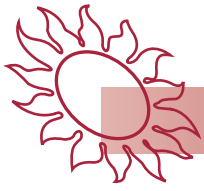

CHAPTER 59

Prevention of Gonorrhea

By Brenda L. Beagan and Elaine E. L. Wang

Prevention of Gonorrhea

Prepared by Brenda L. Beagan, MSc[1] and Elaine E. L. Wang MD, CM, FRCPC[2]

Despite the development of different diagnostic methods, Gram stain and culture of urethral or vaginal smears remain the methods of choice for diagnosing infection with Neisseria gonorrheae. The prevalence of this organism in asymptomatic individuals is so low that screening should be considered only in high-risk groups. These include individuals under age 30 years with at least 2 sexual partners in the previous year or age ≤16 years at first intercourse, prostitutes, and sexual contacts of individuals known to have a sexually transmitted disease (STD). Of greater note is the increase in penicillin-resistant organisms necessitating changes in antibiotic management. Previous studies have shown that treatment is efficacious.

Burden of Suffering

In 1992, gonorrhea was the second most frequently reported notifiable disease in Canada. However, the incidence of the disease, which peaked at 56,336 cases in 1981, has decreased steadily to 9,045 cases in 1992.<1> In 1987, 15-29 year-olds accounted for 78% of all reported cases in Canada. In 1988, the rate for females 15-19 years old surpassed that in both males and females aged 20-24 due to less of a decline in the younger female group.

In the U.S., gonorrhea was the most frequently reported sexually transmitted disease with 24% to 30% of cases occurring in adolescents. Rates per 100,000 dropped from 573 to 327 cases in males and 356 to 230 cases in females between 1981 and 1991.<2> The highest rate of 1,044 cases per 100,000 is currently in adolescent girls 15-19 years. U.S. rates are highest in black adolescents – the proportion with infection varying regionally from 3.5% to 7.3%. Although gonorrhea is a reportable disease, it is possible that some of the differences result from differential reporting or detection at private physicians' offices versus publically funded clinics. In the former setting, treatment may be administered without laboratory confirmation of infection. This, in turn, may lead to decreased reporting.

While the overall incidence of gonorrhea has been declining, the proportion of gonorrhea organisms that are antibiotic-resistant has been increasing. The first cases of penicillinase-producing *Neisseria*

[1] Formerly Research Associate, Canadian Task Force on the Periodic Health Examination, Department of Pediatrics, Dalhousie University, Halifax, Nova Scotia
[2] Associate Professor of Pediatrics and of Preventive Medicine and Biostatistics, University of Toronto, Toronto, Ontario

gonorrhoeae (PPNG) in Canada and the United States were reported in 1976.<3,4> Only 0.5% of all reported gonorrhea cases in Canada in 1985 were caused by PPNG, compared to 5.5% in 1989, an 11-fold increase.<3> There were PPNG outbreaks in both Ontario and Quebec in 1988.<5> The number of reported cases of PPNG increased from 591 in 1988 to 1046 in 1989.<3> The proportions are highest in Quebec (9.9%) and Ontario (8.6%),<3> where rates are well above the hyperendemic cut-off of 3.0%.<6> Preliminary figures for Ontario and British Columbia for the first half of 1990 show that the percentage of reported cases of gonorrhea due to PPNG has doubled since 1989 in these two provinces.<3,6,7> There have been several major outbreaks of PPNG in several centers in the United States.<4,8,9>

In the U.S., the proportion increased from less than 1% in 1985 to 7% in 1989. In one survey of resistance patterns during 1991, 32% of *N. gonorrheae* were penicillin or tetracycline resistant.<10> However, this survey was conducted in a sentinel system for early detection of resistant bacteria and is therefore an overestimate of the national problem.

Gonococcal infection may be symptomatic, asymptomatic and/or complicated and may involve various anatomical sites. The majority of patients have anogenital and/or pharyngeal infection. Local complications may include epididymitis, lymphangitis, penile edema and urethral stricture in men, and salpingitis or pelvic inflammatory disease in women, as well as systemic complications in men or women, including disseminated gonococcal infection, endocarditis and meningitis. Over 90% of pharyngeal infections are asymptomatic. Women and unborn children carry the major physical impact of gonorrhea in the Western world. Compared with the relatively inconsequential acute gonorrhea in males, gonococcal infections in females lead much more frequently to hospitalization and surgery. Pelvic inflammatory disease (PID), a serious complication of 10-20% of gonococcal infections, can result in serious medical sequelae such as infertility, ectopic pregnancy, and chronic pelvic pain. (PID is also discussed in the Chapter 46 on preventing unintended pregnancy in adolescents). More than 80% of the total cost of gonococcal infections in the U.S. health care system in 1976 went for care necessitated by gonococcal PID.

Maneuver

Given the overall low infection rates, screening of the general population is inappropriate. Several studies have examined risk factors for infection, including a family practice based Canadian study.<11> In this study, two factors were found to be predictive of infection in asymptomatic patients after adjustment in a logistic model: history of contact with a case of STD and age less than 30 years.

In another study in Boston, culture specimens for gonorrhea were obtained from 1,441 obstetric and gynecology patients receiving routine pelvic examinations.<12> Information on sexual history and symptoms was obtained through a self-administered, 50-item questionnaire. Twenty-five (1.7%) women had positive cultures for gonorrhea. Multivariate analysis showed five factors were independently associated with gonococcal infection: partners with gonorrhea or urethral discharge (Odds Ratio = 5.7), endocervical bleeding induced by swab (OR = 4.6), age at first intercourse ≤16 (OR = 4.2), payment by Medicaid (OR = 2.8), and low abdominal or pelvic pain (OR = 2.6). Race was not an independent risk factor. The authors calculated that the risk of infection for a woman with one or more risk factors was 2.5%, compared to 0.2% for a woman with no risk factors.

A group in Cleveland devised a diagnostic index for estimating the probability of cervical infection with either gonorrhea or chlamydia.<13> The index, developed from examining and questioning 190 gynecologic patients, identified three independent predictors of cervical infection: age, purulent vaginal discharge, and high-risk sexual contact (a new partner in the prior 6 months, or a partner with a suspected genital infection). Points were assigned to the variables based on their multiple regression logistic coefficients, as follows: age <20 years – 2 points; age 20-29 years, 1 point; and 1 point each for purulent vaginal discharge and high-risk sexual contact. When the diagnostic index was tested on 588 women, the rate of cervical infection was directly associated with the index scores ($p<0.001$), with infection occurring in 28% of women with 3 or 4 points, 7% of women with 2 points, 3% of women with 1 point, and 0% of women with 0 points.

Gram stain and culture remain the most widely available and accurate method to identify *N. gonorrheae*

The standard diagnostic tests for gonorrhea are culture and Gram stain of clinical specimens. However, they have some limitations. The specificity of stained smears is 95-100% at all anatomical sites, and its diagnostic sensitivity for urethral specimens from males with acute symptomatic gonorrhea is high, ranging from 90-95%.<14> The Gram stain is relatively insensitive in asymptomatic males (50-70%), for female anogenital infections (45-70%), and for all pharyngeal and rectal infections.

Bacterial cultures have superior diagnostic sensitivity for female anogenital gonorrhea, male asymptomatic gonorrhea, and all pharyngeal gonococcal infections. In women, single endocervical cultures are estimated to have a sensitivity of 80-95%. Culture procedures may be limited by the inhibition of growth by antibiotics in the selective culture medium, such as the failure to detect vancomycin-susceptible strains using the usual culture medium. Also, results may be unsatisfactory if clinical specimens are inadequate or if the medium is not quality controlled, stored, inoculated, incubated and transported properly.

More recently developed diagnostic maneuvers include serological tests to detect serum antigonococcal antibodies, tests for specific endotoxins, enzymes or fatty acids, demonstration of gonococcal antigens using enzyme immunoassays or DNA hybridization techniques. Alternatives to Gram stain and culture have not been studied in an asymptomatic population. Studies in symptomatic individuals with urethral or vaginal discharge may not be generalizable to a population visiting their physician who do not have such complaints.

Serology, which was developed for population screening, is not accurate enough for detection.<3> Similarly, tests for gonococcal bacterial products are also insufficiently accurate when compared with bacterial culture.

Enzyme immunoassays for detection of gonococcal antigens in male urethral specimens have a sensitivity and specificity of 95% or more. These immunoassays also have a very high accuracy when performed on urine as compared with male urethral specimens.<4> Because obtaining urine specimens for diagnosis is substantially less uncomfortable, this diagnostic method may be of use in screening if accuracy is as high in asymptomatic men. However, the sensitivity and specificity of this test on specimens taken from the female genital tract range from 60% to 100% and 70% to 98%, respectively.<5>

Assays based on DNA hybridization techniques are limited to laboratories with molecular diagnostic capabilities. Sensitivity and specificity of this method were found to be greater than 97% and 99%, respectively.<6,8> Again, the accuracy of this method compared with culture is higher for male urethral specimens than for female cervical specimens. This methodology, however, will not shorten time for diagnosis to a clinically significant degree. Furthermore, diagnostic tests which reveal the presence or absence of *N. gonorrheae* do not give information about antibiotic susceptibility.

Effectiveness of Prevention and Treatment

Antibiotics for Treatment of Uncomplicated Gonorrhea

Early detection of gonorrhea in asymptomatic persons may prevent the development of complications, through antibiotic treatment. It may also facilitate the notification of sexual contacts.

If *N. gonorrheae* is susceptible to penicillin, oral amoxicillin remains the drug of choice for management, because it is relatively inexpensive. In areas with a high frequency of resistant *N. gonorrheae*, however, alternative agents are now the first line drugs. In general, these newer agents are substantially more expensive than amoxicillin. In uncontrolled trials, ceftriaxone had an average cure rate of 99.2%;

the cure rate for four different quinolones ranged from 93.3% to 100%, with an average of 99.5%. Numerous clinical trials have now been conducted comparing the efficacy of a number of quinolones to intramuscular ceftriaxone. The advantage of the quinolones and cefixime, another third generation cephalosporin, is that they may be administered orally. No significant difference has been observed with single-dose oral agents compared with ceftriaxone.<9,15> Because the efficacy rate of treatment of uncomplicated gonorrhea should be at least 95%, recommendations to evaluate new treatments rigorously have been made.<16>

Impact of Educational Interventions

Three controlled trials have examined the impact of an educational intervention at the initial STD visit on treatment behavior and compliance. Giving patients educational pamphlets on gonorrhea did not increase the overall follow-up rate in men, compared to a control group, but did increase the rate of follow-up attendance in women.<17> In one U.S. study, 340 men diagnosed with gonorrhea were given either routine counselling about medication and follow-up, or an intensive educational counselling session based on six compliance-enhancing strategies.<18> Compliance with taking medication was not affected, but the educational intervention increased the follow-up attendance rate from 66% in the control group to 71% in the experimental group ($p=0.05$). Similarly, a ten-minute soap-opera style educational videotape which was randomly shown or not shown to 902 men diagnosed with gonorrhea did not affect the patients' willingness to contact all their sexual partners, but did increase the rate of attendance for follow-up, from 43.3% in the control group to 53.5% in the experimental group ($p<0.003$).<19>

Prevention Maneuvers

Primary prevention through avoiding exposure is the best means of controlling the spread of gonorrhea and other STDs. Condoms, used properly, may reduce the risk of infection and transmission. There is epidemiological and case-control evidence that consistent condom use does reduce the frequency of gonorrhea.<20> There are also indications that condom use may be increasing, at least in selected populations. However, there are no data on the frequency or causes of either user failure or product failure.

There has also been a general assumption, and some epidemiological evidence, that spermicidal preparations help to prevent gonococcal infections. However, large-scale well-designed studies have been lacking. A recent randomized, double-blind, placebo-controlled trial of 818 women has clearly shown benefit from the use of a vaginal gel containing Nonoxynol-9.<21> The study, which had a six-month follow-up rate of 78% (n=636, spermicide group, 317; placebo group,

319), found that the relative rate of gonococcal infection in the spermicide group was 0.75 (90% confidence limits, 0.58 and 0.96). Among women reporting at least 50% compliance, the relative rate was reduced to 0.61 (p=0.0031; 95% confidence limits, 0.42 and 0.87). (Also see Chapter 46).

Recommendations of Others

In 1989, the U.S. Preventive Services Task Force recommended that routine cultures for gonorrhea be performed in high-risk groups, including prostitutes, persons with multiple sexual partners or whose partner has multiple sexual partners, persons with a history of repeated episodes of gonorrhea, and sexual contacts of persons with gonorrhea.<22> Specific treatment regimens were not addressed.

The U.S. Centers for Disease Control recommend that all cases should be diagnosed or confirmed by culture, to facilitate a system of antibiotic susceptibility testing. Their recommended treatment regimen for uncomplicated urogenital or rectal infection is a single intramuscular dose of Ceftriaxone 250 mg, plus Doxycycline 100 mg orally twice daily for 7 days to treat for presumptive coexisting chlamydial infection.

The Laboratory Centre for Disease Control in Canada recommends ceftriaxone as a preferred treatment plus tetracycline or doxycycline (for *Chlamydia trachomatis*).<23> Alternatives to ceftriaxone have been listed as spectinomycin, ciprofloxacin, cefixime or cefuroxime axetil. In areas with active monitoring for resistance and resistance levels below 3%, oral amoxicillin or ampicillin with probenecid may replace ceftriaxone. High-risk groups for screening include sexual contacts of cases, sexually active adolescents, children who have been sexually abused and their siblings, and adults with two or more of the following risk factors: age under 25, ≥2 sexual partners in the previous year, a new sexual partner within the previous two months, a history of STD, non-use of contraception or use of non-barrier methods, and anal intercourse with a high-risk partner. They also strongly recommend screening for women who are pregnant, seeking an abortion, or being seen for insertion of an IUD.

Conclusions and Recommendations

Abstinence is the most effective way to prevent transmission of STDs. There is also fair evidence to support the use of condoms. Given the effectiveness of counselling, educational pamphlets and educational videotape in improving compliance with clinic follow-up, there is fair evidence to provide counselling or educational materials to prevent the spread of gonorrhea (B Recommendation).

The low prevalence rate of infection with *N. gonorrheae* would make mass screening of the general population an inefficient

intervention (D Recommendation). However, screening should be performed in certain populations: 1) individuals under 30 years, particularly adolescents, with at least 2 sexual partners in the previous year; 2) prostitutes; 3) sexual contacts of individuals known to have a sexually transmitted disease; and 4) age ≤16 years at first intercourse (A Recommendation). The frequency with which such screening should take place has not been examined, but subjects are presumably at risk when they continue behaviours that place them at increased risk, such as prostitution.

Because of the high rates of penicillin resistance, treatment of gonorrhea should be initiated with ceftriaxone, cefixime or a quinolone

Intramuscular ceftriaxone or oral quinolones, cefuroxime axetil, and cefixime should be used as initial therapy unless there is epidemiologic information indicating that the patient is unlikely to be infected with a resistant strain of *N. gonorrheae*. An effective agent against *C. trachomatis* should be initiated at the same time because of the high frequency of co-infection.

Unanswered Questions (Research Agenda)

The test characteristics of newer diagnostic methods, particularly less invasive urine tests, should be studied in asymptomatic subjects. These would be more acceptable specimens for mass screening. Whereas, current management of patients attending sexually transmitted disease clinics includes initiation of treatment prior to laboratory confirmation, rapid tests may be particularly helpful when screening asymptomatic individuals. A trial of early initiation of antibiotics compared with specific therapy in subjects with proven infections is indicated in this setting. More information is needed on the most efficient frequency of screening. Methods to increase the wearing of condoms need to be studied, particularly since condoms may prevent the transmission of many infectious pathogens in addition to *N. gonorrheae*. Diligent surveillance with culture and susceptibility testing in sentinel sites continues to be needed to provide warning about the development of resistance to newer anti-infective agents. As new drugs become available, clinical trials should determine their efficacy with more resistant organisms.

Evidence

A MEDLINE search was conducted using the major MESH heading Gonorrhea, with the subheadings Complications, Diagnosis, Drug Therapy, Epidemiology, Prevention and Control, Therapy, and Transmission, for the years 1981 to January 1994. Relevant articles identified through the search were reviewed, with emphasis on screening and treatment. Pertinent references from these studies were also reviewed, along with references from recent review articles. In general, priority was placed on articles that dealt with trials, rather than editorials, case reports, letters or commentaries. Only published

articles were reviewed. This review was initiated in November 1991 and recommendations were finalized by the Task Force in March 1994.

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Prevention of Gonorrhea

MANEUVER	EFFECTIVENESS	LEVEL OF EVIDENCE <REF>	RECOMMENDATION
Counselling, educational pamphlets, educational videotape	Counselling and educational materials result in no increase in compliance with medications or willingness to inform sexual contacts, but increase compliance with clinic follow-up.	Randomized controlled tirals<17-19> (1)	Fair evidence to provide counselling to prevent spread of gonorrhea (B)
	Abstinence prevents transmission of sexually transmitted disease (STD) and use of condoms reduces STD transmission	Case-control study<20> (11-2)	
Screening for *N. gonorrheae* with Gram stain and culture of cervical or urethral smear	Screening the general population has low yield. Yield higher with increased prevalence in high-risk* subpopulation.	Cohort studies<5-7> (11-2)	Fair evidence not to screen the general population (D); good evidence to screen those at high-risk* (A)
	Good evidence that treatment of patients with gonorrhea with ceftriaxone, oral cephalosporins, or quinolones results in >95% eradication.	Randomized controlled trials<14-16> (1)	

* **High-risk groups include: individuals under age 30 years with at least 2 sexual partners in the previous year or age ≤16 years at first intercourse, prostitutes, sexual contacts of individuals known to have a sexually transmitted disease.**