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Diagnosis and Treatment of Gonorrhea

Paul A. Kvale, M.D.*

The various methods for diagnosis of gonorrhea are reviewed. Gram-stained smear of urethral exudate in the male is appropriate, but for the female emphasis is placed on the use of culture on Thayer-Martin medium. Currently effective modalities of treatment are detailed, pointing out that higher doses of antibiotics are generally required for females with pelvic inflammatory disease than for males with acute gonococcal urethritis. The necessity for follow-up is also discussed.

In the year 1971 gonorrhea has reached epidemic proportions. Nearly 500,000 cases were reported to the Public Health Service in 1969 with an estimated one million additional cases unreported during the same year.¹ Since then the incidence has continued to increase—a fact recognized by medical personnel and widely reported in the lay mass communications media.

It is incumbent upon physicians dealing with gonorrhea to make an accurate diagnosis and to follow it with treatment which will afford the best possible chance of cure. The synopsis presented here reviews some of the latest methods available for diagnosis and treatment of gonorrhea in its most common forms: acute urethritis in the male, and acute or chronic pelvic inflammatory disease in the female. A complete discussion of the complicated forms of gonorrhea will not be attempted.

Diagnostic Methods

The disease is so different in the

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two sexes that it should almost be considered two separate entities.

In the male, the traditional gram-stained smear of urethral exudate is adequate for diagnosis as it affords 98-99% accuracy.² In the early post-treatment assessment of cure, the gram-stained smear is inadequate and cultures should be done. This is because there may be a temporarily reduced number of organisms in the discharge; consequently, the organisms often cannot be seen. Later in the post-treatment course, the organisms will multiply and the quantity of exudate will usually increase. Once again the smear becomes fairly reliable to assess the results of treatment. If results are doubtful or if exudate is present *after* treatment, greater accuracy can be obtained with a culture.³

Svihus et al in 1961 suggested that *Mima polymorpha* var. *oxidans* rather than *N. gonorrhoeae* was the causative agent for "penicillin-resistant" acute gonococcal urethritis in males.⁴ This is no longer thought to be true, and most venereologists concur that the

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gonococcus has gained *relative*, not absolute, resistance to penicillin.⁵⁻⁷

In the female with gonorrhea the gram-stained smear of vaginal or cervical exudate is grossly unreliable. In studies conducted in the Philippines less than half of the readings were correct with a gram-stained smear.⁸ Because of the volume of secretions usually found in the vaginal vault and cervical areas and the presence of many different kinds of bacteria, there will be false positive as well as false negative readings with the gram-stained smear. Culture is the best means for diagnosing gonorrhea in the female.

Two reports have confirmed that cultures of the endocervix are the most productive.⁹⁻¹⁰ Nearly 50% of all infected females will yield a positive culture from the anal canal. A small but significant number (7%) have positive cultures only in the anal canal.¹⁰⁻¹² The vaginal vault and external os should be wiped clean of debris with ring forceps. A Culturette* cotton-tipped applicator (or platinum wire loop, when direct plating is done) should be inserted 1-2 cm into the endocervical canal to obtain the specimen for culture. If a second site is to be cultured, it should be the anus.

The time-in-cycle when cultures are obtained is debated among venereologists. A previous study showed the highest incidence of positive cultures during the first five days of the cycle (menses and immediately following), and the lowest yield occurred during mid-cycle (sixteenth through twentieth days).⁹

Thayer-Martin medium is currently

employed for maximum growth of *N. gonorrhoeae*. Thayer-Martin medium is an enriched chocolate agar to which has been added a nutrient supplement called Isovitalax** and the antibiotics vancomycin, colistimethate and nystatin (VCN). *Direct* plating onto petri dishes gives the optimum yield, but is usually not practical in a hospital setting. A suitable alternative is the use of transport medium such as Culturettes. It has been shown that, with infected patients actively shedding organisms, use of a transport medium results in only a 5% loss in 12 hours, 17% loss in 24 hours, and 23% loss in 48 hours.¹³

Cultures are transferred to Thayer-Martin medium and incubated in candle jars under 10% carbon dioxide tension. Typical gonococcal colonies are picked after 24-48 hours of incubation and gram-stained for their morphological characteristics. Oxidase reactions will confirm the diagnosis and sugar fermentations usually need not be done. Except for the pathogenic *Neisseria*, almost all organisms are inhibited by Thayer-Martin medium, including the saprophytic *Neisseria*.

Since 1959 fluorescent antibody staining by delayed technique has also been used to diagnose gonorrhea.³ The author believes it is no more accurate than culture using the Thayer-Martin medium; it is less accurate in assessing cure, so it is seldom used.

Development of serologic techniques for the diagnosis of gonorrhea is currently underway but not clinically available at the present time. It should broaden the scope of diagnosis in the future.¹⁴

*Culturette: Medical Supply Company, Rockford, Illinois.

**Isovitalex, Baltimore Biologic Laboratories.

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Treatment

Penicillin is still the treatment of choice for gonorrhea, but benzathine penicillin has no place in the modern management of gonorrhea. The average *in vitro* sensitivity of stains isolated from treatment failures has increased from 0.1 u/ml in 1954 to 0.5 u/ml in 1969. The minimal inhibitory concentration (MIC) of the most resistant strains has shifted from a high of 0.2 u/ml to 3.5 u/ml in the same period of time.¹⁵ The incidence of strains which require serum levels of penicillin greater than 0.5 u/ml has increased to the point that adequate serum levels cannot be achieved by using benzathine penicillin. Until recently the relatively resistant strains were encountered mostly in the Pacific and, to a lesser extent, on the West Coast. Probably this was the result of suboptimal treatment and/or self-

administration of readily available drugs by prostitutes and servicemen overseas.⁹ Martin has shown what is now widely appreciated as a nearly universal *relative* resistance of the gonococcus to penicillin.¹⁵ However, penicillin in *adequate* doses is still our treatment of choice in 1971.

MALES: (Table I) In a small pilot study in the Pacific in 1966, Holmes found that the Public Health Service recommendations for using 2.4 million units of procaine penicillin G resulted in 28.6% failures.¹⁶ An expanded study showed that addition of probenecid to the 2.4 million units of procaine penicillin G reduced the failure rate to 2.4% in a series of 391 men.¹⁷ This therapeutic program has been confirmed in a more recent study by Keys in the same geographic area.¹⁸ For males with acute gonococcal urethritis

TABLE I

TREATMENT FOR MALES WITH ACUTE GONOCOCCAL URETHRITIS

Procaine Penicillin G 2.4×10^6 units IM + Probenecid 1.0 gm oral

Ampicillin

3.5 gm oral, or 2.0 gm IM

 + Probenecid 1.0 gm oral

Tetracycline 1500 mg "load", then 500 mg q. i. d. x 4-7 days

Erythromycin 1500 mg "load", then 500 mg q. i. d. x 4-7 days

Cephaloridine 2.0 gm IM

Kanamycin 2.0 gm IM

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who have no history of hypersensitivity to penicillin, the administration of 1.0 gm probenecid orally either an hour before or simultaneously with 2.4 million units aqueous procaine penicillin G IM is the current treatment of choice.

Several alternative programs are available. For instance, ampicillin has similar *in-vitro* inhibitory patterns to benzyl penicillin (G),¹⁹ and some of the more resistant strains of *N. gonorrhoeae* are also more sensitive to ampicillin than to benzyl penicillin.²⁰ Several single dose ampicillin programs have been reported recently.^{18,21,22} Each of the more successful programs utilizes the drug probenecid to retard the renal excretion of the ampicillin. Keys reported a 99% cure rate (105 of 106) using 2.0 ampicillin IM with probenecid.¹⁸ Kvale noted that 3.5 gm oral ampicillin gave only 71.7% cures when this drug was used alone. When probenecid was added, the cure rate was 96% (194 of 202).²¹ Nearly identical results were obtained by a Scandinavian group in 1969, employing a similar program of 2.0 gm oral ampicillin with probenecid.²² On the other hand, phenoxymethyl penicillin—even with probenecid—fails to produce satisfactory cure rates and should not be used for the treatment of gonorrhea.²¹

For the patient who presents with a history of hypersensitivity to penicillin, alternative drugs are available. A four- or seven-day program with an initial "loading" dose of 1.5 gm oral tetracycline, followed by 500 mg q.i.d., was 98% effective in 530 men.¹⁷ This program is the treatment of choice for both men and women who are hypersensitive to penicillin. Erythromycin in the same doses will also produce a sat-

isfactory cure rate.²³ A single dose of 2.0 gm cephaloridine IM was 83.5% effective in Keys' series.¹⁸ In the same report, Keys noted that a single IM dose of 2.0 gm kanamycin was 93.4% effective. Both cephaloridine and kanamycin should be used with caution in patients who have any evidence of renal insufficiency.

FEMALES: (Table II) In general, the dose of antibiotics used must be larger for females than for males. Anatomical differences allow sequestration of organisms and this is felt to be responsible for the larger doses necessary to cure females. Lucas noted an 8.7% failure rate in 1967 when he used a single dose of 2.4 million units of aqueous procaine penicillin G in a series in the United States.²⁴ He reduced his failure rate to 4% when the dose was increased to 4.8 million units. Johnson evaluated nine different programs in the Pacific in 1968.²⁵ Several regimens employed a combination of crystalline and aqueous procaine penicillin G in doses up to 6.0 million units, and failure rates were still as high as 13%. When probenecid was added to the regimen using 6.0 million units of penicillin, the "cure" rate was 100%. Likewise, a 100% "cure" rate was seen with an oral dose of 3.5 gm ampicillin, either alone or with probenecid.²⁵ It is probable that the cure rates reported would have been lower had the patients been followed for longer than the seven days of hospitalization. However, it seems reasonable to conclude that the large dose of parenteral penicillin or oral ampicillin when used in combination with probenecid will be satisfactory for use in females. Parenteral ampicillin (2.0 or

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more grams) with probenecid can also be used.

In the same series Johnson reported several different single dose tetracycline regimens. Using 250 mg of oxytetracycline IM plus 1.0 gm of oral tetracycline administered simultaneously, the cure rate was 85% (21 of 25). The cure rate was increased somewhat (94%, 33 of 35) when the dose was increased to 500 mg of oxytetracycline IM plus 1,500 mg of tetracycline orally. No failures were seen in 11 patients treated with a single oral dose of 2.5 gm tetracycline, but this dose was poorly tolerated by patients (3 of 11 vomited). For the female who is hypersensitive to penicillin the most practical approach for treatment is the same program outlined for males: a loading dose of 1.5 gm tetracycline is given orally and is followed for four to

seven days with 500 mg tetracycline q.i.d. This program should not be used in the pregnant female during the latter half of pregnancy because of the possibility of staining the fetal teeth. In such a case, erythromycin on an equal gravimetric schedule is the preferred antibiotic.

Follow Up

It is imperative in treating either sex to assure adequate follow up. A single post-treatment examination of the male approximately one week later is generally satisfactory. Ideally, the patient should be seen in the morning, prior to voiding, and examined for the presence of urethral exudate or material which can be expressed after prostatic massage. If any material is obtained, this should be examined by gram-stain and by culture. With the

TABLE II

TREATMENT FOR FEMALES* WITH PELVIC INFLAMMATORY DISEASE (CHRONIC OR ACUTE)

Procaine Penicillin G 4.8×10^6 units IM + Probenecid 1.0 gm oral

Ampicillin 3.5 gm oral, or
2.0 (or more) gm IM + Probenecid 1.0 gm oral

Oxytetracycline 500 mg IM
1500 mg oral Simultaneous, single dose

Tetracycline 1500 mg "load", then 500 mg q.i.d. x 4-7 days

Erythromycin 1500 mg "load", then 500 mg q.i.d. x 4-7 days

* Note: Re-culture endocervix weekly x 4 after treatment.

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penicillin treatment programs described here, there will often be thin white mucoid material (negative by culture for *N. gonorrhoeae*) which may or may not be accompanied by irritative GU symptoms. This syndrome, called "postgonococcal urethritis" (PGU),²⁶ uncommonly follows treatment with broad spectrum antibiotics. If PGU is asymptomatic, it generally requires no treatment other than reassurance of the patient and careful neglect. If symptoms are severe or discharge is copious, satisfactory results can usually be achieved by a four- to seven-day course of tetracycline.

Follow up of the female who has been treated for gonococcal pelvic inflammatory disease should include examinations at weekly or biweekly intervals for not less than one month. Endocervical cultures should be obtained at each examination. A single negative examination after treatment does not assure treatment success.

In all cases of gonorrhea, serologic examination for syphilis should be done at the time of initial treatment and monthly for three months after treatment.

If doubt exists when the patient first presents and the clinical suspicion is high, it is far preferable to err on the side of over-treatment than under-treatment. Any named contact or consort of a patient should likewise be treated on epidemiologic grounds, regardless of culture results. This is particularly true for females. Simultaneous treatment (or re-treatment) of husband-wife pairs should be practiced whenever this is possible.

Epidemiologic reporting of gonorrhea to public health officials is an ideal method of management and should be done in each case. Careful attention to all features of this disease may help reverse the epidemic trends we now see.

Generic And Trade Names Of Drugs

Ampicillin—*Amcill, Ampi-Co, Omnipen, Penbritin, Polycillin, Principen, Supen, Totacillin*; Benzathine penicillin—*Bicillin, Permapen*; Cephaloridine—*Loridine*; Erythromycin—*E-Mycin, Erythrocin, Erythromycin, Ilosone*; Kanamycin—*Kantrex*; Oxytetracycline—*Oxy-Kesso-Tetra, Terramycin*; Penicillin G procaine (benzyl)—*Crysticillin, Duracillin, Pentids-P, Wycillin*; Phenoxymethyl penicillin—*Betapen-VK, Compocillin-VK, Ledercillin-VK, V-Cillin-K, Veetids*; Probenecid—*Benemid*; and Tetracycline—*Achromycin V, Kesso-Tetra, Panmycin, Rexamycin, Streclin, Sumycin, Tetrachel, Tetracyn*.

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