Azithromycin in the treatment of infection with
Neisseria gonorrhoeae

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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 phar-
cmacokinetics 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,2 3 and seems a partic-
ularly attractive option as an oral, single-dose
in 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 ‘macrole’ 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 gonor-
rhoeae is summarised in table 1. The treatment
outcome for 35 rectal and 46 pharyngeal 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 gonor-
rhoeae 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 520/539 (96.3%; 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
98% CI exceeding 95% in summed clinical trials.18
The addition of retrospective data by Habib and
Fernando15 on clinical outcome of 1 g azithromycin
in the treatment of gonorrhoea increases the
proportion cured by this dose to 688/709 (97.0%; 98%
CI 95.2% to 97.9%). Treatment efficacy was
not diminished against N gonorrhoeae showing in
vitro resistance to penicillin, tetracycline or quino-
lines. 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 erythrom-
ycin in the treatment of gonococcal urethritis and
failure was associated with higher minimal inhibi-
tory concentrations (MICs).19
Most reported side effects of azithromycin are
gastrointestinal. Handsfield et al10 reported a rate of
35.5% 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

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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-coding genes (erythromycin ribosome methylation) encode for 23S rRNA methylases and these genes can be transferred between 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.25–30 This pump system is regulated by proteins coded by the repressor MtrA gene and activator MtR gene. Different mutations in these controlling genes confer decreased susceptibility and low-level resistance to azithromycin.26–28

EPIEDEMOLOGY 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 $\geq 1$ mg/l.\textsuperscript{31} One isolate with an MIC of 2 mg/l and Mtr phenotype was identified among 300 strains collected in 1984 and 1985.\textsuperscript{32} 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.\textsuperscript{33} The number of isolates with resistance has remained low in the Gonococcal Isolate Surveillance Project with 27 of 6009 (0.4%) having an MIC $\geq 2.0$ mg/l in 2007.\textsuperscript{34}

Cases have been geographically scattered, with the exception of a cluster in Kansas City in 1999-2000.\textsuperscript{35} Five isolates with an MIC of 4 mg/l were identified among 91 isolates collected in Cuba between 1995 and 1998.\textsuperscript{36} Reduced susceptibility was also reported in isolates from Brazil and Caribbean.\textsuperscript{37} 38 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.\textsuperscript{39} 40 In Europe, two isolates with an MIC of 4 mg/l were collected in Spain in 2000 to 2001.\textsuperscript{40} 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 $\geq 1$ 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 $\geq 256$ mg/l.\textsuperscript{41} 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.\textsuperscript{42} Azithromycin resistance exceeded 9% in five of seven federal districts in Russia in 2007, with lower levels reported in 2008.\textsuperscript{43} Data on resistance in Africa are limited but no azithromycin resistance was identified in Lilongwe, Malawi in 2007.\textsuperscript{44}

A strain of \textit{N gonorrhoeae} highly resistant to azithromycin (MIC $> 2048$ mg/l) was isolated in Argentina in 2001 and has recently been shown to be associated with a mutation in the 23S rRNA gene.\textsuperscript{25} 45 More recently, high-level azithromycin resistance (MIC $\geq 256$ mg/l) has been identified in Scotland,\textsuperscript{46} England and Wales\textsuperscript{47} and Italy.\textsuperscript{48} High-level azithromycin resistance was first detected in Scotland in 2004 and was present in 33/845 (3.9%) isolates tested in 2007.\textsuperscript{46} \textit{N gonorrhoeae} multi-antigen sequence typing (NG-MAST) revealed that these highly resistant strains belong to a small number of sequence types. High-level azithromycin resistance emerged in England and Wales in 2007 with six isolates of the same sequence type identified.\textsuperscript{47} 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 \textit{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 \textit{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.\textsuperscript{49} Treatment failures in clinical trials and in a series of case reports have not shown pretreatment resistance.\textsuperscript{50} 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. Furuya \textit{et al} investigated in vitro synergy between azithromycin and cefixime in 25 isolates of \textit{N gonorrhoeae} from male patients with urethritis in Japan.\textsuperscript{51} 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.\textsuperscript{52} 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 \textit{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 \textit{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 $\geq 5\%$ of strains demonstrate resistance.\textsuperscript{53} 54 In response to an increasing prevalence of penicillinase-producing \textit{N gonorrhoeae} in 1987, the CDC proposed a lower threshold of $>3\%$ for switching treatment recommendations.\textsuperscript{55} These thresholds may not be appropriate for an antimicrobial agent such as azithromycin for which treatment failure does not seem

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**Key messages**

- A single 2 g dose of azithromycin has shown good efficacy in clinical trials in the treatment of infection with \textit{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.
closerly 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 argue against the routine use of azithromycin as single antimicrobial treatment for gonorrhoea.

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