

# TREATMENT OF PHARYNGEAL GONORRHOEA WITH EXTENDED ORAL AMPICILLIN

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## SYNOPSIS

Uncomplicated genital gonococcal infections are reliably treated with single dose oral ampicillin therapy. This regimen has been found to be inadequate for eradicating infections from the pharynx. An evaluation was done to establish the efficacy of extended oral ampicillin therapy for pharyngeal infection. The regimen consisted of a single oral dose of 3.5 g ampicillin trihydrate and 1 g probenecid on day one of treatment followed by 0.5 g of ampicillin four times a day on days two and three. One follow-up culture was taken 7-28 days after completing therapy. Out of a total of 105 patients who completed this therapy, three had positive follow-up pharyngeal cultures. The failure rate of 2.8% compares favourably with the current preferred modes of treatment.

## INTRODUCTION

Gonococcal infections of the pharynx are being diagnosed with increasing frequency in heterosexual as well as homosexual populations (1). Kraus (2) has reviewed the literature with regard to the prevalence of pharyngeal gonorrhoea in various populations at different facilities. In one study cited, "15.3% of military dependents attending a prenatal clinic in Thailand had gonococcal pharyngitis."

There is still some question as to whether or not this infection contributes to the spread of disease and whether these individuals need to be treated especially if they are asymptomatic. In spite of the above controversy, there have been a number of clinical trials to establish the most effective mode of treatment for this type of infection (3, 4, 5, 6, 7, 8).

Current Centers for Disease Control (CDC) guidelines (9) state: "Tetracycline or aqueous procaine penicillin G (APPG) is the preferred therapy for pharyngeal gonorrhea infections." In the Central Venereal Disease Clinic of the Santa Clara County Health Department, all uncomplicated cases of pharyngeal gonorrhea are treated as follows (unless the patient is allergic to penicillin): A loading dose of ampicillin trihydrate (Principen) 3.5 g plus probenecid (Benemid) 1 g are given orally on day one followed by 0.5 g of ampicillin trihydrate taken four times a day on day two and day three, for a total of 7.5 g of the medication. This regimen which has been in use since October 1975, was evaluated for its efficacy and results published in 1978 (7). The present study is a retrospective evaluation of the same treatment, to see if the failure rate established at that time (1.3% — 3.9%) still holds or if there had been some change. Patients seen from January to December 1981 are included in this report.

## MATERIALS AND METHODS

The patients were selected by the following criteria. The laboratory log book was used to obtain the names of all patients who had positive gonorrhea tests on their pharyngeal cultures. The charts of all these patients were reviewed and the following were included in the study: patients who had confirmed gonococcal infection of the throat, received the regimen under study, took the medication as prescribed, and had a follow-up test of cure culture within 7-28 days of completing therapy. A total of 167 patients were initially identified with positive throat cultures. 143 of these were treated with the regimen under study, 20 were treated with an alternate regimen, four elected to be treated by their private physicians. Out of the total number treated altogether, 105 of these fulfilled the selection criteria described above. Any person seen more than once for a new infection was counted each time he or she came in throughout the study period. Patients were often treated on epidemiological grounds before culture results were known.

Pharyngeal cultures were obtained by swabbing the posterior pharynx and tonsillar crypts with a wooden cotton tipped applicator and inoculated immediately on Thayer-Martin medium. The plates were incubated at 35° C in a humid atmosphere of 10% carbon dioxide and read at 24 and 48 hours (72 hours on weekends) after incubation. Isolates were identified as *Neisseria gonorrhoeae* on the basis of typical colony morphology, positive oxidase test, Gram-negative diplococci and sugar fermentation test results — the last as described by Brown (10). These procedures are the same as described in the original article (7). On the basis of the good results obtained in the past (7), it was decided to cut back to taking only one follow up culture instead of two. An exception was made in the case of patients who presented as treatment failures for whatever reason and were retreated. In addition patients who were not treated with the extended ampicillin regimen or aqueous procaine penicillin G were advised to obtain two negative tests-of-cure cultures at weekly intervals.

Whenever specifically requested by the clinic physician and routinely on all positive test-of-cure cultures confirmed as *Neisseria gonorrhoeae*, tests were performed on the isolates to determine whether or not they were beta-lactamase producers and/or resistant to penicillin. A rapid iodometric test (11) was used to determine beta-lactamase production. A disc-agar diffusion test for screening penicillin resistance (12) was performed using a 10 unit penicillin disc. Isolates with

inhibitory zone diameters of 22 mm or less were interpreted as resistant. In this series of 105 patients, 58 (55.2%) were males with an age range of 14-65 years, median age of 28. The females comprised 44.8% (47) of the group with an age range of 15-51 and a median age of 24. Ninety per cent of the total (94) were infected at two or more sites; 51 males had multiple infections and 43 of the females. None of the patients reported adverse reactions to the medication. There were no reported observed cases of disseminated infection.

## RESULTS

Of the 105 patients treated with the regimen under study there were three patients who had positive follow-up throat cultures, within 7-28 days of completing therapy. The infections from other infected sites, if present, had cleared up in all patients, including the ones who had persistent pharyngeal infections.

Patient #1, a 20 year old male had positive throat and presumptively positive urine cultures for *Neisseria gonorrhoeae* taken on the same clinic visit. He returned ten days after completing therapy for test-of-cure cultures. The pharyngeal culture was positive; the urine culture was negative. He was retreated, this time with aqueous procaine penicillin G (APPG) 4.8 million units intramuscularly and 1 g probenecid orally. A follow-up throat culture taken seven days later was negative, but a second culture one week after that was again positive for *Neisseria gonorrhoeae*. The patient denied any sexual contact after diagnosis. He was treated again with APPG 4.8 million units and probenecid 1 g followed by ampicillin 0.5 g four times a day for four days. Two follow-up cultures one week apart, the first done ten days after completing therapy were negative. The throat isolate was negative for penicillinase production. When tested for penicillin resistance by the penicillin disc method, it gave a zone size of 25 mm.

Patient #2, a 25 year old male had a urethral discharge which failed to reveal Gram-negative diplococci on smear but was presumptively positive for gonococci. His throat culture was positive for *Neisseria gonorrhoeae* on culture. His rectal culture was negative. He came back for test-of-cure cultures 19 days after taking the initial loading dose. He denied re-exposure but had taken only five instead of eight ampicillin capsules after taking the initial loading dose. His urine culture was negative but his throat culture was positive. He was retreated with the same regimen. He failed to return for test-of-cure cultures but returned about three months later because of a urethral discharge. A throat culture done at that time was negative. His throat isolate was negative for beta-lactamase production. The test for penicillin resistance gave an inhibitory zone diameter between 21 and 22 mm indicating a borderline resistant strain.

Patient #3 was a 28 year old female. Her only site of gonococcal infection was the pharynx. Her cervical and rectal cultures were negative. Her first test-of-cure culture after taking the drug regimen under study was positive. The isolate produced beta-lactamase and there was no zone of inhibition around the penicillin disc. This treatment failure is not surprising since one would not expect PPNG strains to respond to ampicillin.

## DISCUSSION

Pharyngeal infections with *Neisseria gonorrhoeae* pose a dilemma for the treating physician. Some researchers (13) attach no clinical significance to the infection at this site arguing that it may be a site of

colonization as opposed to being a source of infection while others (5, 14, 15) have cited oropharyngeal infections as a source of disseminated infection. Be that as it may, all researchers agree that pharyngeal infections are more resistant to treatment than uncomplicated urogenital infections, and high failure rates are obtained with some modes of therapy effective for uncomplicated urogenital infections.

Bro-Jorgensen and Jensen (4) treated 38 patients with pharyngeal gonorrhea with single dose oral ampicillin 1 or 2 g plus probenecid 1 g orally. There were 21 failures or 55%. This same "treatment had proved to be almost 100% effective in curing uncomplicated urogenital and rectal infections." Jones et al (8) treated 25 patients who had urethral or cervical infections with cefoxitin. All were cured of infection at these sites. Seven of the above patients had concomitant rectal infections and all were cured of infection at this site. However, of the seven who had concomitant oropharyngeal infection there were four treatment failures.

High cure rates in treating uncomplicated urogenital gonorrhea are achieved with single dose oral amoxicillin 3 g with probenecid 1 g orally or single dose ampicillin 3.5 g with probenecid 1 g orally (16, 17). Felman et al (16) for example, reported cure rates of 100% with amoxicillin and 96.4% with ampicillin. However, CDC data provided by Kraus (2) in his review article published in 1979 indicated that these same regimens are associated with high failure rates when used to treat pharyngeal gonorrhea. The amoxicillin regimen was associated with a failure rate of 50% (7 of 14) and the ampicillin regimen was associated with a failure rate of 42.9% (12 of 28).

The results of this study confirm the previous observation in this clinic with extended oral ampicillin therapy for pharyngeal gonorrhea (7). If the two studies are combined (see table 1) a total of 182 (105 + 77)

TABLE 1: RESULTS OF EXTENDED ORAL AMPICILLIN FOR PHARYNGEAL GONORRHEA

	Number of Patients Treated	Number Who Failed Treatment	Failure Rate
Previous Study (7)	77	1-3*	1.3%-3.9%
Present Study	105	1-3†	0.9%-2.8%
Combined	182	2-6	1.09%-3.2%

\* Two of the failures may represent reinfections.

† One patient did not take all the prescribed medication. Another patient was infected with a PPNG strain.

#### Medication used in this study:

Ampicillin trihydrate (generic name) 500 capsules produced by E. R. Squibb & Sons of Princeton, NJ. The proprietary name is Principen.

Probenecid (generic name) 500 mg tablets produced by Merck Sharp & Dohme of West Point, PA. The proprietary name is Benemid.

Both drugs were purchased by the Health Department.

patients were treated with the extended therapy, out of whom six had persistent infection, giving a failure rate of 3.2%. If one excludes the two patients who may have been reinfected, the one patient who missed three doses and the one patient infected with a PPNG strain, there are only two treatment failures for a failure rate of only 1.09%. Support for the concept that multiple dose oral ampicillin might be effective in the treatment of pharyngeal gonorrhea comes from the work of Sands (18). He observed a treatment failure of 10.7% when treating males with anorectal gonorrhea with a single dose of 3.5 g of ampicillin orally plus 1 g

of probenecid orally. Repeating the ampicillin plus probenecid dose once in 8-14 hours reduced the failure rate to 1.6%.

Other drugs effective for the treatment of pharyngeal gonococcal infections are aqueous procaine penicillin G (APPG) 4.8 million units intramuscularly with 1 g of probenecid orally, and tetracycline hydrochloride for a total dosage of 9.5 to 10.0 g orally over a five day period.

Cumulative studies reported by Wiesner et al (5) with the APPG regimen indicated a failure rate of 4.4% (2 of 45). Data provided by Kraus (2) from the Center for Disease Control (Atlanta, Ga.) program of therapy monitoring, United States 1978 showed a failure rate of 9.3% (4 of 43). Sands (19) reported a failure rate of 5.9% (7 of 102). Fiumara (20) also employed the APPG regimen but without concomitant probenecid: He reported a failure rate of 3% (1 of 34).

Although several authors (19, 20) reported 100% cure rates with the tetracycline regimen other authors (6, 21) have reported occasional failures so that the cumulative failure rate of 71 patients treated is 4.2% (three patients). It should be noted that Karney (6) who reported two of the failures used a total dose of only 9.0 g.

Due to the emergence of penicillinase producing *Neisseria gonorrhoeae* (PPNG) strains, studies are being done to determine their response to therapy. It would not be anticipated that ampicillin, amoxicillin or APPG which are susceptible to beta-lactamase action would be effective in treating pharyngeal or urogenital infections due to PPNG strains. Since spectinomycin, at least in single dose therapy, is ineffective in eradicating non-PPNG strains from the pharynx (5, 6), one would not expect it to be effective in eradicating PPNG strains. Lindberg et al (3) studied seven patients with PPNG positive pharyngeal infections and found only one responded favourably to a single dose of spectinomycin. These same authors reported that only one out of four PPNG strains responded to cefuroxime when used as a single dose. However extended therapy with cefuroxime for three days or for seven days was successful in all cases.

Another drug combination that shows some promise in pharyngeal infections is trimethoprim/sulfamethoxazole (80/400 mgs.) combined in a single dose tablet in various dosage schedules. Bro-Jørgensen and Jensen (4) used a dosage of two tablets two or three times a day for one week in 35 patients and had an almost 100% success rate. These results were published in 1973 prior to the emergence of PPNG strains. Since trimethoprim/sulfamethoxazole has activity against PPNG strains and is effective against treating pharyngeal gonorrhea due to non-PPNG strains, it seems reasonable to expect that this drug combination will be effective in treating pharyngeal gonorrhea due to PPNG strains. Although there are no published data to support these assumptions CDC (9) currently recommends using it as follows; nine tablets in daily single dose for five days for a total of 45 tablets for PPNG infections.

There is some controversy as to whether or not individuals from whom gonococci have been isolated on throat cultures should be treated especially if these are asymptomatic. It is generally agreed that such individuals are not an important reservoir of infection, although it is speculated that transmission might occur in some cases. Perhaps the chief rationale for therapy has been the concern that the pharynx may be a source of disseminated disease (5). It is also possible that the pharynx may be colonized as a result of dissemination. This study does not contribute to the resolution of this controversy, and for the present it is still clinic policy to treat such individuals. It is the im-

pression of the authors that most authorities recommend treatment of pharyngeal gonorrhoea.

While single dose therapy is preferable especially with the patient population seen in VD clinics, extended ampicillin therapy seems to be effective and practical. It does not have the disadvantages of parenteral penicillin — e.g. procaine reactions, greater risk of anaphylaxis and eliminates the need to observe patients following the injections.

Since in this community PPNG strains do not pose a special problem, the incidence being 20 cases in 1981 (22 in 1982) in the whole county, which has a population of over one million, the ineffectiveness of ampicillin against PPNG strains is not an important consideration. Penicillin resistant non-PPNG strains are also uncommon. While not pertinent to pharyngeal gonorrhoea, in the context of total patient management, ampicillin has the disadvantage of not being as effective against chlamydia as tetracycline. Tetracycline is also more likely to be effective against penicillin resistant strains (both PPNG and non-PPNG). However the initial loading dose of ampicillin and probenecid followed by extended oral ampicillin medication has the advantage of rendering the patient with gonorrhoea non-communicable faster than the oral tetracycline regimen and is effective in treating anorectal infections in both male and females (unpublished data compiled by senior author). High failure rates have been reported by Washington (22) in a review article and by Sands (18) when the tetracycline regimen has been used to treat anorectal infections in males. Sands (18) for example, reported a failure rate of 14.4% (14 of 97).

In summary, although many questions remain unanswered, from the experience in this particular facility, an oral treatment schedule consisting of an initial loading dose of 3.5 g ampicillin trihydrate with probenecid 1 g, plus ampicillin 0.5 g four times daily on day two and day three (for a total of 7.5 g ampicillin) seems to be an effective mode of treatment for uncomplicated urogenital, anorectal and pharyngeal gonorrhoea in both males and females in the clinic population studied which has low incidence of infections due to penicillin resistant strains of either the PPNG or non-PPNG variety.

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