>11.7</td>
<td>15.2</td>
<td>19.0</td>
</tr>
<tr>
<td>1</td>
<td>1.4</td>
<td>7.8</td>
<td>7.1</td>
<td>15.2</td>
</tr>
<tr>
<td>2</td>
<td>0.0</td>
<td>1.4</td>
<td>0.0</td>
<td>7.1</td>
</tr>
<tr>
<td>4</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

| Ceftriaxone im |        |        |                     |                   |
| 125 mg        | 50.3   | 58.7   | 67.2                | 75.6              |
| 250 mg        | 41.8   | 50.3   | 58.7                | 67.2              |
| 500 mg        | 32.9   | 41.4   | 49.9                | 58.3              |
| 1 g           | 24.3   | 32.8   | 41.3                | 49.8              |
| 2 g           | 15.6   | 24.3   | 32.8                | 41.3              |

Dark shading \(<10 \text{ h above MIC}\), light shading \(10–20 \text{ h above MIC}\), no shading \(>20 \text{ h above MIC}\).
the dose extended but flattened the serum curve (Figure 1). Thus, a 2 × 200 mg cefixime regimen gave longer \( f_{T>MIC} \) values than a single 400 mg dose (Table 3). This differential was 26.1 h versus 22.2 h at an MIC of 0.06 mg/L and 19.0 h versus 15.3 h at an MIC of 0.25 mg/L. A 2 × 400 mg regimen, again with the doses 6 h apart, gave an \( f_{T>MIC} \) of 29.5 h at an MIC of 0.06 and 22.6 h at an MIC of 0.25 mg/L.

**Monte Carlo simulations**

The limitation of the \( f_{T>MIC} \) data shown in Table 3 is that they do not reflect the diversity inherent within patient populations. To allow for this aspect we performed Monte Carlo simulation, a statistical method that allows for the variability in the input parameters in the pharmacokinetic simulations. Multiple pharmacokinetic curves are generated, each slightly different; these are then used to generate a pharmacokinetic-pharmacodynamic index, in this case \( f_{T>MIC} \) (h), along with its associated confidence intervals.

Such analyses (Table 4) showed that, for some patients, \( f_{T>MIC} \) will be considerably shorter (or longer) than the ‘average’ values listed in Table 3. For cefixime 400 mg po, the lower 95% CIs roughly corresponded to a one-doubling-dilution reduction in the MIC for which the regimen provided an equal \( f_{T>MIC} \). Thus, for example, the median \( f_{T>MIC} \) at an MIC of 0.125 mg/L was 18.0 h (Table 4), whilst the lower 95% CI for an MIC of 0.06 mg/L was 17.9 h. The differential between the median \( f_{T>MIC} \) and its lower 95% CI was greater for ceftriaxone than cefixime, especially at low dosage, probably because of the injectable compound’s very variable elimination rate (represented by the large standard deviation of \( k_{10} \) in Table 1). Thus, the median \( f_{T>MIC} \) for ceftriaxone 250 mg im was 15.4 h but, at the lower 95% CI, this duration of coverage was achieved only up to an MIC of 0.06 mg/L. Moreover, whilst 1 g ceftriaxone im gave median \( f_{T>MIC} \) periods of 31.6 h and 23.1 h at MICs of 0.25 and 0.5 mg/L respectively, the lower 95% CIs were less than half as long, at 15.4 and 11.1 h, respectively.

**Discussion**

Over 99% of the gonococci collected under the ambit of GRASP since 2004 remained extremely susceptible to cephalosporins, with MICs of \( \leq 0.06 \) mg/L cefixime and \( \leq 0.03 \) mg/L ceftriaxone.
These drugs are now the standard therapy, meeting the WHO criterion of being effective in >95% of cases of genital infection. Nevertheless, and disturbingly, the GRASP data reveal small but significantly growing (P < 0.001) proportions of gonococci with decreased susceptibility. Based on national surveillance (‘KC60’) returns, there were ~17000 cases of N. gonorrhoeae infection in the UK in 2008, including a few cases of disseminated and neonatal disease. Projecting the GRASP data onto these totals suggests that, in the whole year, there would have been around 68 patient isolates (0.4%) with ceftriaxone MICs $\geq 0.125$ mg/L and 476 (2.8%) with cefixime MICs $\geq 0.125$ mg/L, with considerable overlap between these two groups. Whilst these numbers are small in absolute terms, the trend is disturbing and is reminiscent of that seen with penicillin in the 1950s and 60s. Molecular research, to be published separately, reveals that many of the isolates with diminished susceptibility are clonal, but that they are scattered geographically and present among multiple sexual networks (S. A. Chisholm, S. Alexander and C. A. Ison, unpublished results). Their emergence accords with worldwide trends, with decreased cephalosporin susceptibility among N. gonorrhoeae reported in recent years in other European countries, including Spain,26 Greece,27 Sweden28 and the Netherlands29 as well as in the USA,30 Australia,31 and particularly in Asia, with cefixime MICs as high as 2 mg/L reported in Japan31 and China.12 The mechanism for decreased susceptibility to cephalosporins in gonococci is only partially elucidated but, for cefixime, a major component is mosaic gene formation in penA, which encodes PBP-2. The mosaics arise through acquisition of DNA from commensal Neisseria spp.,33 with higher-level resistance engendered by subsequent mutations of mtr, an efflux determinant, and porB1 (penB), encoding a major porin. The latter mutations are relatively more important than mosaic penA in reducing susceptibility to ceftriaxone.34 where there is some evidence to suggest ceftriaxone MICs of $\geq 0.06$ mg/L also may arise by spontaneous mutation (e.g. A501V) within non-mosaic penA.35,36,37

In general, the clinical efficacy of β-lactam antibiotics relates to $T_{>\text{MIC}}$ and Jaffe et al.37 experimentally found that penicillin efficacy in male urethritis was predicted by total (i.e. serum-bound plus free) penicillin levels at least four times MIC for at least 10 h, roughly corresponding to an $T_{>\text{MIC}}$ of 7–10 h. In a previous analysis we assumed that this duration would also predict success for cephalosporins, and should apply also for gonococcal infection at other anatomical sites.38 These assumptions are challenged by the clinical findings of Deguchi et al.,39 who used a 2 x 200 mg cefixime regimen, with the doses 6 h apart, and saw consistent therapeutic success (45/45 cases) in male urethritis only up to MICs of 0.06 mg/L, with 5/11 failures at MICs of 0.125 mg/L and 3/5 at higher MICs. As modelled in Figure 1 and Table 3, this two-dose regimen is pharmacodynamically superior to the 400 mg po single-dose regimen routinely used in the UK, giving an $T_{>0.125}$ mg/L for around 22.6 h versus 18.4 h. If, in reality, cefixime at 400 mg is reliably effective only up to an MIC of 0.06 mg/L, even as a divided dose, it follows that an $T_{>\text{MIC}}$ of 20–24 h is needed for efficacy with cephalosporins. On this basis, the data in Table 2 suggest that the highest MICs of both cephalosporins are already into the range where clinical failures are to be expected. The fact that failures remain rare in practice may be because most gonorrhoea patients receive a second antibiotic, usually azithromycin, to treat any concurrent non-gonococcal infection. Over 90% of the patients participating in GRASP 2008 were prescribed a third-generation cephalosporin and ~70% of them also received azithromycin to treat Chlamydia trachomatis co-infection.9 Azithromycin is not, however, reliable against gonorrhoea at a standard 1 g dose39 and a few N. gonorrhoeae strains have high-level resistance, implying that they would be resistant irrespective of the dose administered.40,41 Once treatment failures do arise, some of them in individuals with multiple sexual partners, the dynamics of gonorrhoea carry a severe risk of rapid spread through sexual networks, as seen previously for penicillinase-producing and ciprofloxacin-resistant strains.42,43

Debate is urgently needed on how best to maintain therapeutic efficacy in the face of this challenge, especially as there are few good anti-gonococcal drugs in reserve behind the cephalosporins.44 Up to five approaches might be proposed for adoption: (i) to administer cephalosporins at a higher dose; (ii) to administer ceftriaxone at the GUM clinic followed by oral cefixime for several days; (iii) to use cephalosporins together with second drugs active against N. gonorrhoeae, irrespective of whether the patient has concurrent non-gonococcal infection or not; (iv) to adopt laboratory-guided patient-individualized treatment based on antibiotic susceptibility profiles; and (v), longer term, to rotate antibiotics, seeking to create ‘firebreaks’. These options are not mutually exclusive and the best approach may not be the same in all regions of the world, varying with the medical, financial and laboratory resources available. Moreover, it may be that treatment should be varied according to the oetiology and anatomical site of disease and in relation to the patient’s likelihood of being an onward transmitter. Strategically, for example, one could consider giving more powerful regimens to high-risk individuals for the development and dissemination of resistant strains, such as men who have sex with men and commercial sex workers, as well as individuals with pharyngeal gonorrhoea.

Increasing the cephalosporin dosage is the simplest reaction to rising MICs and corresponds to what was done with penicillin in the 1950s and 60s. There may be limited scope to do this with cefixime, as 400 mg is the highest licensed dose and higher doses were associated with gastrointestinal side effects in the licensing trials performed over 20 years ago.45 It may, however, be possible to administer cefixime as 2 x 400 mg doses 6 h apart, giving a median $T_{>0.25}$ mg/L of 22.6 h. There is more certain scope to increase the dose of ceftriaxone, which is already used at 1 g im or iv for gonorrhoea in the Far East46 and where iv doses as high as 2 g are well tolerated in patients with community-acquired pneumonia. Nevertheless, whilst these doses extend the mean $T_{>\text{MIC}}$ (Table 3), the lower 95% CI remains stubbornly short (Table 4). Thus, the use of even 1 g ceftriaxone as a sole antimicrobial agent would be expected to fail in some patients once MICs of 0.125 and 0.25 mg/L become commonplace. Moreover, (i) most patients prefer oral therapies, which are also to be preferred in settings with a high prevalence of HIV and other blood-borne viruses that may be transmitted by needlestick injuries, (ii) ceftriaxone injections are painful if not administered with 1% lidocaine, and this is often omitted in resource-poor countries where patients are seen in settings lacking the doctors required to manage rare medical emergency side effects, such as cardiac arrhythmias and arrest, and (iii) regular use of painful injections...
may have a negative public health impact by discouraging health-seeking behaviour, particularly among asymptomatic contacts and those with repeat gonococcal infections.

The second option—of administering parenteral ceftriaxone 1 g im followed by 2 days of oral cefixime—should be more effective than simply raising the amount of cephalosporin given in a single- or double-dose regimen. Even in the worst case, where (i) MICs of the both cephalosporins are 0.25 mg/L and (ii) all dosages achieve only the lower 95% CI limits for $f_{T>MIC}$ (Table 4), the free drug concentration should exceed the MIC for 40% of the treatment period, corresponding to the general predictor of success for a β-lactam.47 Issues nevertheless remain about the pain associated with large ceftriaxone injections if no anaesthetic is included.

The third option—of giving an anti-gonococcal cephalosporin together with another drug, most often azithromycin—is widespread already, largely to cover against concurrent chlamydial urethritis; over 90% of the patients participating in GRASP 2008 were prescribed a third-generation cephalosporin and 65% received a third-generation cephalosporin and azithromycin.9 The limitation, already noted, is that the standard azithromycin 1 g po regimen has borderline efficacy against gonorrhoea and may select for resistance. A 2 g po regimen is more reliable,39 and the recent introduction (initially for respiratory infection) of an extended-release 2 g formulation may lessen the gastrointestinal side effects that previously resulted in poor tolerability for some patients. A greater difficulty, though, is that there is already some UK dissemination of highly azithromycin-resistant gonococci, particularly in Scotland.44,51 Along with a trend for higher azithromycin MICs among isolates with elevated ceftriaxone MICs in the current study population (data not shown). Despite these limitations and concerns, azithromycin remains much preferable as a second agent compared with the alternative of a 1 week course of doxycycline 100 mg every 12 h, as commonly used for the syndromic treatment of urethral and vaginal discharges in many parts of the world. High-level tetracycline resistance is now frequent among gonococci in many countries, owing to dissemination of plasmids encoding Tet(M). Likewise, the use of fluoroquinolones as part of a combination therapy is unlikely to be a viable option as all the GRASP isolates with decreased susceptibility to cefixime were also resistant to ciprofloxacin (data not shown). In the future it may be necessary to use multidrug therapy for gonorrhoea with combinations of cephalosporins, azithromycin and either spectinomycin or gentamicin.44,68 And, here, it would be wise to undertake randomized controlled treatment efficacy trials whilst there is still time, to determine which regimens and drug combinations are likely to best delay the onset of widespread cephalosporin resistance.68 Such trials should include defined numbers of patients with rectal and pharyngeal infections in addition to those with the more prevalent urethral and cervical infections, and should collect information on pharmacodynamic parameters as well as clinical and microbiological outcomes. Careful consideration will be required to determine how best to define microbiological cure, now that nucleic acid amplification tests have substantially replaced culture as the primary diagnostic method.

The fourth option—of guiding antibiotic therapy by reference to susceptibility profiles of cultured organisms—may be appropriate for cervical, pharyngeal and rectal gonorrhoea, where the sensitivity of microscopy is poor and asymptomatic infection is common, meaning that treatment is often delayed anyway. However, it would not be ethical to await culture results before treating men with clinically apparent and/or microscopically confirmed gonococcal urethritis, owing to the risk of complications and onward transmission. Even if only applied to non-urethral infection, such an approach would require extremely high rates of patient follow-up and there would be a need to revert to microscopy, culture and susceptibility testing, or to upgrade molecular tests—now increasingly used for the diagnosis of gonorrhoea—so that they detect relevant resistance determinants. Since cephalosporins have relatively low efficacy in the treatment of pharyngeal compared with genital gonorrhoea, there is a strong argument to treat infections of the throat with ciprofloxacin if the isolate is found susceptible on laboratory testing.

The final option, of rotating first-line treatments, should create ‘firebreaks’ against the spread of resistance. Although antibiotic cycling proved disappointing as a means of controlling resistance in intensive care units,49 it may work better in the more straightforward milieu of genital infection. Possible clinical approaches might be to treat index patients differently from their contacts, to treat men and women with different antibiotic regimens, or to simply rotate first-line antibiotic regimens every few months. Unfortunately, cycling is not a realistic option at present, due to the loss of the quinolones and the difficulty of sourcing spectinomycin, although it might easily have been attempted 15 years ago, when cefixime, ciprofloxacin and spectinomycin were all consistently active and readily available in the UK. It may re-emerge as an approach if new anti-gonococcal agents become available. None is in advanced development, but inhibitors of FabI, a fatty acid biosynthesizing enzyme, are of some interest; one such compound, MUT056399, has a long serum half-life and a spectrum including Chlamydia trachomatis as well as N. gonorrhoeae.50 Novel pleuromutilins too are reported to be active against both pathogens, are suitable for systemic use, and may have some potential,51 as may various non-quinolone topoisomerase inhibitors.52

In summary, this analysis confirms a disturbing upward creep in the MICs of cephalosporins for gonococci isolated in England and Wales. Despite uncertainties about the exact $f_{T>MIC}$ needed to reliably predict therapeutic success, pharmacodynamic analysis suggests that the isolates with the highest MICs now being seen (0.25 mg/L for both cephalosporins) are at the border of reliable responsiveness to current regimens, and that we are in the very early stages of an emergent problem of cephalosporin resistance. We contend that the time to intervene is now, whilst there are still viable options and strategies available, rather than waiting until the WHO’s 5% threshold of resistance is reached.44,68 Whether the strategies suggested in this paper will contain this threat in practice depends not only on their adoption but also—particularly outside the developed world—on the relative impact of other factors, such as access to drugs in informal health settings, the quality of generic drugs provided, poor systemic control of antibiotic use and the effect of travel on the dissemination of resistant strains from one country to another.44 In practice, given that gonococcal strains resistant to oral cephalosporins are already circulating in the Far East, it is most likely that antimicrobial-resistant gonococci will be imported into countries like the UK and the USA, and therefore that spread rather than de novo evolution will be the critical issue for which the developed world must be prepared.
Surveillance and microbiological testing remain critical for this. Last, and looking forward, there is an urgent need for the pharmaceutical industry to add gonococci to the growing list of ‘bad bugs’ for which new drugs are needed.

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References