A microbiological study of failed penicillin therapy for gonococcal urethritis in Durban

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Summary

Seventy-five men presenting with persistent urethral discharge after penicillin therapy were investigated for sexually transmitted pathogens during July - September 1987. The major aetiological agent isolated was *Neisseria gonorrhoeae* (58 patients (77,3%)). Penicillinase-producing *N. gonorrhoeae* (PPNG) accounted for 58,6% of 58 isolates. *Chlamydia trachomatis* was detected in 10,7% of patients and *Trichomonas vaginalis* in 14,7% of patients. When there is a high prevalence of PPNG, the use of penicillin as a first-line agent for therapy should be discontinued in favour of an agent active against PPNG and non-PPNG strains. Furthermore, in view of the relatively high prevalence of *T. vaginalis*, patients returning with persistent urethral discharge should be investigated and treated for infection with this protozoan.

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Neisseria gonorrhoeae has been shown to be the most common cause of acute urethritis in untreated black men in South Africa,[1-3] with studies from several centres revealing prevalences in excess of 90%.[4,5]

In Durban, the prevalence of penicillinase-producing strains of *N. gonorrhoeae* (PPNG), which were first detected in 1977,[6] has increased steadily to reach 26,2% in December 1985.[5]

Despite the high prevalence of PPNG, at the time of this study the standard antibiotic therapy employed locally (at the Sexually Transmitted Diseases Clinic) for patients presenting with untreated acute gonococcal urethritis (diagnosed at the clinic by Gram staining) was intramuscular procaine penicillin in a dose of 4,8 million units plus oral probenicid 1 g. For penicillin-allergic patients, oral minocycline (100 mg twice a day for 7 days) was given as alternative therapy.

Patients treated with the above regimen occasionally return to the clinic complaining of persistent urethral discharge. Because of the high local prevalence of PPNG and the relatively low prevalence of associated chlamydial infection — 12% reported from Johannesburg[7] and 17% reported locally[5] — it has been assumed that most persistent infections are due to PPNG and such patients are usually treated with intramuscular spectinomycin or oral tetracycline, depending on the findings obtained from Gram-stained endo-urethral smears.

Since no systematic study had previously been performed to ascertain the aetiology of urethritis in such patients, a study was therefore undertaken to determine the aetiology of urethritis in patients who, having received procaine penicillin plus probenicid therapy for gonococcal urethritis, returned with persistent urethral discharge.

Patients and methods

A total of 75 black men were investigated during the period July - September 1987. All patients had returned to the Sexually Transmitted Diseases (STD) Clinic at King Edward VIII Hospital complaining of persistent urethral discharge after having been given the standard treatment. On specific questioning, all patients denied having had any sexual contact subsequent to treatment. Informed consent was obtained before collection of specimens.

Endo-urethral specimens were obtained from each patient using sterile calcium alginate-tipped swabs. These swabs were processed as follows: (*i*) a smear for Gram staining; (*ii*) a wet-mount; and (*iii*) a smear for direct immunofluorescence staining for *Chlamydia trachomatis* (Microtrak; Syva).

Gram-stained urethral smears were examined microscopically for the presence of inflammatory cells and bacteria. Urethritis was regarded as being present if more than 4 inflammatory cells per high-power oil-immersion field (× 1 000) were

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observed. Immunofluorescence staining and microscopic examination for the detection of *C. trachomatis* were performed according to the manufacturer's instructions. Wet-mounts were examined microscopically for inflammatory cells, yeasts and motile trichomonads.

The following culture media were directly inoculated with specimens at the clinic: (*i*) modified New York City medium (MNYC)[8] for the isolation of *N. gonorrhoea*; (*ii*) human blood agar for *Gardnerella vaginalis*; (*iii*) modified Diamond's medium[9] for *Trichomonas vaginalis*; and (*iv*) Shepard's U9 broth[10] for genital mycoplasmas. Inoculated media were immediately placed in a candle extinction jar and transported to the laboratory within 2 hours of collection.

In the laboratory, MNYC and human blood agar plates were incubated at 36° C in an atmosphere of 10% CO_2 for 48 - 72 hours. Colonies of *N. gonorrhoeae* were identified by their colonial morphology, appearance in Gram-stained smears, positive oxidase test results and characteristic carbohydrate fermentation. All isolates were tested for penicillinase production by a chromogenic cephalosporin method.[11]

The U9 broths were incubated anaerobically at 36° C and observed daily for up to 7 days for colour change (owing to alkalinity resulting from urea hydrolysis)[12] in the absence of turbidity; whereupon they were subcultured onto Shepard's A-7 agar.[13] Inoculated A-7 plates were incubated anaerobically for 48 hours and then examined under 100 × magnification for characteristic colonies of *Ureaplasma urealyticum* and *Mycoplasma hominis*.

The modified Diamond's media were incubated anaerobically at 36° C. Wet-mounts were prepared daily for up to 7 days, and examined microscopically for the presence of *T. vaginalis*, which was identified by its characteristic motility and morphology.

Results

On average, patients returned to the clinic 11,5 days after initial penicillin therapy (range 3 - 30 days). The mean age of the patients was 27 years (range 16 - 51 years). Urethritis was present in all patients as determined by the presence of more than 4 inflammatory cells per high-power field in Gram-stained smears.

N. gonorrhoea was detected in 58 patients (77,3%) by culture. In 57 of these, typical Gram-negative intracellular diplococci were seen. Of the 58 *N. gonorrhoeae* isolates, 34 (58,6%) produced penicillinase.

The micro-organisms detected in endo-urethral specimens are summarised in Table I. *T. vaginalis* was detected in 11 patients (14,7%); 7 by culture in Diamond's medium and 8 by positive wet smears.

A single aetiological agent was identified in 44 patients. *N. gonorrhoeae* was the most common, being present in 31 patients (41,3%). *T. vaginalis* was the sole agent detected in 5 patients (6,7%) while in only 1 patient was *C. trachomatis* the sole organism detected. There were 3 patients in whom none of the micro-organisms sought were detected.

Mixed infections were detected in 28 patients. These data are presented in Table II. In 17 of these (22,7%) *U. urealyticum* was present in association with *N. gonorrhoeae*.

TABLE II. MULTIPLE MICRO-ORGANISMS ISOLATED FROM 28 PREVIOUSLY TREATED PATIENTS

Micro-organism	Positive No.	Positive %
N. gonorrhoeae* + *U. urealyticum	**17**	**22,7**
N. gonorrhoeae* + *C. trachomatis	**5**	**6,7**
N. gonorrhoeae* + *T. vaginalis	**4**	**5,3**
C. trachomatis* + *T. vaginalis	**1**	**1,3**
N. gonorrhoeae* + *T. vaginalis* + *C. trachomatis	**1**	**1,3**

Discussion

Urethral inflammation or discharge which persists in patients successfully treated for gonococcal urethritis is generally regarded as post-gonococcal urethritis (PGU). The micro-organisms commonly implicated in the aetiology of PGU include *C. trachomatis* and *U. urealyticum*, while *T. vaginalis* and *G. vaginalis* are regarded as unusual or rare causes.[14]

In this study of patients previously treated with penicillin for gonococcal urethritis and who emphatically denied re-infection, the single major aetiological agent of persistent urethral discharge was *N. gonorrhoeae*. Furthermore, in only 11 of the patients (14,7%) was a recognised mixed infection detected. This high prevalence of *N. gonorrhoeae* is in keeping with its high prevalence in patients with untreated acute urethritis reported from this centre (87% and 96%).[2,5] The fact that nearly 60% of isolates were PPNG was not surprising in view of the high prevalences (up to 26,2%) of PPNG recorded in studies on patients with untreated gonococcal urethritis at the same clinic.[5]

TABLE I. MICRO-ORGANISMS ISOLATED FROM ENDO-URETHRAL SPECIMENS OF 75 PREVIOUSLY TREATED PATIENTS

Micro-organism	Total patient isolates	%	No. of patients in whom micro-organism was sole isolate	No. of patients in whom micro-organism was associated with other micro-organism(s)
N. gonorrhoeae	**58**	**77,3**	**31**	**27**
T. vaginalis	**11**	**14,7**	**5**	**6**
C. trachomatis	**8**	**10,7**	**1**	**7**
U. urealyticum	**25**	**33,3**	**2**	**23**
M. hominis	**7**	**9,3**	**3**	**4**
β-haemolytic streptococcus	**2**	**2,7**	**2**	**0**
G. vaginalis	**0**	—	—	—

Number of patients in whom 1 or more micro-organisms detected = 72 (96%); no micro-organism(s) detected = 3 (4%); number of patients with mixed infections = 28 (37%); number of patients with single infection = 44 (59%).

Patients treated at this clinic for gonococcal urethritis are normally requested to return within 7 days for follow-up. For this study, patients returning within 30 days of therapy with a urethral discharge and denial of sexual contact were included. However, we realise that all patients may not necessarily have abstained from sexual activity and this may explain the finding of 41,4% non-PPNG strains.

The importance of *C. trachomatis* in the aetiology of acute urethritis appears to differ significantly in different communities in South Africa. In a Johannesburg study of acute urethritis,[7] *C. trachomatis* was isolated from significantly fewer black men than white men. Moreover, the majority of chlamydial infection in black men was found to be associated with *N. gonorrhoeae*. In a local study,[5] we detected *C. trachomatis* in 17% of black men presenting with urethral discharge and these were predominantly associated with gonococcal infection. The finding of 10,7% *C. trachomatis* in this study group gives support to a less important role for this agent in acute urethritis among lower socio-economic groups. Alternatively, as suggested by Ballard *et al.*,[7] high antichlamydial antibodies present in this population group may result in failure to isolate the organism.

T. vaginalis is generally considered to cause self-limiting, asymptomatic infections in men. In the USA, it has been shown to infect up to 4% of men attending STD clinics.[15] A recent report from Zimbabwe recorded a 5,5% prevalence among men attending an STD clinic in Harare.[16] However, in women *T. vaginalis* is a frequent cause of vaginitis and a prevalence of over 40% has been shown for women attending the STD clinic in which this study was performed.[17] The relatively high prevalence of 15% in this study suggests an important aetiological role for *T. vaginalis* in patients that have persistent urethritis after penicillin treatment. It is our opinion that such patients should be appropriately investigated for infection with this protozoan and treated accordingly.

G. vaginalis was not isolated from any of the patients investigated. *U. urealyticum* was the sole isolate in only 2 patients while it was isolated from 17 patients with *N. gonorrhoeae* infection, indicating a less important aetiological role. This view is supported by other workers and the results of previous studies performed locally.[5]

The high prevalence of PPNG isolates, which did not respond to therapy with penicillin, and the relatively high prevalence of *T. vaginalis* among the study group raises important diagnostic and therapeutic considerations. The present study also confirms previous findings that the recommended antibiotic therapy for gonococcal infection is ineffective in the eradication of *C. trachomatis* and *T. vaginalis*. Some workers have suggested that first-line antibiotic therapy against *N. gonorrhoeae* be changed from penicillin to an agent active against PPNG and non-PPNG when PPNG levels reach 3% or greater.[18]

In view of the above, we agree that with such high levels of PPNG as were present in this patient group, the use of penicillin as first-line agent should be discontinued. Single-dose antimicrobial agents recommended by the Centers for Disease Control in Atlanta[19] for the treatment of gonococcal urethritis due to both PPNG and non-PPNG are spectinomycin or ceftriaxone. It should be noted that since the completion of this study, ceftriaxone has been made available at this clinic for first-line therapy for gonococcal urethritis. However, patients returning with persistent urethral discharge after such treatment should be investigated for *C. trachomatis* and *T. vaginalis* and treated appropriately.

Ideally such patients ought to be investigated for concurrent sexually transmitted pathogens at their first clinic visit, but such an undertaking is not possible logistically or economically due to overstressed facilities at this clinic.

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