Azithromycin in the treatment of infection with Neisseria gonorrhoeae

Chris Bignell, Janet Garley

ABSTRACT
The efficacy of azithromycin as sole antimicrobial treatment for infection with Neisseria gonorrhoeae is reviewed. Aggregate cure rates for urethral and endocervical infection were 520/539 (96.5%; 95% CI 94.3% to 97.6%) for a 1 g dose from nine studies and 392/396 (99%; 95% CI 97.5% to 99.6%) for a 2 g dose from two studies. Azithromycin cured 46/47 (97.9%) cases of rectal infection evaluated within the clinical trials. Reports of in vitro resistance to azithromycin reveal a wide geographical spread of clinical isolates, with raised minimal inhibitory concentration to azithromycin and the emergence of high-level resistance in 2001. Concerns about resistance preclude azithromycin from general recommendation as sole antimicrobial therapy for gonorrhoea. However, azithromycin may have a valuable role in specific clinical situations and in combination with extended spectrum cephalosporins in the treatment of gonorrhoea.

INTRODUCTION
Azithromycin is an azalide derived from the macrolide class of antibiotics. It offers better oral absorption, better tissue penetration, unique pharmacokinetics and a wider spectrum of antimicrobial activity than erythromycin. The mode of action of azithromycin is inhibition of RNA-dependent peptide synthesis by binding to the 50 s ribosomal subunit. Azithromycin levels in tissues are up to 50 times higher than in plasma and tissue depletion half-life is 2–4 days.1 In animal studies high concentrations of azithromycin have been found in phagocytes, resulting in high concentrations of the drug being delivered to sites of infection.

Azithromycin has activity against the major bacterial sexually transmitted pathogens—notably, Chlamydia trachomatis, Neisseria gonorrhoeae, Ureaplasma urealyticum, Mycoplasma genitalium, Treponema pallidum and Haemophilus ducreyi. It is the recommended treatment for uncomplicated genital infection with C. trachomatis,3 and seems a particularly attractive option as an oral, single-dose treatment in syndromic and epidemiological management of bacterial STIs. This paper reviews published data on the use of azithromycin as sole treatment for infection with N. gonorrhoeae and the growing resistance to this antimicrobial agent.

AZITHROMYCIN AS TREATMENT FOR GONORRHOEA
A Medline search was conducted using PubMed under the major headings of ‘gonorrhoea and azithromycin’, ‘N. gonorrhoeae’ and azithromycin’ and ‘macrolide’ and ‘antimicrobial resistance.’ The search was not confined to randomised controlled trials but was confined to the English language. Thirteen studies on treatment outcome were identified and reviewed.4–16 Microbiological outcome for azithromycin in the treatment of urethral and endocervical infection with N. gonorrhoeae is summarised in table 1. The treatment outcome for 35 rectal and 4 lepharyngeal infections is presented in table 2. Studies show considerable variation in report detail, design, size, recruitment and the proportion and definition of evaluable patients. Aggregate microbiological cure rates for urethral or endocervical infection with N. gonorrhoeae in the clinical trials were 392/396 (99%; 95% CI 97.5% to 99.6%) for patients receiving a single 2 g oral dose of azithromycin and 520/559 (96.5%; 95% CI 94.3% to 97.6%) for patients receiving 1 g of azithromycin. This would suggest that the clinical efficacy of a 1 g dose of azithromycin fails to meet the stringent criterion for consideration in US Centers for Disease Control and Prevention (CDC) treatment guidelines, defined by Moran and Levine as a 95% cure rate with the lower level of the 95% CI exceeding 95% in summed clinical trials.16 The addition of retrospective data by Habib and Fernandez17 on clinical outcome of 1 g azithromycin in the treatment of gonorrhoea increases the proportion cured by this dose to 688/709 (97.0%; 95% CI 95.2% to 97.9%). Treatment efficacy was not diminished against N. gonorrhoeae showing in vitro resistance to penicillin, tetracycline or quinolones. Treatment failures in the reviewed studies were not generally attributable to resistance, although post-treatment sensitivities were rarely performed or cited. Where described, pretreatment isolates did not show in vitro decreased suscepti-

bility to azithromycin. Of historical note, a failure rate exceeding 20% was observed with erythromycin in the treatment of gonococcal urethritis and failure was associated with higher minimal inhibitory concentrations (MICs).19 Most reported side effects of azithromycin are gastrointestinal. Handsfield et al90 reported a rate of 35.3% for gastrointestinal symptoms with a 2 g oral dose and this study is widely cited as rendering azithromycin untenable as a treatment for gonorrhoea. Studies using 2 g as a single oral dose in the treatment of syphilis report much lower rates of gastrointestinal side effects (11.4%) and these were rated only mild to moderate and not sufficient to deter patients repeating the treatment.20 21 Side effects are either low or not reported in the other studies reviewed. Azithromycin tablets taken with food have bioequivalence to capsules taken on an empty stomach. There appears to be no data on...
whether the frequency of side effects differs between capsules and tablets. Studies rarely cite the form of azithromycin used, but a capsule preparation appears to have been used in the Handsfield study. The frequency and generally mild nature of gastrointestinal side effects should not discount the use of a 2 g single dose of azithromycin as treatment for gonorrhoea.

**RESISTANCE TO AZITHROMYCIN**

There are three main mechanisms by which bacteria acquire resistance to antibiotics: by alteration of the target site, by alteration in antibiotic transport and by modification of the resistance to azithromycin.26

**Table 1** Studies reporting outcome of azithromycin treatment of *Neisseria gonorrhoeae* infection of the urethra or endocervix

<table>
<thead>
<tr>
<th>Author and year of publication</th>
<th>Participants</th>
<th>Study design</th>
<th>Azithromycin dose</th>
<th>Sensitivity testing to azithromycin</th>
<th>Bacterial cure rate of evaluable participants</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handsfield 1994⁴</td>
<td>Male and female STD clinics, USA</td>
<td>RCT versus ceftriaxone</td>
<td>2 g</td>
<td>No</td>
<td>370/374 (98.9%)</td>
<td>Side effects reported by 35.3% (moderate 10.1%; severe 2.9%)</td>
</tr>
<tr>
<td>Khaki 2003⁵</td>
<td>Males STD clinic, New Delhi</td>
<td>RCT versus ceftriaxone</td>
<td>2 g</td>
<td>Yes</td>
<td>22/22 (100%)</td>
<td>Side effects &lt;10%—all mild</td>
</tr>
<tr>
<td>Lassus 1990⁶</td>
<td>Male and female Helsinki Central Hospital</td>
<td>RCT versus doxycycline</td>
<td>1 g 500/250/250 mg</td>
<td>Yes</td>
<td>20/20 (100%)</td>
<td>No side effects reported by patients</td>
</tr>
<tr>
<td>Steinigrimsson 1990⁷</td>
<td>Males + 1 female. STD clinic Reykjavik</td>
<td>RCT versus doxycycline</td>
<td>1 g 500 mg&gt;2 500/250/250 mg</td>
<td>Yes</td>
<td>11/12 (91.7%)</td>
<td>Failure MIC 0.125 mg/l</td>
</tr>
<tr>
<td>Odugbemi 1993⁸</td>
<td>Male and female STD clinics Nigeria</td>
<td>None</td>
<td>1 g</td>
<td>No</td>
<td>114/120 (95%)</td>
<td>Cure = clinical + bacteriological readiness; 2.7%—all mild/moderate</td>
</tr>
<tr>
<td>Waugh 1993⁹</td>
<td>Male and female, STD clinic Leeds, Non-comparative UK</td>
<td></td>
<td>1 g</td>
<td>Yes</td>
<td>27/28 (96.4%)</td>
<td>Failure MIC 0.125 mg/l Side effects 'negligible'</td>
</tr>
<tr>
<td>Steinigrimsson 1994¹⁰</td>
<td>Males only. STD clinic Reykjavik</td>
<td>RCT versus doxycycline</td>
<td>1 g</td>
<td>Yes</td>
<td>27/28 (96.4%)</td>
<td>Failure MIC 0.125 mg/l Side effects 'negligible'</td>
</tr>
<tr>
<td>Gruber 1995¹¹</td>
<td>Men; STD centre Rijeka, Croatia</td>
<td>RCT versus doxycycline</td>
<td>1 g</td>
<td>No</td>
<td>24/25 (96.0%)</td>
<td>No details on failure. Gastrointestinal side effects 4/6 (6%)</td>
</tr>
<tr>
<td>Gruber 1997¹²</td>
<td>Male and female, Rijeka, Croatia RCT versus ciprofloxacin</td>
<td></td>
<td>1 g</td>
<td>No</td>
<td>48/50 (96.0%)</td>
<td>Gastrointestinal side effects 4/50 (8%)—all mild</td>
</tr>
<tr>
<td>Swanston 2001¹³</td>
<td>Male and female STD clinic Trinidad Non-comparative</td>
<td></td>
<td>1 g</td>
<td>Yes</td>
<td>125/127 (98.4%)</td>
<td>Failures MIC 0.064 mg/l and 0.994 mg/l No side effects</td>
</tr>
<tr>
<td>Rustomejee 2002¹⁴</td>
<td>Symptomatic women. STD clinic Durban, S. Africa</td>
<td>RCT versus ciprofloxacin + doxycycline</td>
<td>1 g</td>
<td>No</td>
<td>30/31 (96.8%)</td>
<td>One failure in dual infected patient. Side effects 'few and minor'</td>
</tr>
<tr>
<td>Habib 2004¹⁵</td>
<td>Male and female STD clinic Wolverhampton, UK</td>
<td>Retrospective review</td>
<td>1 g</td>
<td>Not stated</td>
<td>168/170 (98.8%)</td>
<td>Failures: 1 'due to azithromycin-resistant strain'; 1 attributed to vomiting soon after 1 g dose</td>
</tr>
</tbody>
</table>

**Table 2** Outcome of azithromycin treatment of rectal and pharyngeal infection with *Neisseria gonorrhoeae*

<table>
<thead>
<tr>
<th>Author and year of publication</th>
<th>Azithromycin dose</th>
<th>Bacterial cure rate of evaluable participants</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Handsfield 1994⁴</td>
<td>2 g</td>
<td>26/27</td>
<td></td>
</tr>
<tr>
<td>Lassus 1990⁶</td>
<td>1 g 500/250/250 mg</td>
<td>3/3</td>
<td></td>
</tr>
<tr>
<td>Waugh 1993⁹</td>
<td>1 g</td>
<td>4/4</td>
<td></td>
</tr>
<tr>
<td>Total rectal</td>
<td></td>
<td>34/35 (97.1%)</td>
<td></td>
</tr>
<tr>
<td>Pharyngeal infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Handsfield 1994⁴</td>
<td>2 g</td>
<td>19/19</td>
<td></td>
</tr>
<tr>
<td>Dan 2006¹⁶</td>
<td>2 g</td>
<td>20/21</td>
<td>Pre- and post-treatment MIC of failure 0.5 mg/l</td>
</tr>
<tr>
<td>Lassus 1990⁶</td>
<td>1 g 500/250/250 mg</td>
<td>1/1</td>
<td></td>
</tr>
<tr>
<td>Waugh 1993⁹</td>
<td>1 g</td>
<td>2/2</td>
<td></td>
</tr>
<tr>
<td>Steinigrimsson 1994¹⁰</td>
<td>1 g</td>
<td>1/1</td>
<td></td>
</tr>
<tr>
<td>Manavi 2005¹⁷</td>
<td>1 g</td>
<td>1/1</td>
<td></td>
</tr>
<tr>
<td>Total pharyngeal</td>
<td></td>
<td>46/47 (97.9%)</td>
<td></td>
</tr>
</tbody>
</table>

MIC, minimal inhibitory concentration; RCT, randomised control trial.

antibiotic. Selection pressures on gonococci are both antibiotic and host driven with changes occurring from spontaneous mutation and from acquisition of genes from other bacteria (horizontal gene transfer).22 Azithromycin resistance to *N gonorrhoeae* is attributable to modification of the ribosomal attachment site and to changes in permeability and antibiotic transport. Alterations of the 23S rRNA ribosomal target by genetic mutation and by methylase-associated modification have been described.23–25 Mutations affecting the peptidyl-transferase loop of domain V of 23S rRNA have been described.23–25 Erm genes (erythromycin ribosome methylation) encode for 23S rRNA methylases and these genes can be transferred between *N gonorrhoeae* and oral commensal *Neisseria* species by conjugation.24

Efflux pumps actively export toxic compounds including antibacterial peptides and several antibiotics from the bacterial cell. In *N gonorrhoeae*, the mtr(CDE)-encoded efflux pump is one system that exports macrolides and, while not the major mechanism, this efflux pump also contributes to chromosomal resistance to penicillin, tetracyclines and quinolones.26–30 This pump system is regulated by proteins coded by the repressor MtR gene and activator MtA gene. Different mutations in these controlling genes confer decreased susceptibility and low-level resistance to azithromycin.26–29

**EPIEMIOLOGY OF RESISTANCE IN N GONORRHOEAE TO AZITHROMYCIN**

Monitoring trends in the antimicrobial susceptibilities of *N gonorrhoeae* has proved crucial in ensuring the appropriate recommendation of gonococcal treatment. In vitro susceptibility testing of *N gonorrhoeae* in surveillance programmes is the principal source of data on azithromycin resistance. Resistance of *N*
gonorrhoeae to azithromycin is generally defined as an MIC $\geq 1\, \text{mg/l}$. One isolate with an MIC of 2\,mg/l and Mtr phenotype was identified among 300 strains collected in 1984 and 1985. The Gonococcal Isolate Surveillance Project in the USA was established in 1986, with azithromycin susceptibility testing introduced in 1992. An isolate with resistance to azithromycin was first identified in 1993 in New Mexico. The number of isolates with resistance has remained low in the Gonococcal Isolate Surveillance Project with 27 of 6009 (0.4%) having an MIC $\geq 2.0\, \text{mg/l}$ in 2007.

Cases have been geographically scattered, with the exception of a cluster in Kansas City in 1999/2000. Five isolates with an MIC of 4\,mg/l were identified among 91 isolates collected in Cuba between 1995 and 1998. Reduced susceptibility was also reported in isolates from Brazil and Caribbean. The Australian Gonococcal Surveillance Programme has been reporting since 1996 and is linked to the WHO Western Pacific Region Gonococcal Antimicrobial Surveillance Programme. These programmes report a ‘low proportion of resistance to azithromycin’ with no high-level resistance.

In Europe, two isolates with an MIC of 4\,mg/l were collected in Spain in 2000 to 2001. The Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP) was established in England and Wales in 2000. Susceptibility testing for azithromycin was added in 2001, when six of 2550 isolates (0.3%) were found to have an MIC $\geq 1\, \text{mg/l}$. The prevalence of resistant isolates in GRASP increased annually until 2007 when 4.1% showed resistance to azithromycin, including six isolates with MIC $\geq 256\, \text{mg/l}$. Resistance fell in 2008 to 0.8% with no high-level resistance identified. The European Surveillance of Sexually Transmitted Infections programme reported an overall prevalence of resistance to azithromycin of 8.2% (79/965) in isolates collected in 2004, with considerable variation between participating countries.

Azithromycin resistance exceeded 9% in five of seven federal districts in Russia in 2007, with lower levels reported in 2008. Data on resistance in Africa are limited but no azithromycin resistance was identified in Lilongwe, Malawi in 2007.

A strain of N. gonorrhoeae highly resistant to azithromycin (MIC $> 2048\, \text{mg/l}$) was isolated in Argentina in 2001 and has recently been shown to be associated with a mutation in the 23S rRNA gene. More recently, high-level azithromycin resistance (MIC $\geq 256\, \text{mg/l}$) has been identified in Scotland, England and Wales and Italy. High-level azithromycin resistance was first detected in Scotland in 2004 and was present in 33/845 (3.9%) isolates tested in 2007. N. gonorrhoeae multi-antigen sequence typing (NG-MAST) revealed that these highly resistant strains belong to a small number of sequence types. This outbreak is linked to high-level resistance in Scotland. No high-level resistance was detected in 2008 in GRASP. The multiclonal and geographically disparate emergence of low-level and high-level azithromycin resistance in surveillance programmes strongly argues for caution in the use of azithromycin as the sole treatment for gonorrhoea.

**RESISTANCE AND CLINICAL OUTCOME**

Azithromycin is not a recommended treatment for gonorrhoea and does not appear to be widely used as sole antimicrobial therapy. MICs provide an indicator as to whether resistant mechanisms are present in an isolate of N. gonorrhoeae. The correlation between MIC and treatment failure with azithromycin has not been well studied and relies on observations from clinical trials and case reports of treatment failures. In 1997 Young et al reported a case of azithromycin treatment failure with characterisation of the pre- and post-treatment isolate. The azithromycin MIC pretreatment was 0.125\,mg/l and post-treatment 3.0\,mg/l. Treatment failures in clinical trials and in a series of case reports have not shown pretreatment resistance.

This indicates that treatment failure cannot be reliably predicted on the basis of in vitro MICs and test of cure may be advisable if azithromycin is used as the sole antimicrobial agent to treat gonorrhoea. Cases with high-level resistance identified in surveillance programmes do not appear to have received treatment with azithromycin.

If azithromycin is not sufficiently robust as a single agent in the treatment of gonorrhoea, it might potentially have a role in combination with other antimicrobial agents. Furuja et al investigated in vitro synergy between azithromycin and cefixime in 25 isolates of N. gonorrhoeae from male patients with urethritis in Japan. Significant decreases in the median MICs of both cefixime (0.25\,mg/l to 0.008\,mg/l) and azithromycin (0.125\,mg/l to 0.05\,mg/l) were observed when cefixime was combined with azithromycin. Dual treatment has been advocated for oropharyngeal gonococcal infection. Azithromycin may have a valuable role in combination with extended-spectrum cephalosporins to maintain treatment efficacy in the presence of the progressive increase in MICs to oral cephalosporins.

**SUMMARY**

The ability of N. gonorrhoeae to acquire resistance to antimicrobial agents is a major concern and challenge in maintaining effective treatment and control of this infection. Clinical trials of the efficacy and acceptability of azithromycin as a treatment for gonorrhoea were conducted more than a decade ago in an era when azithromycin resistance was rare. Surveillance programmes of antimicrobial resistance have clearly documented a shift in the susceptibility of N. gonorrhoeae to azithromycin and the emergence of high-level resistance. It has been suggested that an antimicrobial agent should not be used for the treatment of gonorrhoea when $> 5\%$ of strains demonstrate resistance. In response to an increasing prevalence of penicillinase-producing N. gonorrhoeae in 1987, the CDC proposed a lower threshold of $> 3\%$ for switching treatment recommendations. These thresholds may not be appropriate for an antimicrobial agent such as azithromycin for which treatment failure does not seem inevitable.

**Key messages**

- A single 2\,g dose of azithromycin has shown good efficacy in clinical trials in the treatment of infection with N. gonorrhoeae.
- Subsequent to clinical trials, in vitro resistance of clinical isolates has been widely described, including high-level resistance.
- Azithromycin cannot be generally recommended as a sole antimicrobial treatment for gonorrhoea but may have a role in specific circumstances or in combination therapy with third-generation cephalosporins.
- Pretreatment MIC may not predict treatment outcome and test of cure should be considered when azithromycin is used as the sole antimicrobial agent for treatment of gonorrhoea.
closely predicted by pretreatment MIC. Surveillance programmes remain crucial for updating recommendations of effective antimicrobial treatment. The history of acquisition of antimicrobial resistance to multiple classes of antimicrobial agents and the resistance data we now have on azithromycin are guides to the routine use of azithromycin as single antimicrobial treatment for gonorrhoea.

Competing interests None.

Contributors CB conceived the review. CB and JG contributed to the literature review, drafted sections of the paper and edited the final manuscript.

Provenance and peer review Commissioned; externally peer reviewed.

REFERENCES


