

Update on the Management of Gonorrhea in Adults in the United States

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Gonorrhea, the second most commonly reported notifiable disease, is an important cause of cervicitis, urethritis, and pelvic inflammatory disease. The selection of appropriate therapy for gonorrhea (i.e., safe, highly effective, single dose, and affordable) is complicated by the ability of *Neisseria gonorrhoeae* to develop resistance to antimicrobial therapies. This article reviews the key questions and data that informed the 2006 gonorrhea treatment recommendations of the Centers for Disease Control and Prevention. Key areas addressed include the criteria used to select effective treatment for gonorrhea, the level of antimicrobial resistance at which changing treatment regimens is recommended, the epidemiology of resistance, and the use of quinolones, cephalosporins, and other classes of antimicrobials for the treatment of uncomplicated gonorrhea.

BACKGROUND

Infection with *Neisseria gonorrhoeae*, a gram-negative diplococcus, is an important cause of cervicitis, urethritis, and pelvic inflammatory disease (PID). Infection is less frequently found in the pharynx, rectum, conjunctivae, liver capsule, skin, heart valves, joints, and meninges, or it can be disseminated in the bloodstream. Untreated infection can result in infertility, ectopic pregnancy, and chronic pelvic pain [1]. Infection with *N. gonorrhoeae* has also been associated with increased HIV shedding [2].

Gonorrhea is the second most commonly reported notifiable disease in the United States [3]. In 2004, a total of 330,132 new cases of gonorrhea were reported [4]. The estimated national prevalence of gonococcal infection among persons 14–39 years of age was 0.25% in the National Health and Nutrition Examination Survey (NHANES) and was 0.43% among persons 18–26 years of age in the National Longitudinal Study of Adolescent Health (Add Health) [5, 6]. However, the prev-

alence is higher within specific populations (e.g., 2.1% among black young adults in Add Health) and in some areas (e.g., 5.5% among men 16–24 years of age entering the National Job Training Program in Georgia) [4, 6]. The direct cost of gonorrhea and PID attributable to gonorrhea was estimated to be approximately \$790 million in 1994 dollars [7].

Given the scale of the public health impact of gonorrhea, selection of appropriate therapy for gonorrhea is essential. However, gonorrhea treatment is complicated by the ability of *N. gonorrhoeae* to develop resistance to antimicrobial therapies. To assist clinicians and public health practitioners in the selection of gonorrhea treatment, the Centers for Disease Control and Prevention (CDC) reviews the scientific literature on the treatment of gonorrhea and consults with experts to produce national sexually transmitted disease (STD) treatment guidelines. The present article reviews the key questions and data behind the recommendations in the 2006 CDC STD treatment guidelines for the treatment of *N. gonorrhoeae* infections in adults [8].

METHODS

A Medline search was conducted in February 2005, using PubMed, for articles published since 2000 under the major headings of “gonorrhea/drug therapy,” “gon-

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orrhoea/therapy,” or “*Neisseria gonorrhoeae*/drug effects.” Additional searches were performed for related reports posted on the Internet by internationally recognized public health agencies.

The articles identified through the methods described above were compiled and presented to a panel of expert consultants in April 2005. The panel used evidence-based methods to review the quality of the data that addressed a series of key questions, and it drafted and approved conclusions and recommendations for these key areas. The CDC incorporated these expert consultant recommendations into the revised national STD treatment guidelines published in August 2006 [8]. Although the present article largely reflects material prepared for the April 2005 meeting, Medline searches were updated before guidelines publication, and preliminary 2006 data (January through June 2006) from the Gonococcal Isolate Surveillance Project (GISP) were reviewed. Given the importance of the GISP data, a decision was made to further update the August 2006 published guidelines and include those changes in this article.

WHAT CRITERIA SHOULD BE USED TO SELECT EFFECTIVE TREATMENT FOR GONORRHEA?

It is widely accepted that, whenever possible, the treatment for gonorrhoea should be a safe, highly effective, single-dose, and affordable regimen [9]. The safety and efficacy of gonorrhoea treatment are important because of the large number of patients who are treated for gonorrhoea and the high proportion of them who become reinfected and require repeated courses of therapy [10]. Single-dose oral therapies are recommended to improve patient compliance and to reduce risk of iatrogenic infection associated with the use of injections. The large number of gonorrhoea infections diagnosed and treated each year requires that gonorrhoea therapy be affordable in a wide variety of primary and specialty care settings [4].

The definition of efficacy for the treatment of gonorrhoea, however, has not been easily delineated. The World Health Organization has supported the concept that an efficacious treatment is one that results in $\geq 95\%$ of infections being cured, but it has done so without strongly documented evidence as to the rationale behind the recommendation [9]. The United States has also struggled to define acceptable efficacy for the treatment of gonorrhoea. In 1992, Handsfield et al. [11] recommended that an acceptable clinical efficacy be defined as a cure rate of $\geq 95\%$ with a lower 95% CI of at least 90%. A more stringent criterion for clinical efficacy, defined as a 95% cure rate with a sufficient number of subjects studied to establish a lower 95% CI of $\geq 95\%$ in summed clinical trials, was articulated in a 1995 publication by Moran et al. [12]. At the time this criterion was proposed, there was a wide variety of antimicrobial regimens with summed overall cure rates $>95\%$. Therefore, Moran et al. [12] suggested that limiting recommendations to only those regimens with the optimal perfor-

mance (i.e., those with a lower 95% CI of $\geq 95\%$) would perhaps reduce the risk of therapeutic failure and limit the development of antimicrobial resistance.

The pharmacokinetic profile of a regimen is also important in predicting the efficacy of a regimen. Jaffe et al. [13] found that curing gonococcal urethritis in males by use of penicillin was best predicted when the serum penicillin concentration was 3–4 times the MIC for 7–10 h. Subsequent work has evaluated the applicability of this standard for other gonorrhoea treatment regimens and for populations rather than individuals [11, 12]. It is generally accepted that efficacy of a regimen in a population is likely if the serum concentration of a regimen is at least 4 times the MIC₉₀ for at least 10 h after the peak concentration is reached [12].

The CDC adopted the more stringent clinical efficacy criterion of 95% efficacy with a lower 95% CI of $\geq 95\%$ in the preparation of the 1993, 1998, and 2002 STD treatment guidelines. On the basis of this criterion, ceftriaxone (125 mg intramuscularly [im]), cefixime (400 mg orally [po]), and fluoroquinolones (ciprofloxacin [500 mg po], ofloxacin [400 mg po], and levofloxacin [250 mg po]) were the recommended regimens in the 2002 STD treatment guidelines for the treatment of uncomplicated gonococcal infections of the cervix, urethra, and rectum. All patients treated for gonorrhoea should also be treated with a regimen effective against uncomplicated genital infection with *Chlamydia trachomatis* unless chlamydial infection has been ruled out. Alternative regimens in the 2002 guidelines (spectinomycin [2 g im], ceftizoxime [500 mg im], cefoxitin [2 g im] plus probenecid [1 g po], cefotaxime [500 mg im], gatifloxacin [400 mg po], norfloxacin [800 mg po], and lomefloxacin [400 mg po]) were regimens that may have met the stringent criterion but were more expensive, injectable, or had limited clinical data, compared with the primary recommended regimens. Because of the emergence of quinolone resistance, quinolones were not recommended in 2002 for infections acquired in Asia or the Pacific, including Hawaii, as well as in California and other areas with increased prevalence of quinolone-resistant *N. gonorrhoeae* (QRNG) infection [14]. In 2004, the CDC further recommended limiting quinolone use to heterosexual men and women, on the basis of identification through GISP and other data sources of a high prevalence of QRNG infection among men who have sex with men (MSM) [15].

The recent widespread emergence of QRNG (see further discussion below), combined with the recent unavailability of cefixime [16] and a lack of new therapeutic options for the treatment of gonorrhoea, means that the more stringent US criteria may not allow for the use of oral agents in many settings. In response to these challenges, experts at the 2005 STD treatment guidelines meeting decided that the primary recommended regimens should meet the stringent criteria but that alternative

Table 1. Selected reports of quinolone-resistant *Neisseria gonorrhoeae* (QRNG) published between January 2000 and June 2006, sorted by region, population, and year.

Region and population	Year(s) of data collection	No. of isolates tested	Methodology	Prevalence of resistant isolates ^a	Reference
North America					
Canada	2003	NR	NR	2.0%; "as high as 12.5% in some provinces"	PHAC [20]
Canada	2001	~3000–5000	NR	2.1% (Atlantic Canada, 4.4%; central Canada, 2.1%; western Canada, 2.4%)	Sarwal et al. [21]
Hawaii	2001	267	Agar dilution, disk diffusion, CLSI	20%	Newman et al. [22]
Michigan	2004	540	Disk diffusion, Etest, CLSI	1.5%	Macomber [23]
Michigan	2003	582	Disk diffusion, Etest, CLSI	2.9%	Macomber [23]
United States (GISP)	2004	6322	Agar dilution, CLSI	Overall, 6.8%; MSM, 23.8%; heterosexual men, 2.9%; when data from CA, HI, and MSM were excluded, 1.3%	CDC [24]
South America/Caribbean					
Argentina	2000	1	Agar dilution, CLSI	1 case of QRNG (MIC, 16 µg/mL)	Fiorito et al. [25]
Argentina	1995–1996	81	Agar dilution, CLSI	0%	Famiglietti et al. [26]
Brazil	1998	81	Agar dilution, CLSI	0%	Dillon et al. [27]
Cuba	1995–1999	120	Agar dilution, CLSI	0%	Llanes et al. [28]
Trinidad and Tobago	1999	128	Agar dilution, CLSI	0%	Castor et al. [29]
Trinidad, Guyana, St. Vincent	1994–1995	282	Agar dilution, CLSI	0%	Dillon et al. [30]
Argentina, Chile, Colombia, Peru, Uruguay, and Venezuela	1990–1999	2806	Agar dilution, CLSI	2 resistant isolates in Venezuela in 1995; 2 resistant isolates in Uruguay in 1997	Dillon et al. [31]
Europe					
Austria	2002	202	Disk diffusion, CLSI	59.4%	Uthman et al. [32]
Denmark	1997	177	Agar dilution, CLSI	5.6%	Su and Lind [33]
Denmark	1998	197	Agar dilution, CLSI	6.1% "due to importation of resistant strains"	Su and Lind [33]
England and Wales (GRASP)	2004	1744	Agar dilution	Overall, 14.1%; women, 5.0%; heterosexual men, 10.7%; MSM, 27.1%	GRASP [34]
England, London	2003	952	Agar dilution	7.9%; QRNG is "spreading endemically in high risk groups"	Martin et al. [35]
Finland (FiRe)	1998	118	Disk diffusion, CLSI	5.1%	Nissinen and Huovinen [36]
France (RENAGO)	2001–2003	473	Etest, CLSI	9.7%	Herida [37]
Germany	2004–2005	65	Etest, CLSI	47.7%	Enders [38]

Greenland	1998–1999	61	Agar dilution, Etest, disk diffusion	0%	Dragsted et al. [39]
Ireland	2003–2004	158	Disk diffusion, CLSI	7%	Hopkins [40]
Netherlands	2003	772	Disk diffusion	7.3%; MSM, 10.5%; heterosexual men, 3.4%; women, 0%	Kolader et al. [41]
Netherlands	2004	1529	Disk diffusion, Etest, CLSI, and Dutch guidelines	14.9%	Borgen [42]
Scotland	1999	540	Agar dilution, Etest	2.2%	Forsyth et al. [43]
Sweden	2003	NR	NR	“Increased ciprofloxacin resistance among heterosexual men and women”	Berglund et al. [44]
Sweden	1998–1999	348	Etest	Resistant and intermediate susceptibility: overall, 18%; if exposed in Sweden, 8%; if exposed in Asia, 63%	Berglund et al. [45]
Spain	2001	81	Agar dilution, CLSI	9.9%	Arreaza et al. [46]
Turkey	1998–2002	78	Agar dilution, CLSI	1.3%	Aydin et al. [47]
Africa/Middle East					
Benin	1998–1999	143	Agar dilution	0%	Van Dyck et al. [48]
Morocco	2001	154	Agar dilution, CLSI	2.6%	Alami et al. [49]
Israel	2000	100	Etest, CLSI	61%	Dan et al. [50]
Israel	2000	22	Disk diffusion, Etest, CLSI	54.5%	Yagupsky et al. [51]
Kuwait	2003	44	Disk diffusion, CLSI	36.4%	Sharma [52]
Rwanda	1999–2000	139	Agar dilution, CLSI	0%	Van Dyck et al. [53]
Saudi Arabia	1996–2000	93	Disk diffusion, CLSI	<1%	Balkhy et al. [54]
South Africa, Durban	2005	248	NR	42.0%	Moodley [55]
Asia/Central Asia/South Pacific					
Australia	2005	3886	Agar dilution	28.6%	AGSP [56]
Australia, Victoria	2001	645	Agar dilution, CLSI	11%	Veitch et al. [57]
Bangladesh	2003	63	NR	90.5%	ICDDR,B [58]
China	2002	100	Agar dilution	98%	Fei et al. [59]
India	2000–2001	241	Etest, WHO	67.3%	Bala et al. [60]
Indonesia	1996	267	Agar dilution, CLSI	0%	leven et al. [61]
Indonesia, Bali	2004	147	Agar dilution, CLSI	40.1%	Donegan et al. [62]
Japan	2002	221	Agar dilution	78.3%	Ito et al. [63]
Kyrgyzstan	1999–2000	120	Agar dilution, CLSI	Cpfx resistance, 10.0%; Ofx resistance, 15.0%	Dorlencourt et al. [64]
Mongolia	Before 2001	56	NR	25.0%	Lkhamsuren et al. [65]
Nepal	2003	16	Agar dilution, CLSI	87.5%	Chaudhary [66]
New Zealand	2002	413	Agar dilution	6.8%	Hefferman et al. [67]
Pakistan, Karachi	2002	26	Etest, CLSI	42%	Jabeen [68]
Philippines	1996–1997	115	Agar dilution, Etest	63%	Aplasca De Los Reyes et al. [69]

Taiwan		2003	29	Agar dilution, CLSI	93.1%	Hsueh et al. [70]
Thailand		1999	110	Agar dilution, CLSI	25.4%	Trees et al. [71]
Australia		2004	3542	Various	21.4%	WHO WPGASP [72]
Brunei		2004	113	Various	40.7%	WHO WPGASP [72]
China		2004	1203	Various	94.3%	WHO WPGASP [72]
Hong Kong		2004	2811	Various	94.2%	WHO WPGASP [72]
Japan		2004	261	Various	81.6%	WHO WPGASP [72]
Korea		2004	93	Various	70.0%	WHO WPGASP [72]
Laos		2004	48	Various	88.0%	WHO WPGASP [72]
New Zealand		2004	773	Various	19.1%	WHO WPGASP [72]
Papua New Guinea		2004	92	Various	1.0%	WHO WPGASP [72]
Philippines		2004	175	Various	47.4%	WHO WPGASP [72]
Singapore		2004	160	Various	50.0%	WHO WPGASP [72]
Vietnam		2004	156	Various	52.5%	WHO WPGASP [72]
Bangladesh		1999–2000	110	Disk diffusion, CLSI	76%	Ray [73]
India, Chennai		2001	80	Disk diffusion, CDS	11.2%	Ray [73]
India, New Delhi, SJH		2001	108	Disk diffusion, CDS	88.4%	Ray [73]
India, New Delhi, MAMC		2001	10	Disk diffusion, CLSI	100%	Ray [73]
India, Hyderabad		2001	46	Disk diffusion, CDS	57%	Ray [73]
India, Kolkata		2001	58	Disk diffusion, CLSI	22.4%	Ray [73]
India, Nagpur		2001	74	Disk diffusion, CDS	35.1%	Ray [73]
India, Pune		2001	37	Disk diffusion, CLSI	10.6%	Ray [73]
Nepal		2001	9	Disk diffusion, CLSI	11.1%	Ray [73]
Sri Lanka		2000	235	Disk diffusion, CLSI	8.2%	Ray [73]

NOTE. Italics indicate a ORNG prevalence $\geq 2\%$; bold italics indicate a ORNG prevalence $\geq 5\%$. AGSP, Australian Gonococcal Surveillance Programme; CDS, calibrated dichotomous sensitivity; CLSI, Clinical and Laboratory Standards Institute; Cpfx, ciprofloxacin; FiRe, Finnish Study Group for Antimicrobial Resistance; GISP, Gonococcal Isolate Surveillance Project; GRASP, Gonococcal Resistance to Antimicrobials Surveillance Programme; ICDDR,B, International Centre for Diarrhoeal Disease Research, Bangladesh; MAMC, Maulana Azad Medical College; MSM, men who have sex with men; NR, not reported; Ofx, ofloxacin; PHAC, Public Health Agency of Canada; RENAGO, National Reference Centre for *Neisseria gonorrhoeae*; SJH, Safdarjung Hospital; WHO, World Health Organization; WPGASP, Western Pacific Gonococcal Antimicrobial Surveillance Programme.

^a Data are the percentage of resistant isolates, unless otherwise indicated.

regimens could include those with a clinical efficacy of $\geq 95\%$ and a lower 95% CI of $\geq 90\%$.

AT WHAT THRESHOLD OF ANTIMICROBIAL RESISTANCE SHOULD A TREATMENT REGIMEN BE ABANDONED?

In addition to the intrinsic efficacy of a regimen against fully susceptible strains, selection of a recommended regimen must also take into account the epidemiology of antimicrobial resistance, because infection with a resistant strain can result in treatment failure. The World Health Organization has suggested that an antimicrobial should not be used when $>5\%$ of strains demonstrate resistance [9]. Although, ideally, the assessment of “resistance” would be based on the clinical failure rate, in reality the most readily available data are generally in vitro data, which have a close but not perfect correlation with clinical failure rates. In 1987, in response to an increasing prevalence of penicillinase-producing *N. gonorrhoeae* (PPNG), the CDC proposed lower thresholds for modifying treatment recommendations; such recommendations were based on input from subject-matter experts, because there was a paucity of available evidence [17]. A “nonendemic area” was defined as an area where $<1\%$ of gonorrhea reported in a 2-month period was caused by PPNG. In nonendemic areas, a basic control program (e.g., antimicrobial susceptibility testing of treatment failures and gonococcal isolates from public laboratories and routine treatment with a regimen effective against penicillin-susceptible strains) was sufficient. In “endemic areas,” those areas where $1\%–3\%$ of gonorrhea was caused by PPNG, it was recommended that antimicrobial susceptibility testing of specimens in both private and public laboratories be conducted and that only providers whose patients with gonorrhea were from areas with known increased prevalence of PPNG should be encouraged to switch regimens. A “hyperendemic area” was defined as one in which PPNG accounted for $>3\%$ of all gonococcal strains. In hyperendemic areas, all providers should be encouraged to switch regimens in addition to performing antimicrobial susceptibility testing for all patients. Even in the 1980s, when gonococcal culture was widely used to diagnose gonorrhea, these guidelines were impractical for many areas because they required more knowledge of local susceptibility patterns than was generally available. Although GISP now provides routine susceptibility data from ~ 30 sites around the United States, the dramatic shift in recent years to the use of nonculture techniques for the diagnosis of gonorrhea means that guidelines based on knowledge of prevalence of resistance are still impractical for most areas in the United States [18].

A more comprehensive approach to identifying when to switch treatment strategies requires knowledge of not only the prevalence of resistance but also of other factors, such as gonorrhea prevalence and the cost of drugs and diagnostic testing.

For example, Roy [19] modeled cost-minimizing strategies from the health care system perspective for both diagnosis (culture followed by antimicrobial susceptibility testing vs. non-culture-based testing) and treatment (ciprofloxacin vs. ceftriaxone) of gonorrhea in women. Her analysis suggested that switching from ciprofloxacin to ceftriaxone was optimal when the prevalence of gonorrhea was $>3\%$ and the prevalence of ciprofloxacin resistance was $>5\%$. However, models such as that used by Roy [19] cannot take into account such factors as the benefits of keeping in reserve an already existing antimicrobial agent, such as ceftriaxone, for as long as economically feasible in a setting in which alternative regimens are limited.

On the basis of the evidence and opinions presented above, the CDC STD treatment guidelines expert consultants felt that the CDC should continue to use 5% as the resistance threshold at which an antimicrobial therapy should no longer be routinely recommended. The decision of whether or not to abandon quinolones when QRNG levels are $3\%–5\%$ should take into consideration other factors, such as the prevalence of gonorrhea, costs, and antimicrobial susceptibility monitoring capacity.

SHOULD THE CDC CONTINUE TO RECOMMEND THAT QUINOLONES BE USED FOR THE TREATMENT OF GONORRHEA IN HETEROSEXUALS IN THE UNITED STATES?

A review of published literature and Web-based national reports of the global prevalence of QRNG, sorted by region, is summarized in table 1. The data in this table are notable for the high prevalence of QRNG seen in recent years in Europe, Asia, Central Asia, and the South Pacific. A few countries in Africa and the Middle East have reported high levels of QRNG. However, for these regions, as well as for South America, there are inadequate susceptibility data available (either data are not recent or geographic representation is limited) to be confident that quinolones are appropriate therapy in these regions.

Since 1986, the United States has maintained routine national gonococcal susceptibility surveillance through GISP. In 2004, of 6322 GISP gonococcal isolates, 6.8% were resistant to ciprofloxacin (MICs $>1.0 \mu\text{g}/\text{mL}$). When isolates from California and Hawaii were excluded, 3.6% of isolates were QRNG. QRNG was more common among MSM than among heterosexual men (23.8% vs. 2.9%). In 2004, the prevalence of QRNG among heterosexual men with gonorrhea outside of California and Hawaii was 1.4% [24].

In 2002, the CDC advised that quinolones not be used in California and Hawaii, because of the high prevalence of QRNG in these areas [74, 75]. Increases in QRNG prevalence in other areas of the United States resulted in changes in recommended treatment regimens by other state and local areas. On the basis of a review of 2004 QRNG prevalence data, the CDC recommended that quinolones not be used for the treatment of gon-

Table 2. Oral cephalosporin and macrolide antimicrobials for the treatment of uncomplicated gonococcal infections of the urethra, cervix, or rectum.

Antimicrobial, dose, reference	No. of evaluable patients	No. of patients cured	Patients cured, ^a %	MIC ₉₀ , (mg/L) ²	Time that serum concentration is >4× MIC ₉₀ , h
Azithromycin					
1000 mg					
Vaugh [81]	95	89	93.7
Lassus [82]	29	29	100
Habib and Fernando [83]	170	168	98.8
Swanston et al. [84]	127	125	98.4
Aggregate	421	411	97.6 (95.7–98.9)
2000 mg					
Handsfield [85]	264	262	99.2 (97.3–99.9)
Cefixime					
200 mg ×2					
Deguchi et al. [86]	68	60	88.2 (78.1–94.8)	0.125	9.1
400 mg					
Portilla et al. [87]	92	91	98.9
Handsfield et al. [88]	101	97	96.0
Plourde et al. [89]	121	118	97.5
Kuhlwein and Nies [90]	30	30	100
Ramus et al. [80]	52	50	96.2
Aggregate	396	386	97.5 (95.4–98.8)	<0.001–0.015	20–34
800 mg					
Portilla et al. [87]	54	52	96.3
Handsfield et al. [88]	94	92	97.9
Megran et al. [91]	98	97	99.0
Aggregate	246	241	98.0 (95.3–99.3)	<0.001–0.015	42 to >70
Cefdinir					
300 mg, no published data	≤0.06	≥8
600 mg, no published data	≤0.06	≥11
Cefditoren					
400 mg, no published data	≤1	0
Cefpodoxime proxetil					
200 mg					
Upjohn, unpublished data	274	264	96.4
Das et al. [92]	10	10	100
Aggregate	284	274	96.5 (93.6–98.3)	0.03–2	0–9
400 mg					
Novak et al. [93]	10	10	100 (69.1–100)	0.03–2	0–14
Ceftibuten					
400 mg, Chong et al. [94]	112	110	98.2 (93.7–99.8)	0.15–0.5	7–11
Cefuroxime axetil					
1000 mg					
Das et al. [92]	65	62	95.4
Gottlieb and Mills [95]	29	26	89.7
Kingham et al. [96]	78	77	98.7
Reichman et al. [97]	297	289	97.3
Thorpe et al. [98]	315	298	94.6
Aggregate	784	752	95.9 (94.3–97.2)	0.06–2	1–8

^a For aggregate data (shown in bold), mean (95% CI) is given.

orrhoea among MSM, in areas with increased QRNG prevalence in the United States (e.g., California and Hawaii), or for treatment of infections acquired while traveling abroad [8]. Because oral alternatives to quinolones were limited, and because the QRNG prevalence in 2004 was only 1.4% in GISP among heterosexual men with gonorrhoea outside of California and Hawaii, the 2006 STD treatment guidelines stated that the use of quinolones could be continued for heterosexual men and women in areas and populations in the United States not known to have elevated levels of resistance.

In November 2006, however, 2005 GISP data and preliminary 2006 data (January through June) were available for review; these data documented continued increases in QRNG prevalence among MSM and heterosexual men (updated GISP data are available from [76]). In 2005, 9.4% of GISP isolates were QRNG, and 13.3% were QRNG by June 2006. In 2005, the QRNG prevalence was 29% among MSM and 3.8% among heterosexual men. By June 2006, the QRNG prevalence was 38.3% among MSM and 6.7% among heterosexual men. In 2005, the prevalence of QRNG among heterosexual men with gonorrhoea outside of California and Hawaii was 2.7%; by June 2006, it had risen to 5.1%. Furthermore, in 2004, QRNG was present among heterosexuals in 71% (20 of 28) of GISP sites, and, in 2005, QRNG was present in 89% (24 of 27) of GISP sites, suggesting that the geographic distribution of QRNG among heterosexuals was increasing (CDC, unpublished data). Although all 2006 GISP data in this article are preliminary, it is anticipated that the final 2006 data will continue to show increases in QRNG prevalence.

As a result, the CDC issued revised gonorrhoea treatment guidelines and no longer recommends the use of quinolones for the treatment of gonorrhoea. The CDC Web site [77] and state health department Web sites can be consulted for updated information.

WHAT OTHER REGIMENS SHOULD BE USED FOR THE TREATMENT OF GONORRHEA?

Cephalosporins. Ceftriaxone in a single injection of 125 mg provides sustained, high bactericidal levels in the blood. Extensive clinical experience indicates that ceftriaxone is safe and effective for the treatment of uncomplicated gonorrhoea at all anatomical sites, curing 98.8% (95% CI, 97.9%–99.8%) of uncomplicated urogenital and anorectal infections in published clinical trials [78]. Other single-dose, injectable, safe, and highly effective cephalosporin regimens against uncomplicated urogenital and anorectal gonococcal infections exist (e.g., ceftizoxime [500 mg im], cefoxitin [2 g im] with probenecid [1 g po], and cefotaxime [500 mg im]), but none have substantial advantages over ceftriaxone [8].

Cefixime has an antimicrobial spectrum similar to that of ceftriaxone, but the 400-mg oral dose does not provide a bac-

tericidal level that is as high or as sustained as that provided by the 125-mg dose of ceftriaxone. In published clinical trials, the 400-mg dose of cefixime cured 97.6% (95% CI, 95.7%–98.9%) of uncomplicated urogenital and anorectal gonococcal infections [79]. The advantage of cefixime is that it can be administered orally. The efficacy of cefixime (400 mg po) has also been found in a randomized trial to be similar to that of ceftriaxone (125 mg im) in pregnant women [80].

Single-dose cefixime (400 mg po) is currently the only oral cephalosporin recommended as a primary treatment for gonorrhoea. However, cefixime has not been marketed in the United States since October 2002 [16]. In 2004, Lupin (Mumbai, India) received US Food and Drug Administration approval to manufacture generic cefixime, but only a 1000-mg suspension vial is currently available. The CDC plans to post updates on the availability of cefixime in the United States on its Web site as information becomes available [77].

Use of the less-stringent criterion (i.e., a lower 95% CI $\geq 90\%$) allows several oral regimens to be considered as alternative therapies. A summary of oral cephalosporin and macrolide antimicrobials for the treatment of uncomplicated gonococcal infections of the urethra, cervix, or rectum can be seen in table 2 (consult the CDC Web site for available updates [77]). There is evidence to support cefpodoxime as an alternative treatment option. Cefpodoxime proxetil (200 mg po) is less active against *N. gonorrhoeae* than is cefixime, with cure rates of 96.5% (95% CI, 94.8%–98.9%) for urogenital and rectal infection. However, the efficacy of cefpodoxime proxetil (200 mg) in treating pharyngeal infection is low—78.9% (95% CI, 54.5%–94.0%)—and the pharmacodynamic characteristics are less favorable than those of cefixime and ceftriaxone [79]. The 400-mg oral dose of cefpodoxime has better pharmacodynamic characteristics than the 200-mg dose and, in a study of 10 patients, showed 100% efficacy (95% CI, 69.1%–100%) [93]. A larger clinical study is ongoing to assess whether cefpodoxime proxetil at a dose of 400 mg is an acceptable oral alternative (C. Hall, personal communication). Although cefuroxime axetil (1 g po) meets alternative regimen criteria for urogenital and rectal infection, with an efficacy of 95.9% (95% CI, 94.5%–97.3%), studies of the pharmacodynamics of cefuroxime (1 g po) revealed a duration of free drug concentration higher than the MIC₉₀ that was shorter than that seen with cefpodoxime (400 mg), cefixime (400 mg), or ceftriaxone (125 mg). Such poor pharmacodynamic characteristics led Ison et al. [99] to raise the possibility that continued use may select for stepwise increases in cefuroxime resistance, as occurred with penicillin.

Susceptibility to cephalosporins is assayed in >6000 gonococcal isolates each year by GISP. Only 4 GISP isolates with decreased susceptibility to ceftriaxone have been identified since 1987, with the most recent isolate identified in 1997. The MIC distribution for ceftriaxone has also remained relatively stable

in the United States. Since susceptibility testing for cefixime began in 1992, 45 isolates have demonstrated decreased susceptibility to cefixime, with 2 such isolates found in 2004 [24].

Recent reports from Japan suggest that the MICs of ceftriaxone and other cephalosporins (e.g., cefdinir, ceftazidime, and cefixime) may be increasing [63, 100–104]. Some decrease in susceptibility to cephalosporins was also noted in Denmark and in several countries in the World Health Organization Western Pacific Region (Australia, Brunei, China, and Papua New Guinea) in 2004 [105, 106]. A published description of 3 patients with decreased susceptibility to cefixime in Hawaii in 2002 suggested possible epidemiologic links with Asia [107]. Additionally, some of the *N. gonorrhoeae* strains demonstrating reduced cephalosporin susceptibility have also shown reduced susceptibility to multiple drug classes, such as quinolones, macrolides, penicillins, and tetracyclines [100, 104, 107, 108]. Increasing MICs of broad-spectrum cephalosporins and the emergence of multidrug-resistant strains underscore the importance of continued susceptibility monitoring, cautious use of antibiotics, and development of a wider range of antimicrobial options.

Spectinomycin. Spectinomycin (2 g) has long been recognized as a safe and effective option for treating infection with *N. gonorrhoeae* and has been found to cure 98.2% (95% CI, 97.6%–98.9%) of uncomplicated urogenital and anorectal infections [78]. However, it must be given as an intramuscular injection, can be expensive or difficult to obtain, and has poor efficacy against pharyngeal infection (effectiveness in published trials, 51.8%; 95% CI, 38.7%–64.9%) [78]. Spectinomycin is currently not manufactured in the United States or elsewhere in the world [109]. The CDC plans to post updates on the availability of spectinomycin in the United States on its Web site [77] as information becomes available.

The possible emergence of widespread resistance to spectinomycin is another significant consideration when evaluating the use of spectinomycin for the treatment of gonorrhea. High-level resistance to spectinomycin can be the result of a single-step mutation [110, 111]. Resistance to spectinomycin has been rare in the United States (only 5 isolates were ever identified in GISP through 2004), but the use of spectinomycin is also relatively uncommon (1% of patients in GISP were treated with spectinomycin in 2004) [24]. However, in the mid-1980s, high levels of spectinomycin resistance were documented among US servicemen in Korea, in a setting in which this antimicrobial was widely used [112]. Once widespread use of spectinomycin was discontinued, levels of resistance decreased. In recent years, only occasional isolates resistant to spectinomycin have been identified from any country in the Western Pacific Region [106].

As a result of these considerations, the CDC recommends spectinomycin, if available, as an alternative regimen for the treatment of uncomplicated urogenital or anorectal gonorrhea.

Spectinomycin is useful for the treatment of patients who cannot tolerate cephalosporins and for whom quinolones are not appropriate therapy [8].

Azithromycin. A single 2-g dose of azithromycin administered orally is effective against uncomplicated urogenital gonococcal infection (efficacy, 99.2%; 95% CI, 97.2%–99.9%) (see table 2). However, it is not recommended as a treatment for gonorrhea, because that dose is associated with gastrointestinal tract symptoms in ~35% of patients and is expensive; furthermore, such a regimen produces sustained low levels of drug, a situation considered to be favorable for the induction of resistance in gonococci [85, 113, 114]. Resistance by *N. gonorrhoeae* to macrolide antibiotics, such as azithromycin and erythromycin, has been linked, via in vitro studies and clinical studies, to the multiple transferable resistance (mtr) efflux system, which confers resistance to other hydrophobic agents, such as fecal lipids, detergents, and dyes [115–119].

Some authors have suggested the use of azithromycin (1 g po) [83, 84]. Although better tolerated than 2 g of azithromycin, 1 g of azithromycin (efficacy, 97.6%; 95% CI, 95.7%–98.9%) [79] is not recommended for the treatment of gonorrhea, because several studies have documented treatment failures with that regimen and because this dose raises even greater concerns about possible rapid emergence of antimicrobial resistance than does the 2-g dose of azithromycin [114, 120–123].

Gonococcal isolates with reduced susceptibility or resistance to azithromycin have been documented in many countries. For example, GISP data for 2004 showed a shift toward increasing azithromycin MICs in the United States, and, overall, 6.7% (426 of 6322) of isolates demonstrated decreased susceptibility to azithromycin (MIC, ≥ 0.5 $\mu\text{g/mL}$) [24]. Gonococcal Resistance to Antimicrobials Surveillance Programme data for 2004 demonstrated that 1.8% of all isolates in England and Wales had a MIC ≥ 1 $\mu\text{g/mL}$, ranging from 0% to 6.5% among the regions [34].

Penicillin/tetracycline. Although penicillin was the mainstay of gonorrhea treatment for years, the emergence of PPNG in 1976 and subsequent widespread dissemination of PPNG and chromosomally mediated penicillin resistance has made penicillin an unacceptable treatment for gonorrhea. Tetracycline resistance emerged ~10 years later than penicillin resistance, but it also became widespread enough to prohibit the use of tetracycline for the treatment of gonorrhea [1, 8]. Although resistance to penicillin and tetracycline has decreased from a peak in 1992, overall, ~16% of GISP isolates in 2004 were resistant to penicillin, tetracycline, or both [24].

Other drugs. Despite increasing concerns about gonococcal resistance to all classes of antimicrobials used to treat infections with *N. gonorrhoeae*, very little clinical research has been published in recent years. This literature review identified only 4 prospective clinical trials of antimicrobial therapy for gonorrhea

since 2000. The therapies evaluated were as follows: cefixime (400 mg) in pregnant women, gatifloxacin (400 mg and 600 mg; currently unavailable in the United States; for information on availability, see [124]), nonoxynol-9 gel, and cefodizime (1.0 g intravenously) [80, 125–127]. Only 1 retrospective clinical study of azithromycin (1 g) was performed [83]. In vitro evaluations were published for the following new regimens: cefodizime (1 g), chlorhexidine in vaginal lubricants, ertapenem, faropenem, garenoxacin, gemifloxacin, LBM415 (peptide deformylase inhibitor), plant extracts (*Terminalia macroptera*, *Ocimum sanctum*, *Drynaria quercifolia*, and *Annona squamosa*), porphyrins, metalloporphyrins, sitafloxacin, olamufloxacin, telithromycin, tigecycline, and an array of topical microbicides (see table 3). The small number of published clinical studies and the limited number of in vitro evaluations of antimicrobials outside of the current classes used to treat gonorrhea suggest that inadequate attention is being directed toward the development of new antimicrobials for the treatment of gonorrhea, especially in light of emerging antimicrobial resistance.

SPECIAL SITUATIONS

Pregnancy. Pregnant women should not be treated with quinolones or tetracyclines. As was discussed above, because of high levels of resistance to penicillin, this drug is no longer recommended for the treatment of gonorrhea in any patient. Two clinical trials among pregnant women have been conducted since 2000. One randomized controlled trial among 95 pregnant women found a cure rate of 95% (95% CI, 84.2%–99.4%) for ceftriaxone (125 mg im) and a cure rate of 96% (95% CI, 86.8%–99.5%) for cefixime (400 mg po) [80]. Another randomized controlled trial conducted among 252 pregnant women found a cure rate of 95% (95% CI, 90.6%–99.9%) for ceftriaxone (250 mg im), a cure rate of 89% (95% CI, 82.5%–96.0%) for amoxicillin (3 g po) plus probenecid (1 g po), and a cure rate of 95% (95% CI, 90.6%–99.9%) for spectinomycin (2 g im) [145]. Additional reviews of the treatment of gonorrhea in pregnancy are available [146–148]. On the basis of such data, a pregnant woman infected with *N. gonorrhoeae* should be treated with a recommended or alternative cephalosporin. Women who cannot tolerate a cephalosporin should be treated with spectinomycin, if available, or desensitized for cephalosporins [8, 109]. Updates on the availability of spectinomycin may be found at the CDC Web site [77].

Allergy, intolerance, and adverse reactions. Persons who can not tolerate cephalosporins or quinolones should be treated with spectinomycin, if available. Because spectinomycin is not adequately effective against pharyngeal infections, patients who have suspected or known pharyngeal infection should have a pharyngeal culture evaluated 3–5 days after treatment, to verify eradication of infection [148]. An additional treatment option for patients, including pregnant women, with a documented

history of severe allergic reaction to penicillins or cephalosporins is 2 g of azithromycin.

Adolescents. Fluoroquinolones have not been recommended for persons <18 years of age because studies have indicated that they can damage articular cartilage in some young animals. However, no joint damage attributable to quinolone therapy has been observed in children treated with prolonged ciprofloxacin regimens [149]. Thus, children who weigh >45 kg can be treated with any regimen recommended for adults.

HIV infection. Little has been published in recent years about the presentation or response to treatment of gonorrhea in patients with HIV infection. There are no data to suggest that complications of gonorrhea are more common among patients with HIV infection than among those without HIV infection [150]. Patients who have gonococcal infection and also are HIV positive should, therefore, receive the same treatment regimen as those who are HIV negative.

GONOCOCCAL INFECTIONS OF THE PHARYNX

Gonococcal infections of the pharynx are generally asymptomatic [151–153]. Several recent studies have identified a high prevalence of asymptomatic gonococcal infections of the pharynx in specific populations, such as MSM, STD clinic patients, and HIV-positive patients. [154–159]. These studies highlight the importance of having patients who report a history of unprotected oral sex undergo testing for gonococcal infections of the pharynx.

Gonococcal infections of the pharynx are more difficult to eradicate than infections at urogenital and anorectal sites [160]. A recent review found that few antimicrobial regimens reliably cure >90% of infections [148]. On the basis of available data, it is recommended that heterosexual patients be treated with ceftriaxone (125 mg im) for gonococcal infections of the pharynx [8]. MSM and patients with a history of recent travel who are being treated for gonococcal infections of the pharynx should receive ceftriaxone (125 mg im) because of the high prevalence of QRNG in this population. As was noted above, spectinomycin does not adequately treat gonococcal infections of the pharynx and should not be used if pharyngeal gonorrhea is likely. Limited data suggest that 2 g of azithromycin may also be an option for treatment of gonococcal infections of the pharynx [161]. Although chlamydial coinfection of the pharynx is unusual, coinfection at genital sites sometimes occurs. Therefore, treatment for both gonorrhea and chlamydia is recommended.

GONOCOCCAL INFECTIONS OF THE RECTUM

Anogenital gonorrhea is frequently asymptomatic but may present with a wide range of symptoms, from mild pruritis or tenesmus to overt proctitis. Approximately 35%–50% of women with gonococcal cervicitis are also infected in the rec-

Table 3. New gonorrhea therapies under investigation that are not currently included in the Centers for Disease Control and Prevention sexually transmitted diseases treatment guidelines as recommended or alternative therapies for uncomplicated gonorrhea infection, appearing in studies published between January 2000 and June 2006, sorted alphabetically.

Antimicrobial (dose), reference	Study design	Study population/ setting	Outcomes measures	Reported findings
Cefodizime (1 g iv) Matsumoto et al. [127]	Clinical trial	Japan; 72 patients with urethritis or cervicitis	Negative culture results 3–14 days after treatment	All patients had negative <i>Neisseria gonorrhoeae</i> culture results at follow-up and were clinically cured
Tanaka et al. [102]	In vitro	Japan; in 2000, 100 isolates; in 1995, 55 isolates	MIC ₅₀ and MIC ₉₀ via agar dilution	Ceftriaxone (1 g) and cefodizime (1 g) appear to be the most favorable single-dose regimens for the treatment of gonorrhea in Japan
Chlorhexidine (in vaginal lubricants), Rabe and Hillier [128]	In vitro	...	Minimum bactericidal concentration over a pH range of 4–8 with or without blood present	MIC of 25 µg/mL at 30 min and 12.5 µg/mL at 1–2 h; may be appropriate topical microbicide for prevention of gonorrhea; pH and blood affect activity
Ertapenem (im), Livermore et al. [129]	In vitro	652 GRASP isolates, some QRNG	MICs compared with ceftriaxone	90% of MICs were 0.002–0.06 µg/mL; the highest MIC was 0.25 µg/mL; ceftriaxone retained slightly superior activity
Faropenem (po), Jones [130]	In vitro	76 Japanese isolates, 189 US isolates, some QRNG and PPNG	MIC ₅₀ and MIC ₉₀ via agar dilution	MIC ₅₀ of 0.06 µg/mL; MIC ₉₀ of 0.25 µg/mL; less than ceftriaxone but better than cefuroxime and all other agents tested
Garenoxacin (400 mg, BMS 284756), Deshpande et al. [131]	In vitro	137 Japanese, Dutch, and US isolates with some QRNG	MIC ₅₀ and MIC ₉₀ via agar dilution, disk diffusion, and Etest	Activity comparable or 2-fold superior to ciprofloxacin, even for QRNG strains
Gemifloxacin				
Jones et al. [132]	In vitro	150 Japanese, Dutch, and US isolates, some QRNG	MIC ₅₀ and MIC ₉₀ via agar dilution, disk diffusion, and Etest	Overall MIC ₉₀ of 0.12 µg/mL, superior to all other quinolones
Ruiz et al. [133]	In vitro	31 Spanish isolates	MIC ₅₀ and MIC ₉₀ via agar dilution	MIC ₉₀ of 0.06 µg/mL, equal to that of trovafloxacin and moxifloxacin, but lower than that of ciprofloxacin and levofloxacin (MIC ₉₀ , 0.12 µg/mL)
Tanaka et al. [134]	In vitro	Japan; 1992–1993: 94 isolates; 1996–1997: 100 isolates	MIC ₅₀ and MIC ₉₀ via agar dilution	1992–1993: MIC ₉₀ of 0.03 µg/mL; 1996–1997: MIC ₉₀ of 0.125 µg/mL; ciprofloxacin-resistant strains: MIC ₉₀ of 2.0 µg/mL, lower than for other quinolones tested
Berron et al. [135]	In vitro	400 Spanish isolates, 1992–1999	MIC ₅₀ and MIC ₉₀ via agar dilution	Gemifloxacin more active than other quinolones; MIC ₉₀ of 0.007 µg/mL
Pottumarthy et al. [136]	In vitro	50 Japanese QRNG strains, 176 American strains, 24 international strains	MIC ₅₀ and MIC ₉₀ via agar dilution	Gemifloxacin more active than older quinolones, penicillin, and tetracycline; MIC ₉₀ of 1.0 µg/mL
LBM415 (peptide deformylase inhibitor), Jones [137]	In vitro	157 international isolates	MIC ₅₀ and MIC ₉₀ via agar dilution	MIC ₅₀ of 4 µg/mL; MIC ₉₀ of 8 µg/mL; all comparison agents more active than LBM415

Nonoxonyl-9 gel, Roddy et al. [126]	Randomized controlled trial	Cameroon, sexually active women who were not sex workers	Event rate (gonorrhoea and/or chlamydia) per 100 person-years for gel and condom vs. condom only	Gel and condom: 43.6 cases/100 person-years; condom only: 36.6 cases/100 person-years; nonoxonyl-9 did not protect against gonorrhoea and chlamydia
<i>Ocimum sanctum</i> , <i>Dryaria quercifolia</i> , <i>Annona squamosa</i> , Shokeen [138]	In vitro	Isolates from 24 male patients with urethritis in India, 6 WHO strains	Disk diffusion	All WHO strains tested were susceptible to extracts of all 3 plants, all clinical isolates were susceptible to extracts of <i>O. sanctum</i> and <i>D. quercifolia</i> , and 22 clinical isolates were susceptible to extracts of <i>A. squamosa</i>
Porphyrins and metalloporphyrins, Bozja [139]	In vitro and mouse model	8 laboratory strains	Agar dilution to determine MIC inhibiting all growth	Porphyrins and metalloporphyrins found to have potent bactericidal action in vitro against <i>N. gonorrhoeae</i> and <i>Haemophilis ducreyi</i> and no bactericidal activity against 5 species of lactobacilli; also blocked gonococcal infection in murine vaginal model, suggesting potential development as a topical microbicide
Sitafloxacin (200 mg), olamufloxacin (HSR-903) (200 mg), Tanaka et al. [140]	In vitro	85 Japanese isolates	MIC ₅₀ and MIC ₉₀ via agar dilution	Sitafloxacin (MIC ₉₀ of 0.25 µg/mL) and olamufloxacin (MIC ₉₀ of 0.5 µg/mL) more potent than other fluoroquinolones
Telithromycin, Muratani [141]	In vitro	212 Japanese isolates	MIC ₅₀ and MIC ₉₀ via agar dilution	MIC ₅₀ of 0.125 µg/mL, MIC ₉₀ of 0.25 µg/mL; MIC similar to that of cefixime and lower than that of erythromycin, clarithromycin, minocycline, and levofloxacin
<i>Terminalia macroptera</i> leaves, Silva et al. [142]	In vitro	9 Portuguese isolates	MIC ₁₀₀ via agar dilution	Antibiotic activity comparable to that of penicillin and tetracycline; MIC ₁₀₀ of 100–200 µg/mL
Tigecycline (GAR-936), Despande et al. [143]	In vitro	120 international strains	MIC ₅₀ and MIC ₉₀ via agar dilution	Activity 4-fold superior to that of tetracycline; all isolates with reduced susceptibility to tetracycline were inhibited by ≤1 mg/L
Topical microbicides, Spencer et al. [144]	Mouse model	7 isolates tested at least twice per microbicide	Culture positive 5 days after exposure	Significant protection compared with control and no treatment: Carraguard, ^a UsherCell, ^b and T-PSS; significant protection compared with no treatment but not compared with control: PRO-200, ^c ACIDFORM, ^d and CAP

NOTE. CAP, cellulose acetate phthalate; GRASP, Gonococcal Resistance to Antimicrobials Surveillance Programme; im, intramuscularly; iv, intravenously; po, orally; PPNG, penicillinase-producing *Neisseria gonorrhoeae*; QRNG, quinolone-resistant *Neisseria gonorrhoeae*; T-PSS, polysodium 4-styrene sulfonate; WHO, World Health Organization.

^a Sulfated carrageenan gel (3%) being developed by the Population Council.

^b Sodium cellulose sulfate-based gel; proprietary formulation developed by Polydex Pharmaceuticals.

^c Naphthalene sulfonate polymer manufactured by Indevus Pharmaceuticals.

^d Developed by Program for the Topical Prevention of Conception and Disease, manufactured by Ao Pharmaceutico.

tum, and ~25% of MSM with gonorrhea at any anatomical site are infected in the rectum [1]. Current data support treating anorectal gonococcal infections with the regimens used to treat urogenital gonococcal infections [160].

FOLLOW-UP

Patients who have uncomplicated gonorrhea and who are treated with any of the recommended or alternative regimens do not need a test of cure to confirm that they are cured. Patients who have symptoms that persist after treatment should be evaluated by culture for *N. gonorrhoeae*, and any gonococci isolated should be tested for antimicrobial susceptibility. Persistent urethritis, cervicitis, or proctitis may also be caused by *C. trachomatis* or other organisms.

The high frequency with which patients with *N. gonorrhoeae* infection have a repeat infection diagnosed has been recognized for many years [162]. A large number of recent studies have also documented a high prevalence or incidence of *N. gonorrhoeae* infection among patients who have had gonorrhea in the preceding several months [163–176]. Most infections identified after treatment with one of the recommended regimens likely result from reinfection rather than treatment failure, indicating a need for improved patient education and referral and treatment of sex partners. Although the impact of repeat gonorrhea infection is unclear, repeat chlamydial infection confers an elevated risk of PID and other complications, compared with initial infection, and repeated episodes of PID increase the risk of infertility [177, 178]. Clinicians should consider advising all patients with gonorrhea to be retested 3 months after treatment. The 3-month interval was recommended on the basis of a desire to conform to repeat testing recommendations for chlamydial infections [14] and the limited data on the incidence of repeat gonorrhea infection in the studies referenced above. Given the limited evidence behind this recommendation, if patients do not present for retesting in 3 months, providers are encouraged to repeat testing of patients whenever they next present for care within the following 12 months, even if the patient believes that their sex partners were treated. Retesting (i.e., repeat testing several weeks to months after treatment) is distinct from a test of cure to detect therapeutic failure, which is not recommended.

MANAGEMENT OF SEX PARTNERS

Effective clinical management of patients with treatable STDs requires treatment of the patients' recent sex partners to prevent reinfection and curtail further transmission. Patients should be instructed to refer their sex partners for evaluation and treatment. All sex partners of patients who have *N. gonorrhoeae* infection should be evaluated and treated for *N. gonorrhoeae* and *C. trachomatis* infections if their last sexual contact with the patient was within 60 days before the onset of symptoms

or diagnosis of infection in the patient. If a patient's last sexual intercourse occurred >60 days before onset of symptoms or diagnosis, the patient's most recent sex partner should be treated. Patients should be instructed to avoid sexual intercourse until therapy is completed and until they and their sex partners no longer have symptoms.

For patients with gonorrhea whose partners' treatment cannot be assured or is unlikely, delivery of antibiotic therapy for gonorrhea and chlamydia (either a prescription or medications) by heterosexual male or female patients to their partners is an option (this is also referred to as "patient-delivered therapy"). Use of this approach [169, 179] should always be accompanied by efforts to educate partners about symptoms, to encourage partners to seek clinical evaluation, and to inquire about partner preexisting drug allergies. Male patients should be instructed to inform their female partners about the importance of still seeking medical care to be evaluated for PID. Possible undertreatment of PID in female partners and possible missed opportunities to diagnose other STDs are of concern and have not been evaluated in comparisons of patient-delivered therapy and partner referral. Patient-delivered therapy for patients with gonorrhea should routinely include treatment for chlamydia. This approach should not be considered to be a routine partner management strategy in MSM, because of the risk of comorbidity with undiagnosed HIV infection or other STDs.

FUTURE RESEARCH

Further research is needed to guide future recommendations for the optimal management of gonorrhea. A proposed research agenda includes the following questions: (1) What impact does routine cotreatment for gonorrhea and chlamydia have on gonococcal resistance? (2) What is the efficacy of cefpodoxime (400 mg po in a single dose) for urogenital, anorectal, and pharyngeal gonorrhea? (3) Are there other oral antimicrobials or combinations of antimicrobials that are efficacious for the treatment of urogenital and anorectal gonorrhea? (4) Are there alternative, more efficacious antimicrobials for the treatment of pharyngeal gonorrhea?

SUMMARY

To assist clinicians and public health practitioners, the CDC treatment guidelines strive to identify safe, highly effective, single-dose, oral, available, and affordable treatment for gonorrhea. Because of the ability of *N. gonorrhoeae* to develop resistance to antimicrobial therapy, guidelines for the treatment of gonorrhea will require ongoing review of global surveillance and clinical research.

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