ANTIBIOTIC-RESISTANT STRAINS OF *NEISSERIA GONORRHOEAE*

Policy Guidelines for Detection, Management, and Control

These policy guidelines for the detection, management, and control of antibiotic-resistant strains of Neisseria gonorrhoeae *were established after careful deliberation by a group of experts* and staff of the Centers for Disease Control (CDC). The comments received after preliminary documents were circulated among a large group of public health professionals were also considered. Certain aspects of these guidelines represent the best judgment of experts. The guidelines should not be construed as rules, but rather as a source of guidance within the United States. This is particularly true for topics that are based on limited data.*

1. Introduction

1.1 Background

Although most strains of *Neisseria gonorrhoeae* in the United States are susceptible to a broad range of antimicrobial agents, relative or absolute resistance to some agents, especially penicillin, is a rapidly growing problem. With the introduction and regular use of sulfonamide and penicillin in the 1940s and 1950s, progressive resistance to these drugs evolved. The recommended therapeutic dose of aqueous procaine penicillin G for uncomplicated gonorrhea rose from 200,000 units in 1945 to 4.8 million units in 1972 — a 24-fold increase. Since the emergence of plasmid-mediated resistance to penicillin (penicillinase-producing *Neisseria gonorrhoeae,* PPNG) in 1976, clinically significant resistance has been described for the three most widely used classes of drugs — the penicillins, the tetracyclines, and the aminoglycosides.

Antimicrobial resistance in the gonococcus can be plasmid-mediated, chromosomally mediated, or both. In the United States, many variations have been identified. The three most important, from a public health standpoint, are PPNG; chromosomally mediated resistance to penicillin (CMRNG); and plasmid-mediated, high-level tetracycline resistance (TRNG).

1.1.1 PPNG

PPNG are gonococcal strains that have acquired an extrachromosomal element or plasmid that encodes for beta-lactamase, an enzyme that destroys the beta-lactam ring of penicillin. Of the resistant strains, PPNG has had the greatest impact on public health programs and resources in the mid-1980s. The first case of PPNG in the United States was reported in March 1976. Incidence rose slowly through 1979, and most infections were acquired outside the United States or could be traced to imported cases. From 1980 through 1982, reported incidence rose rapidly, and most cases were no longer linked to foreign travel.

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Over 4,500 cases of PPNG were reported in 1982. The incidence dropped in 1983 to below 3,800 cases, but rose again in 1984, nearly reaching the 1982 level. In 1985, reported cases more than doubled, reaching over 8,800. The only states in 1985 that did not report at least one case of gonorrhea caused by a resistant strain were Nevada and South Dakota. In 1986, only Nevada reported no cases. In that year, the total number of cases for the United States was 16,648.

1.1.2 CMRNG

Unlike strains with plasmid-mediated resistance, strains with chromosomal resistance to penicillin do not produce beta-lactamase. Chromosomally mediated resistance is not limited to penicillin, but is a more general phenomenon that can include resistance to tetracycline, the cephalosporins, spectinomycin, and other aminoglycosides. In most instances to date, these strains have not been associated with treatment failure, either because the levels of resistance have not been high or because the antibiotic in question was not used for therapy.

The first outbreak of gonorrhea in the United States caused by strains with high-level chromosomal resistance to penicillin occurred in North Carolina in 1983. Since then, similar organisms have been reported from several areas. Between January 1983 and October 1984, reports of 185 CMRNG cases were received from 22 states other than North Carolina. Testing for high-level chromosomal resistance to penicillin is still not widespread, however, and the true scope of the problem remains unclear.

1.1.3 TRNG

Gonococcal isolates with plasmid-mediated, high-level resistance to tetracycline (minimum inhibitory concentration $\geq$16 μg/ml) were first identified in 1985. Although many individual cases and clusters of TRNG have since been reported, investigation has shown that in most instances, CDC treatment guidelines were followed regarding dual therapy with penicillin and tetracycline, thus avoiding therapy failure. For nearly all patients with TRNG who have been treated with tetracycline alone, the therapy has not been effective.

1.2 Rationale for Action

No clinical distinctions occur between the infections caused by resistant strains of *N. gonorrhoeae* and the infections caused by sensitive strains. In a community with a high prevalence of resistant strains, however, the sequelae of acute gonococcal infection, such as pelvic inflammatory disease (PID), gonococcal ophthalmia, and disseminated gonococcal infection (DGI), are likely to increase as the numbers of preventable conditions of the "inadequately treated" are added to those of the "never treated." Inadequate therapy can also result in an extended period of infectiousness and an increase in the number of sex partners who become infected.

Resistant strains of *N. gonorrhoeae* in a community also have an adverse impact on the costs of patient management — additional laboratory tests, added drug costs, extra clinic visits, and more extensive disease intervention activities. Although some of these costs (e.g., alternative drugs) are more directly attributable to antimicrobial resistance than others (e.g., the costs of supervising disease intervention specialists), the aggregate fiscal impact on the public health budget of an infected area is substantial.

The goal of these guidelines is to reduce the adverse health and financial consequences of gonorrhea through limiting the transmission of those strains that are resistant to one or more antimicrobial drugs. Success will depend on the accomplishment of a wide variety of complementary activities at the program management, laboratory, clinic, and community levels.

1.3 Scope and Approach

These policy guidelines are divided into four sections: surveillance, control, laboratory methods, and treatment. Within each section, several alternatives may be suggested for each recommended course of action. A preferred alternative is often identified as such; however, varied legal, fiscal, demographic, and other factors will determine which options are preferable for specific localities.

A graduated approach is recommended for many of the program elements discussed in these guidelines. This strategy emphasizes different degrees and types of activities to be implemented as specific prevalence levels of PPNG are reached in a community. Three levels of response are proposed on the basis of the percentage of all gonorrhea caused by beta-lactamase-producing strains (PPNG) reported in a 2-month period: <1%, 1%-3%, and >3% (see **CONTROL** section, 3.1 Levels of Control Activity). For such a strategy to be effective, a sensitive management information system needs to be established and maintained in addition to disease surveillance systems based on clinical diagnoses and laboratory tests (see **CONTROL** section, 3.2 Management Information System). The utility of this approach for controlling CMRNG and TRNG has not been established.

2. Surveillance

Surveillance for antibiotic-resistant gonorrhea must fulfill two requirements: 1) surveillance data must be processed with little or no delay, and 2) a system must be in place for the prompt review and analysis of data so that appropriate adjustments can be made in disease intervention activities and therapy recommendations.

2.1 Testing

At the local level, the primary aim of surveillance is to detect PPNG. Although detection of all types of resistance is ideal, the technical difficulties and costs of performing disk-diffusion and agar-dilution susceptibility tests often preclude comprehensive surveillance for CMRNG and TRNG. The following stratified approach is recommended:

- All isolates of *N. gonorrhoeae* should be tested for beta-lactamase production.
- If a sexually transmitted disease (STD) project area cannot arrange for TRNG and CMRNG testing of all isolates, selected priority isolates should be tested. Priority isolates are of two kinds:
  1. Positive post-treatment isolates, isolates from patients with DGI, and isolates from patients with gonococcal ophthalmia. A determination of susceptibility in these instances may have direct impact on the clinical course of the case.
  2. Isolates from members of specific risk groups that are known to have a high incidence of infection with resistant strains. These groups should be determined locally on the basis of the epidemiologic data compiled in a management information system (see **CONTROL** section, 3.2 Management Information System).

Adequate surveillance depends upon laboratory support. STD programs need to ensure that appropriate funds are maintained for performing these procedures. In areas with a low incidence of gonorrhea, the establishment of multistate regional laboratories for testing should be considered.

2.2 Reporting of Gonorrhea

A useful surveillance system must be both representative and timely. A surveillance system that is representative must accurately observe over time 1) the occurrence of a health event and 2) the distribution of that event within the population. "Timeliness" is a qualitative

measure of the period between the occurrence of a health event and the report of that event to the public health agency responsible for instituting control and prevention measures. Gonorrhea caused by antibiotic-resistant strains usually occurs within the same population groups as gonorrhea caused by penicillin-sensitive strains. To attempt to disrupt the transmission of resistant strains without having knowledge of the total community burden of gonococcal infections would be unrealistic. A gonorrhea morbidity reporting system that is incomplete, or slow, or that excludes the private sector would be of little or no value in designing, implementing, and appropriately modifying an effective control program. To be of value in controlling antibiotic-resistant strains, a local gonorrhea morbidity reporting system must 1) include cases reported by emergency rooms, community clinics (both government and non-government), private physicians, and the military; 2) provide basic demographic information on patients; and 3) limit to 14 calendar days the period from provider's diagnosis to the first aggregation of data by the responsible public health agency. Laboratories should report infections caused by antibiotic-resistant strains by telephone the same day they are identified.

2.3 Building a Local Surveillance Network

Data on the rates of gonococcal resistance in the United States are derived primarily from cases seen in public health clinics. The coordination of individual STD project areas with other components of the health-care system will greatly increase surveillance effectiveness. Some of the more important of these components are:

- United States military preventive medicine commands.
- Health maintenance organizations, community health centers, and correction/detention facilities.
- Large commercial laboratories serving the private sector.
- Professional medical groups and organizations, such as the College of American Pathologists, local and state medical societies, and specific groups of hospital staff members.

2.4 National Surveillance of Antimicrobial Resistance

National surveillance of antimicrobial-resistant strains of *N. gonorrhoeae* will be conducted through a Gonococcal Isolate Surveillance Project, which is being implemented by the Division of Sexually Transmitted Diseases and the Sexually Transmitted Diseases Laboratory Program, CDC. This system will test approximately 400 cultures per month from clinical gonorrhea cases in 20 participating cities. A broad range of antimicrobial susceptibilities will be determined by using a reference method. Quarterly reports summarizing the trends in national *N. gonorrhoeae* resistance will be prepared and published.

3. Control

With the increasing proportion of gonorrhea in the United States caused by PPNG, every health jurisdiction must have surveillance, patient-care, and outbreak-management procedures in place to identify new cases rapidly and thereby limit transmission. Different strategies and mixes of control efforts will be needed in different areas. In addition to incidence and prevalence levels, other factors that must be considered in the design of control efforts include 1) available resources, 2) total and "at-risk" population sizes and characteristics, 3) travel patterns of infected persons, and 4) proximity of the locality to known endemic areas.

The success of disease intervention efforts is directly related to the availability of adequate resources. The greatest impact on disease incidence is achieved when intervention personnel are effectively mobilized before resistant strains become thoroughly "seeded" in traditional gonorrhea core areas. STD control programs should concentrate staff and other

resources in the specific neighborhoods reporting cases of PPNG. In the absence of reported cases of PPNG, staff members need to be concentrated in the neighborhoods traditionally reporting a high incidence of gonorrhea and other STDs.

To enhance monitoring and to focus control efforts, each STD project area should evaluate PPNG 1) using an area no larger than a local health jurisdiction (county, health district, or area served by clinic) for the analysis and 2) on the basis of prevalence, or the percentage of all reported cases of gonorrhea in the area that are caused by beta-lactamase-producing strains.

3.1 Levels of Control Activity

Multiple STD program elements are involved in controlling antibiotic-resistant strains of *N. gonorrhoeae*. Three levels of activity are proposed for each element, corresponding to the proportion of all gonorrhea in the target area that is caused by PPNG during a 2-month period (Table 1). The 2-month period and the PPNG proportion cutoff levels (<1%, 1-3%, >3%) were derived empirically from a review of county-specific PPNG morbidity data reported to the Division of Sexually Transmitted Diseases, CDC, from January 1985 through September 1986.

Non-Endemic areas

A basic control program should be in place in all areas, **REGARDLESS OF WHETHER RESISTANT STRAINS HAVE BEEN DETECTED.** The basic control program is appropriate for non-endemic areas, which are defined as locales in which <1% of gonorrhea reported in a 2-month period is caused by PPNG. In Table 1, this level of activity is described in the left-hand column.

Endemic areas

Activities in addition to those of a basic program should be undertaken in endemic areas, defined as locales in which 1%-3% of gonorrhea reported in a 2-month period is caused by PPNG. The purpose of the additional activities is to focus existing STD control resources on PPNG and intercept the spiraling trend before a hyperendemic level is reached. In Table 1, this level is described by the combination of the left and center columns. The efficacy of these activities in controlling CMRNG and TRNG has not been shown.

Hyperendemic areas

Some different activities are appropriate for hyperendemic areas — those in which more than 3% of the gonorrhea cases reported in a 2-month period are caused by PPNG. In a hyperendemic area, an antibiotic effective against resistant strains should be provided to ALL patients with gonorrhea. Because of this treatment policy, intervention priorities should be based not on the laboratory identification of PPNG, but rather on epidemiologic profiles of high-risk gonorrhea patients. In Table 1, this level is described in the right-hand column. The efficacy of these activities in controlling CMRNG and TRNG has not been shown.

3.2 Management Information System

The success of any STD program in controlling PPNG (as well as other STDs) depends on accurate information, adequate resources, and the energetic application of proven control methods. Accurate information is the keystone. Each STD control program needs a data collection system that permits the quick retrieval of complete information on patients. Hence, every STD program should maintain a continually updated database for all reported cases of PPNG. At a minimum, this database should reflect the demographic characteristics, disease-intervention data, and risk-factor information that can be used to develop patient profiles for the high-risk population. When all relevant information is computerized, timely decisions on prevention and control can often be put into effect before an endemic situation develops.

TABLE 1. Elements of PPNG control for state and local STD programs

Element	Non-endemic areas (PPNG <1%) Basic control program	Endemic areas (PPNG 1% – 3%) Basic control program PLUS	Hyperendemic areas (PPNG >3%) Intensified/targeted program
Management information system	Develop a high-risk patient profile. Identify geographic target areas. Identify key providers. Track impact (individual and collective) of Disease Intervention Specialists (DIS).		Maintain the management information system of a basic program.
GC* culturing	Include: known exposures to PPNG, GC treatment failures, all females <30 years of age seen in STD clinics and at GC screening sites, as well as those with clinical or epidemiologic justification seen by a) public and private primary care providers in high-GC-incidence areas and b) detention centers, and all exposed and/or symptomatic individuals with history of recent travel to endemic or hyperendemic areas or with history of contact with a prostitute.	Include: all males seen in STD clinics, as well as those with clinical or epidemiologic justification seen by a) public and private primary care providers in high-GC-incidence areas and b) detention centers, all male urethritis patients in high-GC-incidence areas, and all females 30-44 years of age seen in STD clinics.	Include: GC treatment failures, selected high-risk asymptomatic persons in appropriate health care settings, and periodic representative samples of GC patients from both high- and low-incidence areas for monitoring trends.

*Gonorrhea

TABLE 1. Elements of PPNG control for state and local STD programs (continued)

Element	Non-endemic areas (PPNG <1%) Basic control program	Endemic areas (PPNG 1% – 3%) Basic control program PLUS	Hyperendemic areas (PPNG >3%) Intensified/targeted program
Testing for antimicrobial resistance	Test all GC isolates in public and military laboratories for β-lactamase production; further test all positive test-of-cure (TOC), ophthalmia, and DGI isolates for antimicrobial sensitivity.	Test all GC isolates in private laboratories for β-lactamase production. Test all isolates from children and PID patients for antimicrobial sensitivity.	Test all GC isolates for β-lactamase production. Also test isolates from periodic representative samples for resistance to public STD clinic's drug of choice for uncomplicated GC.
GC screening quality assurance	Determine monthly smear-culture correlations for all STD clinics. Conduct a semiannual quality assurance (QA) review of all STD clinics and screening sites. Conduct a semiannual QA review of hospitals and GC screening sites with their own laboratories. Offer annual QA review service to other providers testing in volumes of >20/ month.	Replace annual QA reviews of other providers doing GC testing with a system of ongoing voluntary self-assessment with mail-in reports.	Conduct all standard activities of a basic program.
Reporting	Ensure that ALL laboratories report PPNG isolates by telephone the same day they are identified.	Initiate active surveillance of key private providers.	Ensure that ALL laboratories report PPNG isolates by telephone the same day they are identified.

TABLE 1. Elements of PPNG control for state and local STD programs (continued)

Element	Non-endemic areas (PPNG <1%) Basic control program	Endemic areas (PPNG 1% – 3%) Basic control program PLUS	Hyperendemic areas (PPNG >3%) Intensified/targeted program
Treatment	Observe CDC guidelines for prevention and treatment of GC in all STD clinics. Inform all other providers of CDC Treatment Guidelines, and periodically monitor their GC treatment practices. Review all PPNG cases to ensure proper treatment. Selectively treat for PPNG all patients at STD clinics who meet the PPNG patient profile developed through the management information system.	Urge selected providers in PPNG-affected neighborhoods to treat all GC initially with recommended anti-PPNG regimen. Treat with recommended anti-PPNG regimen all GC patients in STD clinics who meet PPNG patient profile.	Provide anti-PPNG therapy as primary regimen for prevention or treatment of GC in STD clinics. Urge all providers in key PPNG-affected neighborhoods to treat initially with recommended anti-PPNG therapy; periodically monitor actual treatment practices. Urge providers in other areas to offer all GC patients anti-PPNG therapy.
Test of cure	Refer for TOC all female GC patients from STD clinics. Recommend to all other providers that females be referred for TOC. Refer for TOC all PPNG patients, and follow up to ensure return visit.	Refer high-risk male patients for TOC. Refer all PPNG patients for 1- to 2-month reculture.	Refer for TOC a representative sample of male GC patients seen in STD clinics (without field follow-up).

TABLE 1. Elements of PPNG control for state and local STD programs (continued)

Element	Non-endemic areas (PPNG <1%) Basic control program	Endemic areas (PPNG 1% – 3%) Basic control program PLUS	Hyperendemic areas (PPNG >3%) Intensified/targeted program
Disease Intervention Specialist activities	Apply related case analysis, clustering, and reinterviewing techniques to all PPNG cases. Set DIS process performance standards. Ensure that DIS are provided ongoing, interactive, first-line supervision and training.	Reorder disease priorities for intervention efforts, and relieve DIS from all activities not related to patient management. Interview all clinic patients who fit the PPNG patient profile, and provide field follow-up of their sex partners. Assign DIS (if available) to major hospitals and other provider sites in high-incidence neighborhoods.	Interview all clinic patients who fit the PPNG patient profile, and provide field follow-up of their sex partners. Apply reinterviewing and clustering techniques on a selective basis.
Education	Develop educational objectives that are specific, measurable, and applicable to PPNG control for GC patients, health providers, members of risk groups, and the community as a whole.	Issue medical alerts to all providers, emphasizing culture methods, presumptive PPNG treatment, and reporting. Visit key providers to reinforce their essential role, update recommendations, and provide feedback. Target high-incidence neighborhoods for posters, pamphlets, and radio public service announcements. Issue press releases on the PPNG problem and the control actions being taken.	Maintain educational activities of a basic control program.

4. Laboratory Procedures

Ongoing surveillance for antimicrobial resistance in gonococcal strains should be an integral part of a standard STD laboratory program. The laboratory plays an important role in two areas. First, among those patients with clinical evidence that treatment has not been effective, the laboratory can often help differentiate true drug failure from reinfection. Second, the laboratory can help define the characteristics of the strains present in the community, enabling health officials to make a rational choice of therapeutic regimens.

Ideally, all isolates should be screened for clinically important antimicrobial resistance. If resources are limited, clinically or epidemiologically important isolates should be tested, using the priority schedule outlined in the **SURVEILLANCE** section, 2.1 Testing. Clusters of treatment failures may suggest an outbreak of a resistant strain. When an outbreak is suspected, a consecutive sample of at least 50 isolates should be evaluated in consultation with a reference laboratory.

4.1 Beta-Lactamase Assay

All gonococcal isolates should be tested for beta-lactamase. Beta-lactamase tests may be done on primary cultures or on pure subcultures. A chromogenic cephalosporin test is preferred, although the iodometric or acidometric procedures can be used. Beta-lactamase-positive and -negative control strains of *N. gonorrhoeae* should be tested with each batch of clinical isolates. No direct method for detecting beta-lactamase in patients' specimens (e.g., urethral exudate) is currently recommended.

4.2 Determination of Antimicrobial Susceptibility

Test results for antimicrobial susceptibility are only a measure of the in vitro susceptibility of an isolate to an antibiotic. Treatment failure may result from a variety of causes, and patients may experience failure of therapy even when infected with isolates that manifest in vitro susceptibility. Test results must be used as an adjunct to—not in place of—clinical evaluation.

4.2.1 Agar-dilution method

Agar-dilution susceptibility testing is the most reproducible and accurate method currently available. CDC recommends testing isolates for susceptibility to penicillin, tetracycline, spectinomycin, cefoxitin, and ceftriaxone. The recommended medium is a GC base with a defined supplement, such as Isovitalex. Mueller-Hinton medium should not be used. Inoculum size is 10^7 organisms/ml. This method should be standardized in accordance with the protocols of the National Committee for Clinical Laboratory Standards (NCCLS). Further details of the protocol, dilution ranges of the antibiotics, and reference strains are available from the Sexually Transmitted Diseases Laboratory Program, Center for Infectious Diseases, Centers for Disease Control, Atlanta, Georgia 30333.

4.2.2 Disk-diffusion method

Disk-diffusion testing is the most common method for determining antibiotic susceptibility in *N. gonorrhoeae*. Test results should correlate with data from reference strains tested with the agar-dilution technique. The protocol and reference strains for the disk-diffusion method may be obtained from the Sexually Transmitted Diseases Laboratory Program. If disk-diffusion susceptibility tests are performed by using non-standardized reagents, the results must be considered presumptive and should be confirmed by using the reference or standardized alternative procedures.

The recommended medium for disk-diffusion testing is supplemented GC-agar base. Recommended disks are penicillin (10 IU), tetracycline (30 μg), spectinomycin (100 μg), and ceftriaxone (30 μg). Culture-plate inoculation and test-reading procedures should conform to the M7-A dilution standards of the NCCLS.

Unfortunately, current data that correlate disk-diffusion test results with clinical outcome are not available for each antibiotic. Three categories of results for susceptibility tests are proposed (Tables 2,3):

1. A *susceptible* result implies a <5% likelihood of treatment failure.
2. An *intermediate* result indicates predictable failure rates of 5%-15% if the patient is treated with the tested antibiotic in the standard dosage (in most cases of intermediate susceptibility, a higher dose or prolonged therapy results in >95% cure rates).
3. A *resistant* result is associated with clinical treatment failure rates of >15%.

TABLE 2. Interpretive categories for penicillin and spectinomycin zone size results

	Size (mm)	Agar-dilution correlates (μg/ml)
Penicillin (10 IU):		
Resistant*	≤25	≥1
Intermediate	26-29	0.06-0.5
Susceptible	≥30	≤0.03
Spectinomycin (100 μg):		
Resistant	≤15	≥64
Intermediate	16-18	§
Susceptible +	≥19	≤32

*Zone sizes with isolates that produce plasmid-mediated beta-lactamase are usually <20 mm.

+ If a zone of inhibition is observed, it may contain resistant colonies.

§Dilutions between 32 and 64 are not usually performed.

4.2.3 Tetracycline and ceftriaxone disk-diffusion testing

Disk-diffusion tests for susceptibility to tetracycline are particularly prone to problems with reproducibility, even when standardized methods are used. Additionally, the wide range of susceptibility to tetracycline and the presence of determinants for both plasmid-mediated and chromosomally mediated resistance have made it difficult to interpret sensitivities determined by tetracycline disk. Tetracycline is recommended as the sole therapy only in unusual situations. Routine screening for tetracycline resistance remains important, however, because of the propensity of strains of TRNG to acquire other resistance determinants. In most cases, tetracycline screening should be targeted at identifying TRNG strains.

Preliminary interpretive criteria for testing susceptibility to ceftriaxone (Table 3) are based on regression data from a similar spectrum-class drug (cefotaxime). These recommendations must be considered tentative, since the incidence of organisms with minimum inhibitory concentrations of >0.03 μg/ml is <5%.

TABLE 3. Interpretive categories for tetracycline and ceftriaxone zone size results

	Size (mm)	Agar-dilution correlates (μg/ml)
Tetracycline (30 μg):		
Resistant*	<20	≥16
Resistant+	≤30	≥1
Susceptible	≥35	≤0.5
Ceftriaxone (30 μg):		
Resistant	≤30	≥1
Intermediate	31-34	0.06-0.5
Susceptible	≥35	≤0.03

*Plasmid-mediated, high-level resistance (TRNG)
+Chromosomal resistance

4.3 Antibiotic-Containing Media

Penicillin-containing selective media have not been sufficiently evaluated to be recommended as a screening method for identifying resistance of directly plated specimens.

For subculture screening, supplemented GC-agar base containing 1 μg/ml penicillin can be used to screen for penicillin resistance, and media containing 10 μg/ml tetracycline can be used to screen for plasmid-mediated high-level tetracycline resistance. Further details of these procedures can be obtained from the Sexually Transmitted Diseases Laboratory Program, CDC.

4.4 Vancomycin-Sensitive N. gonorrhoeae

Vancomycin-sensitive strains may not grow on selective media, which commonly contain 4 μg/ml vancomycin. If *N. gonorrhoeae* isolation rates are abnormally low, strains may be vancomycin-sensitive. Vancomycin-sensitive strains can be detected either by using a bipla culture system that contains chocolate agar plus a selective medium or by using a selectiv medium that contains only 2 μg/ml vancomycin.

5. Therapy

These guidelines are not intended to cover all treatment regimens. Rather, they provide guidance for selected regimens that meet general criteria of efficacy, ease of administratio and acceptability by the patient. In addition, they reflect a consensus of public health opinion about a regimen of treatment for gonorrhea that will effectively treat the commonly associate — but often undetected — chlamydial infection.

Therapy may fail for patients infected with PPNG or TRNG strains of *N. gonorrhoeae* whe they are treated solely with either penicillin or tetracycline. Similarly, gonococci with chr mosomally mediated resistance to penicillin or tetracycline, as well as gonococci that are or moderately susceptible to these drugs, are associated with unacceptably high treatmer failure rates when currently recommended penicillin and tetracycline regimens are followe

5.1 Choice of Regimen

These guidelines suggest an approach to the treatment of patients with gonorrhea base on the known prevalence of PPNG in a community. In cases of chromosomally mediate penicillin resistance, alternative drug therapy is unnecessary unless the community prev lence of strains associated with treatment failure exceeds 5% in a 2-month period. In th

instance, the same therapy approach as indicated for endemic community levels of PPNG would be appropriate. The designation of three levels of prevalence of PPNG follows the scheme outlined in the section on **CONTROL,** 3.1 Levels of Control Activity.

In Non-Endemic Areas

In areas in which PPNG accounts for <1% of all gonorrhea, patients should be routinely treated with a regimen of proven efficacy at all anatomical sites against penicillin-sensitive strains. If regimens such as **amoxicillin** with **probenecid** (or others known to be less effective against antibiotic-resistant strains) are employed, routine susceptibility testing and comprehensive test-of-cure evaluations will be required to assure continued therapeutic efficacy. If budgetary and logistic conditions are amenable, **ceftriaxone** intramuscularly (IM) would be a highly desirable alternative.

In Endemic Areas

In areas in which PPNG accounts for 1%-3% of all gonorrheal strains, a regimen of proven efficacy against all strains of *N. gonorrhoeae* should be used by selected public and private providers in neighborhoods with increased levels of gonorrhea caused by resistant strains. It should also be used by STD clinics for all patients meeting high-risk profile criteria. The drug of choice in this case would be **ceftriaxone** IM. All isolates associated with apparent treatment failure, all isolates from children, and all isolates from patients with complicated gonococcal infections (e.g., disseminated gonococcal infection, pelvic inflammatory disease, and ophthalmia) should be tested for antimicrobial sensitivity. Monitoring of therapeutic responses is as important as monitoring antimicrobial susceptibilities.

In Hyperendemic Areas

In areas in which PPNG accounts for >3% of all gonorrhea, all public and private providers in infected neighborhoods should use therapy effective against resistant strains. The drug of choice in this case would again be **ceftriaxone** IM. Another indicator of the need for this therapy is the occurrence of true treatment failures (e.g., positive cultures for *N. gonorrhoeae* from patients who return for test-of-cure evaluations 3 to 5 days after completion of therapy and who report having had no sexual exposure during this time) at levels of 3%-5% for patients treated with the amoxicillin-probenecid regimen.

Other **third-generation cephalosporins** may prove to be as efficacious as **ceftriaxone.** In all indications for **ceftriaxone** treatment, **spectinomycin** is an alternative. Some site specificity is lost, however, especially for infections of the pharynx.

5.2 Dosage of Ceftriaxone

At present, 250 mg of **ceftriaxone** IM in a single dose is the regimen favored for patients with uncomplicated gonorrhea caused by antimicrobial-resistant strains. Although some investigators report therapeutic success with a lower dose (e.g., 125 mg), insufficient data preclude a general recommendation at this time, especially for areas having a high prevalence of resistant strains. A major concern is that use of the 125-mg dose may accelerate the development of strains resistant to ceftriaxone. As data accumulate from providers who routinely use the 125-mg dose to treat patients with uncomplicated gonorrhea, that choice may be recommended. Thus, it is particularly important that those areas with a high proportion of resistant strains maintain a sensitive monitoring system for ceftriaxone resistance. The national Gonococcal Isolate Surveillance Project coordinated by CDC (see the section on **SURVEILLANCE,** 2.4 National Surveillance of Antimicrobial Resistance) will be examining ceftriaxone resistance in selected areas of the United States and reporting

results regularly in the *Morbidity and Mortality Weekly Report (MMWR)*. Some minimal ceftriaxone resistance has been seen sporadically, but none approaches clinical significance to date.

5.3 Recommendations for Therapy

For adults with uncomplicated urethral, endocervical, pharyngeal, or rectal infections:

IN PPNG-ENDEMIC AND -HYPERENDEMIC AREAS

Ceftriaxone: 250 mg IM

PLUS

Doxycycline:* 100 mg, by mouth, twice a day for 7 days

OR

Tetracycline HCl: 500 mg, by mouth, four times a day for 7 days

OR

For patients for whom tetracyclines are contraindicated (pregnant women and prepubertal children) or not tolerated, the single-dose regimen may be followed by **erythromycin** base or stearate, 500 mg, by mouth four times a day for 7 days **OR erythromycin ethylsuccinate,** 800 mg, by mouth four times a day for 7 days, **OR** equivalent doses of other approved **erythromycin** preparations.

The treatment recommendations for other conditions diagnosed in PPNG-endemic and -hyperendemic areas are contained in the **Appendix;** they follow the format of the CDC *1985 STD Treatment Guidelines* (CDC. *MMWR* 1985;34(suppl 4S):83S-86S,92S-94S).

*The daily cost of generic doxycycline is now equivalent to the daily cost of tetracycline. The twice-a-day regimen results in better compliance on the part of most patients.

APPENDIX

Other Recommendations for Therapy

1. Disseminated Gonococcal Infection

Antibiotic-resistant gonococcal strains may cause disseminated gonorrhea. Hospitalization is recommended in these instances, especially for persons who cannot reliably comply with treatment, have uncertain diagnoses, or have purulent synovial effusions or other complications. Attempts should be made to exclude endocarditis or meningitis. When antibiotic-resistant gonococcal strains are suspected in disseminated gonorrhea, **OR** in all disseminated gonorrhea cases occurring in PPNG-endemic or -hyperendemic areas, the following treatment schedule is recommended:

Ceftriaxone: 1 g, intravenous (IV), once a day for 7 days.

An equivalent **third-generation cephalosporin** may be used in appropriate doses. Most authorities recommend at least a week of antibiotic therapy for patients with purulent arthritis or gonococcal septicemia. If early hospital discharge is required, an expert should be consulted to determine appropriate outpatient follow-up therapy.

2. Meningitis and Endocarditis

Patients with gonococcal meningitis or endocarditis occurring in PPNG-endemic and -hyperendemic areas should be treated with high-dose intravenous **third-generation cephalosporins** in consultation with an expert. Optimal therapy may be guided by results from in vitro susceptibility tests. Most authorities recommend treating patients with meningitis for 10-14 days and those with endocarditis for at least 1 month.

3. Ophthalmia

3.1 Gonococcal Ophthalmia in Adults

In PPNG-endemic and -hyperendemic areas, adult patients with gonococcal ophthalmia should be hospitalized and treated with either **ceftriaxone,** 1 g, once a day, IM or IV, for 5 days, **OR** with equivalent doses of another effective **third-generation cephalosporin.** An ophthalmologist should evaluate the patient for ocular complications. Adjuvant topical antibiotics are not thought to offer any significant advantage. Irrigation of the eyes with saline or buffered ophthalmic solutions may be useful adjunctive therapy to eliminate discharge.

3.2 Gonococcal Ophthalmia in Neonates

Untreated gonococcal ophthalmia in neonates is highly contagious and may rapidly lead to blindness. All neonates with gonococcal ophthalmia in PPNG-endemic and -hyperendemic areas should be treated with **ceftriaxone,** 25 mg-50 mg/kg body weight/day, IV or IM, for 7 days. An equivalent **third-generation cephalosporin** may be used in appropriate doses. Topical antimicrobial preparations alone are not sufficient and are not required when appropriate systemic therapy is given. Irrigation of the eyes with saline or buffered ophthalmic solutions may be useful adjunctive therapy to eliminate discharge. Both parents of newborns with gonococcal ophthalmia must be treated. Simultaneous ophthalmic infection with *Chlamydia trachomatis* has been reported and should be considered if a patient does not respond satisfactorily to recommended treatment.

3.3 Neonatal Prophylaxis and Prophylactic Treatment

All newborns should receive ocular prophylaxis with either 1% **silver nitrate** solution, 1% **tetracycline** solution (or ointment), or 0.5% **erythromycin** ointment. Prophylaxis should be given within 1 hour after birth. No one regimen is completely effective. **Tetracycline** and **erythromycin** are also active against *C. trachomatis.* The prophylaxis failure rate of the antibiotic preparations for infections with resistant gonococcal strains is unknown. However, the intraocular antibiotic concentrations achieved with routine prophylaxis are high. Studies are currently under way to evaluate this problem.

Neonates born to mothers with documented gonococcal infection peripartum should be treated with **ceftriaxone,** 125 mg, IM, in one dose. Low-birth-weight infants should receive 25 mg-50 mg/kg body weight.

4. Acute Pelvic Inflammatory Disease (PID)

(Endometritis, Salpingitis, Parametritis, and/or Peritonitis)

Acute PID refers to the acute clinical syndrome (unrelated to pregnancy or surgery) attributed to the ascent of microorganisms from the vagina and endocervix to the endometrium, fallopian tubes, and/or contiguous structures. Many cases of PID are caused by more than one organism.

Causative agents include *N. gonorrhoeae* (antibiotic-sensitive and antibiotic-resistant strains), *C. trachomatis,* anaerobic bacteria, facultative gram-negative bacilli, *Mycoplasma hominis,* and, rarely, *Actinomyces israelii.* In the individual patient it is often impossible to identify and differentiate among the various causative agents. Because of this difficulty, all persons who have PID in areas endemic or hyperendemic for resistant gonorrhea should be treated with agents effective against a broad range of pathogens, including antibiotic-resistant *N. gonorrhoeae.* Although the treatment of choice is not established, combination therapy is usually indicated. Patients with antibiotic-resistant gonococcal infection who are inappropriately treated are at high risk of developing PID.

4.1 Hospitalization and Inpatient Treatment

Hospitalization of patients with acute PID is indicated when 1) the diagnosis is uncertain, 2) surgical emergencies such as appendicitis and ectopic pregnancy cannot be excluded, 3) a pelvic abscess is suspected, 4) the patient is pregnant, 5) the patient is a pre-pubertal child, 6) severe illness precludes outpatient management, 7) the patient is unwilling or unable to follow an outpatient regimen, 8) outpatient therapy has not been effective for the patient, or 9) clinical follow-up within 72 hours of starting antibiotic treatment cannot be arranged. Many experts recommend that all patients with PID be hospitalized for treatment. Special consideration should be given to adolescents because their compliance with therapy is unpredictable, and the long-term sequelae of PID are particularly severe in this group.

4.2 Combination Regimens with Broad Activity Against Major Pathogens in PID

Inpatient Regimens

Regimen A (preferred when *N. gonorrhoeae* or *C. trachomatis* is suspected as the primary pathogen):

Doxycycline: 100 mg, IV, twice a day

PLUS

Cefoxitin: 2 g, IV, four times a day.*

Continue drugs IV for at least 4 days and at least 48 hours after the patient improves (defervescence, decreased symptoms and signs). Then continue **doxycycline,** 100 mg, by mouth, twice a day to complete 10-14 days of total therapy.

Regimen B (preferred when facultative gram-negative bacilli or anaerobes are suspected as the primary pathogens):

Clindamycin: 900 mg, IV, three times a day

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in the same infusion with

Gentamicin: 2 mg/kg, IV,

followed by 1.5 mg/kg, three times a day for patients with normal renal function. Serum gentamicin levels should be monitored, and dose or dose interval adjusted to maintain a gentamicin serum level of 5-10 μg/ml 30 minutes post-administration. Continue drugs IV for at least 4 days and at least 48 hours after the patient improves. Then continue **clindamycin,** 450 mg, by mouth, four times a day to complete 10-14 days of therapy.

Note: At present, most antibiotic-resistant strains of *N. gonorrhoeae* are susceptible in vitro to the aminoglycosides.

*This regimen is unchanged from that found in the *1985 STD Treatment Guidelines.* PID is a polymicrobial infection which may include *N. gonorrhoeae, C. trachomatis,* anaerobes, and facultative gram-negative bacilli. Some published studies have shown cefoxitin to be a more effective agent than ceftriaxone against anaerobic infection.

Ambulatory Regimen

When the patient is not hospitalized, the following regimen is recommended:

Ceftriaxone: 250 mg, IM, in one dose,

PLUS

Doxycycline: 100 mg, by mouth,
twice a day for 10-14 days.

Comments:

(a) Expert consultation should be sought for patients who do not respond to standard treatment.
(b) Other effective **third-generation cephalosporins** may be substituted in the appropriate doses for **ceftriaxone.**

5. General Notes on Ceftriaxone Treatment

5.1 Penicillin-Allergic Patients

The cross-reactivity of third-generation cephalosporins and penicillin in allergic patients is extremely rare. A careful history should be taken regarding the precise nature of any penicillin allergy. Ceftriaxone should be withheld only from that small minority of patients suspected to have a history of immediate and/or anaphylactic response to penicillin.

5.2 Syphilis

Although ceftriaxone is believed to have some effect against incubating syphilis, the data are insufficient for a recommendation to be made. All patients who are clinically or serologically diagnosed as having syphilis should be treated with the appropriate regimen for syphilis as outlined in the *1985 STD Treatment Guidelines.*