Update on Emerging Infections: News From the Centers for Disease Control and Prevention

Commentators

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Editor's note: *This article is part of a regular series on emerging infection from the Centers for Disease Control and Prevention (CDC) and the EMERGEncy ID NET, an emergency department–based and CDC-collaborative surveillance network. Important infectious disease public health information with relevance to emergency physicians is reported. The goal of this series is to advance knowledge about communicable diseases in emergency medicine and foster cooperation between the front line of clinical medicine and public health agencies.*

Update to the CDC's Sexually Transmitted Diseases Treatment Guidelines, 2010: Oral Cephalosporins No Longer a Recommended Treatment for Gonococcal Infections

[Centers for Disease Control and Prevention. Update to the CDC's sexually transmitted diseases treatment guidelines, 2010: oral cephalosporins no longer a recommended treatment for gonococcal infections, 2012. *MMWR Morb Mortal Wkly Rep.* 2012;61:590-594.]

Gonorrhea is a major cause of serious reproductive complications in women and can facilitate HIV transmission.[1] Effective treatment is a cornerstone of US gonorrhea control efforts, but it has been complicated by the ability of *Neisseria gonorrhoeae* to develop antimicrobial resistance. This report, using data from the Centers for Disease Control and Prevention's (CDC's) Gonococcal Isolate Surveillance Project (GISP), describes laboratory evidence of declining cefixime susceptibility among urethral *N gonorrhoeae* isolates collected in the United States during 2006 to 2011 and updates CDC's current recommendations for treatment of gonorrhea.[2] In accordance with GISP data, CDC recommends combination therapy with ceftriaxone 250 mg intramuscularly and either azithromycin 1 g orally as a single dose or doxycycline 100 mg orally twice daily for 7 days as the most reliably effective treatment for uncomplicated gonorrhea. CDC no longer recommends cefixime at any dose as a first-line regimen for treatment of gonococcal infections. If cefixime is used as an alternative agent, then the patient should return in 1 week for a test of cure at the site of infection.

Infection with *N gonorrhoeae* is a major cause of pelvic inflammatory disease, ectopic pregnancy, and infertility and can facilitate HIV transmission.[1] In the United States, gonorrhea is the second most commonly reported notifiable infection, with greater than 300,000 cases reported during 2011. Gonorrhea treatment has been complicated by the ability of *N gonorrhoeae* to develop resistance to antimicrobials used for treatment. During the 1990s and 2000s, fluoroquinolone resistance in *N gonorrhoeae* emerged in the United States, becoming prevalent in Hawaii and California and among men who have sex with men (MSM) before spreading throughout the United States. In 2007, emergence of fluoroquinolone-resistant *N gonorrhoeae* in the United States prompted CDC to no longer recommend fluoroquinolones for treatment of gonorrhea, leaving cephalosporins as the only remaining recommended antimicrobial class.[3] To ensure treatment of co-occurring pathogens (eg, *Chlamydia trachomatis*) and reflecting concern about emerging gonococcal resistance, CDC's 2010 sexually transmitted diseases (STDs) treatment guidelines recommended combination therapy for gonorrhea with a cephalosporin (ceftriaxone 250 mg intramuscularly or cefixime 400 mg orally) plus either azithromycin orally or doxycycline orally, even if nucleic acid amplification testing (NAAT) result for *C trachomatis* was negative at treatment.[2] From 2006 to 2010, the minimum concentrations of cefixime needed to inhibit the growth in vitro of *N gonorrhoeae* strains circulating in the United States and many other countries increased, suggesting that the effectiveness of cefixime might be waning.[4] Reports from Europe recently have described patients with uncomplicated gonorrhea infection not cured by treatment with cefixime 400 mg orally.[5-8]

GISP is a CDC-supported sentinel surveillance system that has monitored *N gonorrhoeae* antimicrobial susceptibilities since 1986 and is the only source in the United States of national and regional *N gonorrhoeae* antimicrobial susceptibility data. During September to December 2011, CDC and 5 external GISP principal investigators, each with *N gonorrhoeae*–specific expertise in surveillance, antimicrobial resistance, treatment, and antimicrobial susceptibility testing, reviewed antimicrobial susceptibility trends in GISP through August 2011 to determine whether to update CDC's current recommendations[2] for treatment of uncomplicated gonorrhea. Each month, the first 25 gonococcal urethral isolates collected from men attending participating STD clinics (approximately 6,000 isolates each year) were submitted for antimicrobial susceptibility testing. The minimum inhibitory concentration (MIC), the lowest antimicrobial concentration that inhibits visible bacterial growth in the laboratory, is used to assess antimicrobial susceptibility. Cefixime susceptibilities were not determined during 2007 to

2008 because cefixime temporarily was unavailable in the United States. Criteria for resistance to cefixime and ceftriaxone have not been defined by the Clinical Laboratory Standards Institute. However, the institute does consider isolates with cefixime or ceftriaxone MICs greater than or equal to 0.5 μg/mL to have "decreased susceptibility" to these drugs.[9] During 2006 to 2011, 15 isolates (0.1%) had decreased susceptibility to cefixime (all had MICs=0.5 μg/mL), including 9 (0.2%) in 2010 and 1 (0.03%) during January to August 2011; 12 of 15 were from MSM, and 12 were from the West and 3 from the Midwest. No isolates exhibited decreased susceptibility to ceftriaxone. Because increasing MICs can predict the emergence of resistance, lower cephalosporin MIC breakpoints were established by GISP for surveillance purposes to provide greater sensitivity in detecting declining gonococcal susceptibility than breakpoints defined by the Clinical Laboratory Standards Institute. Cefixime MICs greater than or equal to 0.25 μg/mL and ceftriaxone MICs greater than or equal to 0.125 μg/mL were defined as "elevated MICs." The institute does not define azithromycin resistance criteria; CDC defines decreased azithromycin susceptibility as greater than or equal to 2.0 μg/mL.

EVIDENCE AND RATIONALE

The percentage of isolates with elevated cefixime MICs (MICs ≥0.25 μg/mL) increased from 0.1% in 2006 to 1.5% during January to August 2011. In the West, the percentage increased from 0.2% in 2006 to 3.2% in 2011. The largest increases were observed in Honolulu, HI (0% in 2006 to 17.0% in 2011); Minneapolis, MN (0% to 6.9%); Portland, OR (0% to 6.5%); and San Diego, CA (0% to 6.4%). Nationally, among MSM, isolates with elevated MICs to cefixime increased from 0.2% in 2006 to 3.8% in 2011. In 2011, a higher proportion of isolates from MSM had elevated cefixime MICs than isolates from men who have sex exclusively with women, regardless of region.

The percentage of isolates exhibiting elevated ceftriaxone MICs increased slightly, from 0% in 2006 to 0.4% in 2011. The percentage increased from less than 0.1% in 2006 to 0.8% in 2011 in the West and did not increase significantly in the Midwest (0% to 0.2%) or the Northeast and South (0.1% in 2006 and 2011). Among MSM, the percentage increased from 0.0% in 2006 to 1.0% in 2011.

The 2010 CDC STD treatment guidelines[2] recommend that azithromycin or doxycycline be administered with a cephalosporin as treatment for gonorrhea. The percentage of isolates exhibiting tetracycline resistance (MIC ≥2.0 μg/mL) was high but remained stable from 2006 (20.6%) to 2011 (21.6%). The percentage exhibiting decreased susceptibility to azithromycin (MIC ≥2.0 μg/mL) remained low (0.2% in 2006 to 0.3% in 2011). Among 180 isolates collected during 2006 to 2011 that exhibited elevated cefixime MICs, 139 (77.2%) exhibited tetracycline resistance, but only 1 (0.6%) had decreased susceptibility to azithromycin.

Ceftriaxone as a single intramuscular injection of 250 mg provides high and sustained bactericidal levels in the blood and is highly efficacious at all anatomic sites of infection for treatment of *N gonorrhoeae* infections caused by strains currently circulating in the United States.[10,11] Clinical data to support use of doses of ceftriaxone greater than 250 mg are not available. A 400-mg oral dose of cefixime does not provide bactericidal levels as high or sustained as those of an intramuscular 250-mg dose of ceftriaxone and demonstrates limited efficacy for treatment of pharyngeal gonorrhea.[10,11] The significant increase in the prevalence of US GISP isolates with elevated cefixime MICs, most notably in the West and among MSM, is of particular concern because the emergence of fluoroquinolone-resistant *N gonorrhoeae* in the United States during the 1990s also occurred initially in the West and predominantly among MSM before spreading throughout the United States within several years. Thus, observed patterns might indicate early stages of the development of clinically significant gonococcal resistance to cephalosporins. CDC anticipates that increasing cefixime MICs soon will result in declining effectiveness of cefixime for the treatment of urogenital gonorrhea. Furthermore, as cefixime becomes less effective, continued use of cefixime might hasten the development of resistance to ceftriaxone, a safe, well-tolerated, injectable cephalosporin and the last antimicrobial that is recommended and known to be highly effective in a single dose for treatment of gonorrhea at all anatomic sites of infection. Maintaining effectiveness of ceftriaxone for as long as possible is critical. Thus, CDC no longer recommends the routine use of cefixime as a first-line regimen for treatment of gonorrhea in the United States.

According to experience with other microbes that have developed antimicrobial resistance rapidly, a theoretical basis exists for combination therapy using 2 antimicrobials with different mechanisms of action to improve treatment efficacy and potentially delay emergence and spread of resistance to cephalosporins. Therefore, the use of a second antimicrobial (azithromycin as a single 1-g oral dose or doxycycline 100 mg orally twice daily for 7 days) is recommended for administration with ceftriaxone. The use of azithromycin as the second antimicrobial is preferred to doxycycline because of the convenience and compliance advantages of single-dose therapy and the substantially higher prevalence of gonococcal resistance to tetracycline than to azithromycin among GISP isolates, particularly in strains with elevated cefixime MICs.

RECOMMENDATIONS

For treatment of uncomplicated urogenital, anorectal, and pharyngeal gonorrhea, CDC recommends combination therapy with a single intramuscular dose of ceftriaxone 250 mg plus either a single dose of azithromycin 1 g orally or doxycycline 100 mg orally twice daily for 7 days.

Clinicians who diagnose gonorrhea in a patient with persistent infection after treatment (treatment failure) with the recommended combination therapy regimen should culture relevant clinical specimens and perform antimicrobial

susceptibility testing of *N gonorrhoeae* isolates. Phenotypic antimicrobial susceptibility testing should be performed with disk diffusion, Etest (BioMérieux, Durham, NC), or agar dilution. Data currently are limited on the use of NAAT-based antimicrobial susceptibility testing for genetic mutations associated with resistance in *N gonorrhoeae*. The laboratory should retain the isolate for possible further testing. The treating clinician should consult an infectious disease specialist, an STD/HIV prevention training center (http://www.nnptc.org), or CDC (telephone 404-639-8659) for treatment advice and report the case to CDC through the local or state health department within 24 hours of diagnosis. A test of cure should be conducted 1 week after retreatment, and clinicians should ensure that the patient's sex partners from the preceding 60 days are evaluated promptly with culture and treated as indicated.

When ceftriaxone cannot be used for treatment of urogenital or rectal gonorrhea, 2 alternative options are available: cefixime 400 mg orally plus either azithromycin 1 g orally or doxycycline 100 mg twice daily orally for 7 days if ceftriaxone is not readily available, or azithromycin 2 g orally in a single dose if ceftriaxone cannot be administered because of severe allergy. If a patient with gonorrhea is treated with an alternative regimen, he or she should return 1 week after treatment for a test of cure at the infected anatomic site, which ideally should be performed with culture or with a NAAT for *N gonorrhoeae* if culture is not readily available. If the NAAT result is positive, every effort should be made to perform a confirmatory culture. All positive culture results for test of cure should undergo phenotypic antimicrobial susceptibility testing. Patients who experience treatment failure after treatment with alternative regimens should be treated with ceftriaxone 250 mg as a single intramuscular dose and azithromycin 2 g orally as a single dose and should receive infectious disease consultation. The case should be reported to CDC through the local or state health department.

For all patients with gonorrhea, every effort should be made to ensure that their sex partners from the preceding 60 days are evaluated and treated for *N gonorrhoeae* with a recommended regimen. If a heterosexual partner of a patient cannot be linked to evaluation and treatment in a timely fashion, then expedited partner therapy should be considered, using oral combination antimicrobial therapy for gonorrhea (cefixime 400 mg and azithromycin 1 g), delivered to the partner by the patient, a disease investigation specialist, or a collaborating pharmacy.

The capacity of laboratories in the United States to isolate *N gonorrhoeae* by culture is declining rapidly because of the widespread use of NAATs for gonorrhea diagnosis, yet it is essential that culture capacity for *N gonorrhoeae* be maintained to monitor antimicrobial resistance trends and determine susceptibility to guide treatment after treatment failure. To help control gonorrhea in the United States, health care providers must maintain the ability to collect specimens for culture and be knowledgeable of laboratories to which they can send specimens for culture. Health care systems and health departments must support access to culture, and laboratories must maintain culture capacity or develop partnerships with laboratories that can perform culture.

Treatment of patients with gonorrhea with the most effective therapy will limit the transmission of gonorrhea, prevent complications, and likely slow emergence of resistance. However, resistance to cephalosporins, including ceftriaxone, is expected to emerge. Reinvestment in gonorrhea prevention and control is warranted. New treatment options for gonorrhea are urgently needed.

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Chlamydia Trachomatis Infections: Screening, Diagnosis, and Management

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***Chlamydia trachomatis* is a gram-negative bacterium that infects the columnar epithelium of the cervix, urethra, and rectum, as well as nongenital sites such as the lungs and eyes. The bacterium is the cause of the most frequently reported sexually transmitted disease in the United States, which is responsible for more than 1 million infections annually. Most persons with this infection are asymptomatic. Untreated infection can result in serious complications such as pelvic inflammatory disease, infertility, and ectopic pregnancy in women, and epididymitis and orchitis in men. Men and women can experience chlamydia-induced reactive arthritis. Treatment of uncomplicated cases should include azithromycin or doxycycline. Screening is recommended in all women younger than 25 years, in all pregnant women, and in women who are at increased risk of infection. Screening is not currently recommended in men. In neonates and infants, the bacterium can cause conjunctivitis and pneumonia. Adults may also experience conjunctivitis caused by chlamydia. Trachoma is a recurrent ocular infection caused by chlamydia and is endemic in the developing world. (*Am Fam Physician*. 2012;86(12):1127-1132. Copyright © 2012 American Academy of Family Physicians.)**

▶ **Patient information:** A handout on this topic is available at http://familydoctor.org/familydoctor/en/diseases-conditions/chlamydia.html.

Chlamydia trachomatis is a gram-negative bacterium that infects the columnar epithelium of the cervix, urethra, and rectum, as well as nongenital sites. The bacterium is the cause of the most frequently reported sexually transmitted disease in the United States,[1] and is the leading cause of infectious blindness in the world.[2] According to the Centers for Disease Control and Prevention (CDC) in 2009, the rate of sexually transmitted chlamydia infections in the United States was 426 cases per population of 100,000, which represents a 24 percent increase in the rate of infection since 2006.[3] More recent data from 2010 indicates that 1,307,893 chlamydia infections were reported to the CDC from all 50 states and the District of Columbia.[4] The CDC estimates that there are 2.8 million chlamydia cases in the United States annually—more than twice the number actually reported.[5] This is an increase of 5 percent over the past year, and 27 percent from four years ago.[5] From 2000 to 2010, the chlamydia screening rate among young women nearly doubled, from 25 to 48 percent.[5]

Genitourinary Infections

Genitourinary infection affects primarily young adults and persons with multiple sex partners.[6] Women carry a disproportionate burden: CDC statistics show that the overall rate of infection was almost three times higher among women than men,[7] although this may be because of existing screening programs for women. Approximately 79 percent of the U.S. health costs for chlamydia infections can be attributed to women.[8]

Young women 15 to 19 years of age carry the highest incidence of disease, followed by women 20 to 24 years of age. Although chlamydia is common in all races, blacks, American Indians/Alaska Natives, and Hispanic women are disproportionately affected. Other groups at higher risk include adolescents and men who have sex with men.[8]

According to the CDC, chlamydia infection rates in men are also increasing, and at a faster rate than in women. Between 2005 and 2009, the reported infection rate for men rose from 159.4 to 219.3 cases per 100,000 males, a 37.6 percent increase.[7] During the same period, the rate of infection among women increased 29.3 percent.[7]

Prevalence rates among men vary depending on the subgroups screened. One study reported a prevalence of 3.7 percent in men 18 to 26 years of age.[9] Other studies report an overall prevalence among asymptomatic men in the United States of between 6 and 7 percent, and as much as 18 to 20 percent in men attending

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Nucleic acid amplification tests are the most sensitive tests for detecting chlamydia infection, and may be performed on endocervical, urethral, vaginal, pharyngeal, rectal, or urine samples.	C	13
Azithromycin (Zithromax) or doxycycline should be used for the treatment of uncomplicated genitourinary chlamydia infection in men and women.	A	15
Azithromycin or amoxicillin should be used as first-line treatment of genitourinary chlamydia infection in pregnant women.	A	16
The USPSTF recommends screening for chlamydia infection in all sexually active nonpregnant women 24 years and younger, and all nonpregnant women 25 years and older who are at increased risk.	A	24
The USPSTF concludes there is insufficient evidence to recommend for or against the screening of men for chlamydia infection.	C	24
Although the CDC recommends screening for chlamydia infection in all pregnant women, the USPSTF recommends routine screening only in all pregnant women 24 years and younger, and in pregnant women 25 years and older who are at increased risk.	B	1, 24
Some experts recommend screening certain groups of high-risk men (e.g., men who have sex with men) for rectal chlamydia infection.	C	1, 11

CDC = Centers for Disease Control and Prevention; USPSTF = U.S. Preventive Services Task Force.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

inner-city primary care clinics.[10] In select groups, such as men who have sex with men, rates of rectal infections were found to be high.[11] Risk factors for men and women include lack of condom use, lower socioeconomic status, living in an urban area, and having multiple sex partners.

PRESENTATION

Most persons who are infected with *C. trachomatis* are asymptomatic. However, when symptoms of infection are present, in women they most commonly include abnormal vaginal discharge, vaginal bleeding (including bleeding after intercourse), and dysuria.[12] On physical examination, mucopurulent or purulent discharge from the endocervical canal and cervical friability are common. In men, symptoms may include penile discharge, pruritus, and dysuria. However, in one study, only 2 to 4 percent of infected men reported any symptoms.[10]

***Chlamydia trachomatis* is the cause of the most frequently reported sexually transmitted disease in the United States.**

Persons who have receptive anal intercourse can acquire a rectal infection, which can present as pain, discharge, or bleeding. Those engaging in oral sex can acquire a pharyngeal infection from an infected partner.

DIAGNOSIS

Nucleic acid amplification tests (NAATs) are the most sensitive tests for detecting chlamydia and gonococcal infections.[13] NAATs can be performed on endocervical, urethral, vaginal, pharyngeal, rectal, or urine samples (first-void is preferred).[13] The accuracy of NAATs on urine samples has been found to be nearly identical to that of samples obtained directly from the cervix or urethra.[13] On wet mount, a finding of leukorrhea (more than 10 white blood cells per high-power field on microscopic examination of vaginal fluid) has been associated with chlamydia and gonococcal infections of the cervix.[1] Oropharyngeal and rectal swabs may be obtained in persons who engage in receptive oral or anal intercourse.[13]

Point-of-care testing at a physician's office is recommended, although increasingly, researchers have begun to evaluate commercially available mail-in kits. To date, commercial kits have not been shown to be reliable, and have lower sensitivity and specificity than NAATs.[14]

TREATMENT

Uncomplicated genitourinary chlamydia infection should be treated with azithromycin (Zithromax; 1 g, single dose) or doxycycline (100 mg twice daily for seven days; *Table 1* [1,15-22]). Studies indicate that both treatments are equally effective.[15] Although dual therapy to cover gonorrhea and chlamydia is recommended when patients are diagnosed with gonorrhea, additional coverage for gonorrhea is not required with the diagnosis of chlamydia alone.[1]

Alternative regimens for uncomplicated chlamydia infection include erythromycin (500 mg four times daily for seven days), erythromycin ethylsuccinate (800 mg four times daily for seven days), levofloxacin (Levaquin; 500 mg once daily for seven days), or ofloxacin (Floxin; 300 mg twice daily or 600 mg once daily for seven days).[1] Erythromycin is reported to have higher occurrences of gastrointestinal adverse effects.[15]

Table 1. Treatment Recommendations for Chlamydia-Induced Infections

Condition	*Recommended oral treatments*
Uncomplicated genitourinary infection[15]	Azithromycin (Zithromax), 1 g (single dose) *or* Doxycycline, 100 mg twice daily for seven days Alternatives: Erythromycin, 500 mg four times daily for seven days Erythromycin ethylsuccinate, 800 mg four times daily for seven days Levofloxacin (Levaquin), 500 mg once daily for seven days Ofloxacin (Floxin), 300 mg twice daily (or 600 mg once daily) for seven days
Infection during pregnancy[1,16]	Azithromycin, 1 g (single dose) *or* Amoxicillin, 500 mg three times daily for seven days Alternatives: Erythromycin, 500 mg four times daily for seven days, or 250 mg four times daily for 14 days Erythromycin ethylsuccinate, 800 mg four times daily for seven days, or 400 mg four times daily for 14 days
Chronic reactive arthritis[17,18]	Doxycycline, 100 mg twice daily, plus rifampin, 300 mg once daily for six months *or* Azithromycin, 500 mg once daily for five days, then 500 mg twice weekly, plus rifampin, 300 mg once daily for six months
Lymphogranuloma venereum[1]	Doxycycline, 100 mg twice daily for 21 days Alternatives: Erythromycin, 500 mg four times daily for 21 days Azithromycin, 1 g once weekly for three weeks
Neonatal pulmonary infection[19]	Erythromycin or erythromycin ethylsuccinate, 50 mg per kg daily in four divided doses for 14 days
Ocular infection: ophthalmia neonatorum[19]	Erythromycin or erythromycin ethylsuccinate, 50 mg per kg daily in four divided doses for 14 days
Adult-inclusion conjunctivitis[20,21]	Doxycycline, 100 mg twice daily for one to three weeks *or* Erythromycin, 250 mg four times daily for one to three weeks
Trachoma[22]	Azithromycin, 1 g (single dose) *or* Doxycycline, 100 mg twice daily for 21 days

Information from references 1, and 12 through 19.

Pregnant women may be treated with azithromycin (1 g, single dose) or amoxicillin (500 mg three times daily for seven days). Alternative regimens include erythromycin (500 mg four times daily for seven days or 250 mg four times daily for 14 days) and erythromycin ethylsuccinate (800 mg four times daily for seven days or 400 mg four times daily for 14 days). Although all three medications show similar effectiveness, a recent review indicates that azithromycin may have fewer adverse effects when compared with erythromycin or amoxicillin in pregnant women.[16]

Test of cure is recommended three to four weeks after completion of treatment in pregnant women only. If chlamydia is detected during the first trimester, repeat testing for reinfection should also be performed within three to six months, or in the third trimester.[1] Men and nonpregnant women should be retested at three months. If this is not possible, clinicians should retest the patient to screen for reinfection when he or she next presents for medical care within 12 months after treatment.[1]

Partners should be notified of infection and treated appropriately. Studies indicate that expedited partner therapy (partners treated without medical consultation) may improve clinical and behavioral outcomes pertaining to partner management among heterosexual men and women with chlamydia infection.[23] Partners should be referred for evaluation, testing, and treatment if they engaged in sexual contact within 60 days before a diagnosis was made or at the onset of symptoms.[1] Patients should also be instructed to abstain from sexual intercourse until seven days after a single-dose regimen or after completion of a multiple-dose regimen, and after their partner has also completed treatment.[1] Patients infected with human immunodeficiency virus (HIV) should be treated using the same regimens recommended for those who are HIV-negative *(Table 2)*.[1] As of January 2000, all 50 states and the District of Columbia require chlamydia cases be reported to state or local health departments.

SCREENING FOR GENITOURINARY CHLAMYDIA

Currently, the U.S. Preventive Services Task Force recommends routine screening in all sexually active women 24 years and younger, and in women 25 years and older who are at increased risk because of having multiple partners or a new sex partner.[24] Because of the high risk of intrauterine and postnatal complications if left untreated, all pregnant women at increased risk should be routinely screened for chlamydia during

Table 2. Management Recommendations for Genitourinary Chlamydia Infection

Make diagnosis via specimen collection (i.e., urine, urethra, endocervix, pharynx, rectum, or vagina), using a nucleic acid amplification test.
All pregnant women infected with chlamydia should be retested three to four weeks after completing treatment.
Test of cure is not advised for nonpregnant patients who finished one of the recommended courses of treatment.
Repeat testing for reinfection of men and women who were recently infected is recommended at three months after completion of treatment, or within the first year following treatment.
Sex partners should be referred for evaluation, testing, and treatment if they engaged in sexual contact within 60 days before a diagnosis was made or at the onset of symptoms.
Advise patients to abstain from sexual contact until they and their sex partners have finished one of the recommended treatments, and for seven days afterward.

Information from reference 1.

the first prenatal visit.[1] Additionally, any pregnant woman undergoing termination of pregnancy should be tested for chlamydia infection.[25]

There is insufficient evidence to recommend screening in men, although a small number of studies suggest that screening high-risk groups may be useful and cost-effective.[24,26-29] Per the CDC, the screening of sexually active young men should be considered in clinical settings with a high prevalence of chlamydia (e.g., adolescent clinics, correctional facilities, sexually transmitted disease clinics), and in certain groups (e.g., men who have sex with men). In men who have sex with men, some experts recommend screening for rectal infections (a rectal swab in those who have had receptive anal intercourse during the preceding year).[1,11] The CDC includes chlamydia screening with a urine test among the list of annual tests for all men who have had insertive intercourse within the previous 12 months.[1] Testing for *C. trachomatis* pharyngeal infection is not recommended in men who have had receptive oral intercourse.

PREVENTION

There are a number of ways to prevent, or at least significantly reduce, the incidence of genitourinary chlamydia infection. The most definitive methods of prevention are practicing abstinence and being in a long-term, mutually monogamous relationship. Patients should be encouraged to avoid high-risk behaviors such as having unprotected sex or multiple sex partners. In addition, the correct and consistent use of condoms has been shown to reduce the risk of transmission of sexually transmitted diseases. For adolescents who are considered high risk, specific education about the transmission of disease through unprotected vaginal, anal, or oral sex is warranted.[1]

COMPLICATIONS

The health consequences for women who are infected with chlamydia may be substantial and life-threatening. Chlamydia infections put women at an increased risk of developing pelvic inflammatory disease, infertility, or perihepatitis (Fitz-Hugh-Curtis syndrome). Additional negative outcomes include chronic pelvic pain and ectopic pregnancy.

Infection during pregnancy increases the risk of poor outcomes for the fetus. Complications may include miscarriage, premature rupture of membranes, preterm labor, low birth weight, and infant death.[30]

In men, consequences may include epididymo-orchitis, resulting in infertility.[31] A chlamydia infection may also increase a person's susceptibility to HIV, if exposed.[32] For men and women who are already co-infected with HIV, a concurrent chlamydia infection may increase shedding of the virus.[31] Some studies have also documented an association between co-infection, human papillomavirus, and the subsequent development of cervical cancer, although the association is not definitive.[33]

Reactive arthritis (Reiter syndrome), a triad of aseptic arthritis, nongonococcal urethritis, and conjunctivitis, can also occur. Chlamydia-induced reactive arthritis is believed to be underdiagnosed, and emerging data suggest that asymptomatic chlamydia infections may be a common cause.[17] Studies suggest that prolonged antimicrobial therapy, up to six months of combination antibiotics, may be effective.[18]

LYMPHOGRANULOMA VENEREUM

Another sexually transmitted infection caused by *C. trachomatis* (a different serovar) is lymphogranuloma venereum (LGV). It generally presents as a unilateral, tender inguinal or femoral node, and may include a genital ulcer or papule. Anal exposure may result in proctocolitis, rectal discharge, pain, constipation, or tenesmus.[1] If left untreated, it may lead to chronic symptoms, including fistulas and strictures. Diagnosis is based on clinical symptoms and a genital lesion swab or lymph node sample, similar to those used to diagnose the more typical *C. trachomatis* genitourinary infection. Molecular identification may be needed to differentiate LGV from non-LGV *C. trachomatis*. Doxycycline (100 mg twice daily for 21 days) is the preferred treatment. An alternative treatment regimen includes erythromycin (500 mg four times daily for 21 days); azithromycin (1 g once weekly for three weeks) may also be used.[1]

Pulmonary Infection

C. trachomatis is thought to cause about 12,000 cases of neonatal pneumonia per year in the United States.[34,35] Fewer than 10 percent of neonates born to women with active chlamydia infection during labor develop chlamydia pneumonia.[34,35] *C. trachomatis* pneumonia usually manifests one to three months following birth, and should be suspected in a child who has tachypnea and a staccato cough (short bursts of cough) without a fever. Chest radiography may reveal hyperinflation and bilateral diffuse infiltrates, and blood work frequently reveals eosinophilia (400 or more cells per mm^3).[19] In addition, specimens should be collected from the nasopharynx. For neonates who have a lung infection, erythromycin (base or ethylsuccinate, 50 mg per kg daily divided into four doses for 14 days) is the treatment of choice. Follow-up is recommended, and a second course of antibiotics may be required.[19]

Ocular Infection

Ocular *C. trachomatis* infection occurs in three distinct disease patterns: ophthalmia neonatorum/neonatal conjunctivitis, adult inclusion conjunctivitis, and trachoma. Physicians treating immigrant and refugee populations, or those practicing internationally, may encounter chronic trachoma cases and should be familiar with its presentation and management.

OPHTHALMIA NEONATORUM/NEONATAL CONJUNCTIVITIS

This infection is transmitted vaginally from an infected mother, and can present within the first 15 days of life. One-third of neonates exposed to the pathogen during delivery may be affected.[19] Symptoms include conjunctival injection, various degrees of ocular discharge, and swollen eyelids. The diagnostic standard is to culture a conjunctival swab from an everted eyelid, using a Dacron swab or another swab specified for this culture. The culture must contain epithelial cells; exudates are not sufficient.[19]

The recommended treatment is oral erythromycin base or ethylsuccinate (50 mg per kg daily in four divided doses for 14 days).[19] Prophylaxis with silver nitrate solution or antibiotic ointments does not prevent vertical perinatal transmission of *C. trachomatis*, but it will prevent ocular gonococcal infection and should therefore be administered.[1]

ADULT INCLUSION CONJUNCTIVITIS

This acute mucopurulent conjunctival infection is associated with concomitant genitourinary tract chlamydia infection. If the diagnosis is suspected, a specimen from an everted lid collected using a Dacron swab should be sent for culture. Special culture media are required. Treatment consists of doxycycline (100 mg twice daily for one to three weeks) or erythromycin (250 mg four times daily for one to three weeks).[20] According to one study, a single 1-g dose of azithromycin may be just as effective.[21]

TRACHOMA

Trachoma is a chronic or recurrent ocular infection that leads to scarring of the eyelids. This scarring often inverts the eyelids, causing abnormal positioning of the eyelashes that can scratch and damage the bulbar conjunctiva. Trachoma is the primary source of infectious blindness in the world, affecting primarily the rural poor in Asia and Africa.[36] The initial infection is usually contracted outside of the neonatal period. It is easily spread via direct contact, poor hygiene, and flies. Although it has been eradicated in the United States, physicians may encounter cases in immigrants from endemic areas or during global health work.

Treatment has focused primarily on antibiotics *(Table 1*[1,15-22]*)*. Although the World Health Organization has instituted its SAFE (surgery, antibiotics, facial cleanliness, and environmental improvement) program, the large heterogeneity of studies has not clearly identified which of these modalities are most effective at stemming the disease.[22,37] Topical treatment is not effective. Mass community treatment, in which all members of a community receive antibiotics, has been found to be effective for up to two years following treatment, but recurrence and scarring remain problematic.[38]

Data Sources: We performed a Clinical Query PubMed search using the search terms *Chlamydia trachomatis* with limits including: humans, clinical trial, meta-analysis, practice guideline, randomized controlled trial, review, English, and being published within the past five years. The choice of authorship of this review also coincided with the publication of the Centers for Disease Control and Prevention's Sexually Transmitted Diseases: Treatment Guidelines, 2010. Articles referenced in this review were considered. We searched Dynamed, Essential Evidence Plus, the Cochrane Database of Systematic Reviews, the National Guideline Clearinghouse, the Institute for Clinical Systems Improvement, and the U.S. Preventive Services Task Force using the same search terms. Search date: December 16, 2010.

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EDITOR'S CHOICE

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 oropharyngeal infection and 34/35 (97.1%) 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 *Haemophilis ducreyii*. It is the recommended treatment for uncomplicated genital infection with *C trachomatis*[2 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 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 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 520/539 (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.[18] The addition of retrospective data by Habib and Fernando[15] 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 susceptibility 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 al*[4] 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

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

Author and year of publication	Participants	Study design	Azithromycin dose	Sensitivity testing to azithromycin	Bacterial cure rate of evaluable participants	Comments
Handsfield 1994[4]	Male and female STD clinics, USA	RCT versus ceftriaxone	2 g	No	370/374 (98.9%)	Side effects reported by 35.3% (moderate 10.1%; severe 2.9%)
Khaki 2007[5]	Males STD clinic, New Delhi	RCT versus ceftriaxone	2 g	Yes	22/22 (100%)	Side effects <10%—all mild
Lassus 1990[6]	Male and female Helsinki University Central Hospital	RCT versus doxycycline	1 g 500/250/250 mg	Yes	20/20 (100%) 22/22 (100%)	No side effects reported by patients
Steingrimsson 1990[7]	Males + 1 female. STD clinic Reykjavik	RCT versus doxycycline	1 g 500 mg×2 500/250/250 mg	Yes	11/12 (91.7%) 7/8 (87.5%) 7/7 (100%)	Failure MIC 0.125 mg/l Failure MIC 0.5 mg/l Mild sideeffects 8.5%
Odugbemi 1993[8]	Male and female STD clinics Nigeria	Non-comparative	1 g	No	114/120 (95%) Inconsistency of figures in paper	Cure = clinical + bacteriological Gastrointestinal side effects 2.7%—all mild/moderate
Waugh 1993[9]	Male and female, STD clinic Leeds, UK	Non-comparative	1 g	Yes	85/89 (95.5%)	MIC of failures 0.25 mg/l
Steingrimsson 1994[10]	Males only. STD clinic Reykjavik	RCT versus doxycycline	1 g	Yes	27/28 (96.4%)	Failure MIC 0.125 mg/l Side effects 'negligible'
Gruber 1995[11]	Men; STD centre Rijeka, Croatia	RCT versus doxycycline	1 g	No	24/25 (96.0%)	No details on failure. Gastrointestinal side effects 4/66 (6%)
Gruber 1997[12]	Males and females, Rijeka, Croatia	RCT versus ciprofloxacin	1 g	No	48/50 (96.0%)	Gastrointestinal side effects 4/50 (8%)—all mild
Swanston 2001[13]	Male and female STD clinic Trinidad	Non-comparative	1 g	Yes	125/127 (98.4%)	Failures MIC 0.064 mg/l and 0.094 mg/l No side effects
Rustomjee 2002[14]	Symptomatic women. STD clinic Durban, S. Africa	RCT versus ciprofloxacin + doxycycline	1 g	No	30/31 (96.8%)	One failure in dual infected patient. Side effects were 'few and minor'
Habib 2004[15]	Male and female STD clinic Wolverhampton, UK	Retrospective review	1 g	Not stated	168/170 (98.8%)	Failures: 1 'due to azithromycin-resistant strain'; 1 attributed to vomiting soon after 1 g dose

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

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 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 in association with high levels of azithromycin resistance.[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]

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

Author and year of publication	Azithromycin dose	Bacterial cure rate of evaluable participants	Comments
Rectal infection			
Handsfield 1994[4]	2 g	26/27	
Lassus 1990[6]	1 g 500/250/250 mg	1/1 3/3	
Waugh 1993[9]	1 g	4/4	
Total rectal		34/35 (97.1%)	
Pharyngeal infection			
Handsfield 1994[4]	2 g	19/19	
Dan 2006[16]	2 g	20/21	Pre- and post-treatment MIC of failure 0.5 mg/l
Lassus 1990[6]	1 g 500/250/250 mg	1/1 2/2	
Waugh 1993[9]	1 g	2/2	
Steingrimsson 1994[10]	1 g	1/1	
Manavi 2005[17]	1 g	1/1	
Total pharyngeal		46/47 (97.9%)	

EPIDEMIOLOGY 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 ≥1 mg/l.[31] One isolate with an MIC of 2 mg/l and Mtr phenotype was identified among 300 strains collected in 1984 and 1985.[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.[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 ≥2.0 mg/l in 2007.[34]

Cases have been geographically scattered, with the exception of a cluster in Kansas City in 1999/2000.[35] Five isolates with an MIC of 4 mg/l were identified among 91 isolates collected in Cuba between 1995 and 1998.[36] Reduced susceptibility was also reported in isolates from Brazil and Caribbean.[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.[39] In Europe, two isolates with an MIC of 4 mg/l were collected in Spain in 2000 to 2001.[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 2350 isolates (0.3%) were found to have an MIC ≥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 ≥256 mg/l.[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.[42] Azithromycin resistance exceeded 9% in five of seven federal districts in Russia in 2007, with lower levels reported in 2008.[43] Data on resistance in Africa are limited but no azithromycin resistance was identified in Lilongwe, Malawi in 2007.[44]

A strain of *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.[25 45] More recently, high-level azithromycin resistance (MIC ≥256 mg/l) has been identified in Scotland,[46] England and Wales[47] and Italy.[48] High-level azithromycin resistance was first detected in Scotland in 2004 and was present in 33/845 (3.9%) isolates tested in 2007.[46] *N gonorrhoeae* multiantigen 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.[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 *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.[49] Treatment failures in clinical trials and in a series of case reports have not shown pretreatment resistance.[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 *et al* investigated in vitro synergy between azithromycin and cefixime in 25 isolates of *N gonorrhoeae* from male patients with urethritis in Japan.[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 0.03 mg/l) were observed when cefixime was combined with azithromycin. Dual treatment has been advocated for oropharyngeal gonococcal infection.[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 *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.[53 54] 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.[55] These thresholds may not be appropriate for an antimicrobial agent such as azithromycin for which treatment failure does not seem

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 argue against the routine use of azithromycin as single antimicrobial treatment for gonorrhoea.

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