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Non-gonococcal urethritis due to *chlamydia trachomatis:* the Ibadan experience

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Summary
Using a qualitative amplified enzyme-linked immunoassay, two hundred and eighty-nine male patients with symptoms and signs suggestive of urethritis were investigated for *Chlamydia trachomatis* as a cause of non-gonococcal urethritis (NGU). Ninety-one (31.49%) of the 289 male patients investigated had gonococcal urethritis whilst 198 (68.51%) had NGU out of which 112 (56.60%) had chlamydial urethritis and 14 (7.1%) had Trichomonal urethritis. Two (6.7%) of the control subjects had *C. trachomatis* in their urethral swabs. The difference in the occurrence of *C. trachomatis* between the patients and the controls was highly statistically significant *(P<0.001)*. The age range of peak incidence among the patients investigated was 20-29 years. Thirteen of the men treated for gonorrhoea still had watery urethral discharge and irritation and were diagnosed as having post-gonococcal urethritis (PGU), eleven (84.6%) of whom had *C. trachomatis* demonstrated in their urethral swabs. We were able to demonstrate a significant difference in clinical symptoms in men with gonorrhoea and NGU but only a slight difference between men with chlamydia-positive NGU and chlamydia-negative NGU.

Keywords: *Non-gonococcal urethritis, chlamydia trachomatis, Nigeria*

Résumé

Utilisant une un lien qualitative d'enfyme amplifie d'immuno-assay, 289 patients homes ayant les sysmtiomes et signes sugerant l'urethritis ont ete inventorie au chlamydia trachomatis comme cause de l'urethritis non-genoccoque (UNG).91 (31,49%) avaient l'urethritis gonoccoque alors que 198 (68,51%) avaieny UNG. De ces derniers, 112 (56,60%) avaient l'urethritis chlamydiale et 14 (7,1%) l'urethritis Trichomonale. Deux (6,7%) des sujets de controle availent *C.trachomatis* dans l'apparition de C. trachomatis entre les patients et les sujets de controle etait statisticquement significative (P<0,001). L'intervalle d'age de l'incidence la plus elevee parmi les maladies examires etait de 20 a 29 ans. 13 des patients traits de gonorrhea continuaient a avoir des decharges urethrales liquids et des irritations, et ont ete diagnostiques comme ayant l'urethritis post – gonoccoque (UPG) 11 (84,6%) de ceux – ci avaient *C. trachomatis* dans leur pelevent. Noun avons ete en mesure de rolementrer une difference significative ayant la gonorrhea et UNG, mais seulement une faible difference entre les homes ayant la chla mydia – positive UNG et ceux ayant la chlamydia – negative UNG.

Introduction

Sexually transmitted urethritis in men is either gonococcal or non-gonococcal [1]. The incidence of non-gonococcal urethritis (NGU) has risen more rapidly than that of gonorrhoea and it is now recognised as the most common sexually transmitted disease worldwide [2]. Although no reliable statistics on NGU are available in Nigeria, as NGU is not reported, previous studies done from our centre also suggest this trend [2-4].

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Non-gonococcal urethritis accounted for over 60% of all our cases of urethritis in 1989. It has been reasonably established that *Chlamydia trachomatis* is the most common sexually transmitted genital pathogen and is found to cause over 50% of NGUs [3-7]. The role of other microbial agents in the aetiology of NGUs has also been established [4, 8-11]. While the authors found *Trichomonas vaginalis* accounting for 8.4% of cases in 1989 [4], *C. trachomatis* has been incriminated in over 50% of all cases of NGU [5-7,12]. *Ureaplasma urealyticum* accounted for over 30% and less common agents such as *Candida albicans*, Herpes simplex virus and *Gardnerella vaginalis* accounted for less than 1% of cases [2].

The incidence of *Chlamydia trachomatis* infection in men has not been well defined in our environment since the infections are not officially reported or microbiologically confirmed. However, those that were excluded for gonococcal urethritis by microscopic examination and culture we treated for chlamydia and ureaplasma urethritis, both being sensitive to Tetracycline.

Chlamydia trachomatis urethral infection is more often asymptomatic than gonococcal urethritis and when symptoms occur, they are milder [13-14]. Clinically, chlamydia positive and chlamydia negative NGU cannot be differentiated based on signs or symptoms. Both usually present after a 7- to 21-day incubation period with dysuria and mild to moderate whitish or clear urethral discharge. However, many men with asymptomatic chlamydial urethral infection exhibit persistent urethral leucocytosis on Gram stain of urethral secretions, indicating on going inflammation [14]. While there are well-established diagnostic screening procedures in developed countries for *Chlamydia trachomatis*, cases of urethritis due to the agent are still being diagnosed by exclusion in Ibadan. However, this study is intended to determine the incidence of chlamydial infection in patients with urethritis using a qualitative amplified enzyme-linked immunoassay (IDEIA T.M chlamydia test). [15-18]

Material and methods

Study population

The study population consisted of all male patients presenting with urethral discharge with or without dysuria at the Special Treatment Clinic, University College Hospital, Ibadan, from March 1994 to February 1996. A standard medical history was taken from each patient concerning symptoms and signs, marital status, previous genito-urinary symptoms, date of last coitus and sexual consorts (whether casual or regular). The antimicrobial drugs used before attending the clinic were noted. A clinical examination of the lower genito-urinary tract for signs of infection such as urethral discharge and the nature of the discharge was carried out. Urethral discharge was collected from those patients that had obvious urethral discharge using cotton - tipped applicator. Where there was no obvious urethral discharge, urethral specimens were taken using the method advocated by Lanceley [10] by gently stroking the urethral wall with the applicator.

Control group
Thirty male students who had no signs or symptoms suggestive of urethritis served as control subjects.

Gonococcal urethritis
Urethral smears showing Gram-negative intracellular diplococci were considered as presumptive evidence and were confirmed in all cases by a positive culture for *Neisseria gonorrhoeae*. Cultures were made on Thayer-Martin medium incubated at 37° in a candle extinction jar for 24 to 48 hours. Typical colonies were picked and identified after subculture on brain heart infusion agar (BHIA, Oxoid) by oxidase reaction and sugar utilisation tests in serum - free agar medium [19].

Trichomonal urethritis
The specimens were examined for the presence of *Trichomonas vaginalis* by agitating the cotton swab in 1 ml of saline in a test tube and a drop of the resulting suspension transferred to a microscope slide which was covered with a cover slip and then examined at x 100 and x 400 magnification. Culture for *T. vaginalis* was performed using nutrient broth glucose serum medium [20]. Examination for growth of *T. vaginalis* was made at 48 hours and 5 days of incubation by making a wet mount of the sediment from the bottom of the Bijou bottles containing the medium and motile *T. vaginalis* were searched for.

Screening for chlamydia
Urethral specimens were collected by inserting a cotton-tipped swab 2-4 cm into the urethra. The tip was then cut into Bijou bottles containing the transport medium [nonionic detergent in a solution of organic buffer salt containing metal chloride, reducing sugar and an antimicrobial agent] provided. These and those from the controls were vortex mixed for 15 seconds and placed in a boiling water bath for 15 minutes ensuring that the Bijou bottle caps were loosened and that water did not enter the bottles. These were then removed, cooled to room temperature and then vortex mixed before testing.

0.2 ml specimens were added to antibody-coated wells. In addition, 0.2 ml aliquots of treated positive and negative controls were tested. Three negative wells and one positive control well were included with each batch of specimens tested. About 0.5 ml of enzyme-conjugated monoclonal antibodies was then added to each well, which was incubated in a shaker incubator at 37 degrees centigrade for one hour.
The contents of the wells were aspirated removing as much of the liquid as possible. Wells were then washed using diluted washing buffer and the contents well drained using a clean absorbent.

0.1 ml of freshly reconstituted substrate was added to each well and was incubted the plate in a shaker incubator at 37° with shaking for 20 minutes after which 0.1 ml of thawed amplifier was added to each well for colour development and incubated for 10 minutes. The reaction was stopped by adding 0.5ml of the stopping solution to each well and the plate was assessed visually within one hour. Specimens giving red/magenta colour more intense than that of negative controls were considered as positive for chlamydia.

Data analysis
Statistical analysis was done by applying the t-test and the chi-squared test.

Result
During the period of the study, 289 male patients with symptoms and signs suggestive of urethritis were investigated.

Ninety-one (31.49%) of the 289 patients investigated had Gonococcal urethritis whilst 198 (68.51%) had NGU. Amongst those with NGU, *Chlamydia trachomatis* was identified in 112 (56.6%) and Trichomonal urethritis in 14(7.1%). (Table I).

Table 1: Incidence of chlamydiatrachomatis in men with ngu (N=198)

Diagnosis	Number	Percent
C. trachomatis	112	56.6%
Trichomonal urethris	14	7.1%
Non-specific urethritis	72	36.3%
Total	198	100%

Amongst the 30 control subjects, *C. trachomatis* was recovered from two of them. The difference in the occurrence of *C. trachomatis* between the patients and the control group was highly statistically significant ($P< 0.001$). Of the 91 men with gonococcal urethritis examined for the presence of *C. trachomatis*, 11 (12.1%) were positive for *C. trachomatis* (Table 2).

Table 2: Incidence of chlamydiatrachomatis in men with ngu and gonorrhoea

Diagnosis	Number	chlamydia-positive	
		Number	Percent
NGU	198	112	56.6%
Gonorrhoea	91	11	12.09
Control group	30	2	6.7%

The patients that had gonococcal urethritis were treated with a single dose of Ciprofloxacin (Ciprotab by Fidson) and cure was confirmed in 100% by a negative smear and culture one week after treatment. Thirteen of the men treated for gonorrhoea still had watery urethral discharge and irritation with negative culture for *Neisseria gonorrhoeae* and hence were diagnosed as having post-gonococal urethritis (PGU). Eleven (84.6%) of those with PGU had *C. trachomatis* demonstrated in their urethral swabs.

Table3: Age distribution of patients with chlamydia positive urethritis

Age (in years)	Number	Percent	No positive for c. trachomatis	Percent
10 – 19	27	9.3%	13	11.6%
20 – 29	156	54.0%	74	66.0%
30 – 39	69	23.9%	18	16.1%
40 – 49	2	8.3%	6	5.3%
50 and above	13	4.5%	1	0.9%
Total	289	100%	112	100%

Table 3 shows the age distribution of the 289 male patients investigated and those positive for *C. trachomatis*. One hundred and fifty-six [54%] of all the patients were aged between 20-29 years whilst 74 [66.1%] of those positive for *C. trachomatis* were within the same age range.

Two hundred and eight [72%-] of the patients were single whilst 81 (28%) were married. Of the single patients, 76.4 percent had sexual contact with casual consort whilst

23.6%had contact with regular consorts. Of those patients that were married, 59.4 percent had sexual contact with casual consorts and commercial sex workers whilst 24.3 percent had contact with regular consorts. Only 16.3% had contact with their wives.

The degree of promiscuity expressed by the number of recent sexual partners was similar in both patients with gonococcal urethritis and chlamydial urethritis (Table 4).

Table 4: Number of recent sexual partners of men with gonococcal and chlamydial urethritis

Number of partners	Gonorrhea %	Chlamydia %
One	28%	31%
Two	42%	38.4%
Three	30%	30.6%

Dysuria was found significantly more often in patients with gonorrhoea (96%) compared with chlamydia-positive NGU patients (58%) ($-2 = 37.67$, $P<0.001$). There was a significant difference in the nature of the urethral discharge in men with gonorrhoea being mostly purulent in 67% of them and mucopurulent in 42% compared with NGU chlamydia-positive patients, which tended to be more mucoid and/or mucopurulent

All the patients found to be positive for chlamydia were treated with a course of oral Tetracycline.

Discussion

Non-gonococcal urethritis is commoner than gonococcal urethritis and is recognised as the most common sexually transmitted infection worldwide [3,12]. Previous studies from Ibadan showed NGU to be responsible for more than sixty percent of urethritis [3-4, 11]. This is in agreement with studies in the developed world [21-23]. The results of the present study compare favourably with these studies. Of the 289 patients investigated, 91 [31.5%] were observed to have gonococcal urethritis whilst 68.5% had NGU.

We had earlier depended on studies conducted at other centres for the role of *Chlamydia trachomatis* in NGU. *Chlamydia trachomatis* has been incriminated as one of the most common sexually transmitted genital pathogens and is reported to be associated with approximately half of all the cases of NGU [12]. Using a qualitative amplified enzyme-linked immunoassay, 112 [56.6%] of the 198 male patients with NGU were found to have *C. trachomatis*. Our findings are in agreement with those reported by other studies. Holmes *et al.* and Oriel *et al.* in their studies reported 42 % and 48%, respectively [6,24] whilst Alani *et al.* reported 67%. Schacter *et al.* reported 57% [5,25]. We consider this as a major achievement in our centre considering the non-availability of diagnostic facilities such as simplified cell culture technique which can be used to isolate *C. trachomatis* and make it possible to carry out larger epidemiological studies. However all cases of urethritis in which N. gonorrhoea were not isolated were routinely treated with tetracycline or Doxycycline - the drug of choice for *C. trachomatis* and *Ureaplasma urealyticum* while Trichomonal urethritis is more closely associated with Tetracycline-unresponsive NGU [26,27]. However, with excellent activity against *c. .trachomatis* and *Neisseria gonorrhoeae* and prolonged elimination half-life allowing once-daily dosage, the fluoroquinolone trovafloxacin has potential advantages in the treatment of uncomplicated chlamydial infection [28].

A large percentage [66%] of the men with NGU due to C. trachomatis were within the age range of 20-29 years, which is the period of greatest sexual activity, and those in this group tend to be more promiscuous and hence prone to sexually transmitted diseases.

Post-gonococcal urethritis like NGU results from infection with *C. trachomatis* in which the patients acquire gonorrhoea and chlamydial infection simultaneously but due to the longer incubation period of *C. trachomatis*, develop a biphasic illness if their initial gonorrhoea is treated with an agent that does not radicate chlamydia [29]. Of men infected with both *C. trachomatis* and *N. gonorrhoea*, which are successfully treated for gonorrhoea, eighty percent or more develop symptomatic PGU or urethral leucocytosis with symptoms [6,30,31] and our finding in the present study confirms this fact. Thirteen of the 91 men that were successfully treated for gonorrhoea had watery urethral discharge and irritation; 11 (85%) of who had *C. trachomatis* demonstrated in their post-treatment urethral swabs. These were successfully treated with Tetracycline.

In men with NGU, trials using placebos or agents such as Spectinomycin or Ciprofloxacin, which are ineffective against C. trachomatis, have clearly established the greater effectiveness of specific antimicrobial treatment in eliminating both signs and symptoms of infection and eradicating chlamydia [32,33]. Clinical trials indicate that Tetracycline hydrochloride, Doxycycline Minocycline, Erythromycin, Trimethoprim-Sulphamethoxazole all achieve compara-ble clinical cure rates of approximately 85-95 percent in men with chlamydial NGU [34]. However, Tetracycline hydrochloride has been the most widely used agent for the treatment of NGU because of its effectiveness and low cost. This is the drug of choice for NGU in our centre.

The magnitude of the problems posed by the asymptomatic chlamydial urethritis need to be addressed. At least 40 percent of all chlamydial infections seen in STD clinics are asymptomatic and an even greater proportion of chlamydial infections in sexually active populations not seeking health care are probably asymptomatic. They stand the risk of not only transmitting the infection but also developing complications.

Berger and co-workers have shown that *C. trachomatis* causes most cases of what was previously termed as idiopathic epidymitis in young sexually active males [35]. This may be one of the factors responsible for the increased number of azospermic cases being observed among young male patients in our clinic.

It is therefore advocated that diagnostic screening procedures for *C. trachomatis* should be established for high-risk populations seen in STD clinics to identify and treat asymptomatically infected individuals who are a major reservoir for *C. trachomatis*. All women identified as recent partners of men with NGU should be carefully examined for mucopurulent cervicitis and treated. This would go along way in the control of chlamydial genital infection with the attendant complications and sequelae.

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