

Treatment outcomes and loss to follow-up rate of male patients with gonococcal and nongonococcal urethritis who attended the sexually transmitted disease clinic: An 8-year retrospective study

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Abstract

Background: Poor follow-up compliance of patients with infectious urethritis is a recognized and serious public health problem in Thailand. **Aim:** The aim of this study was to determine treatment outcomes and loss to follow-up rate of male patients with gonococcal urethritis (GU) and non-GU (NGU) at a sexually transmitted disease (STD) clinic at Thailand's tertiary hospital. **Methods:** This retrospective chart review of male patients who sought treatment at STDs Clinic, Siriraj Hospital, and who were diagnosed with GU and/or NGU was conducted during January 2007 to December 2014 study period. **Results:** Two hundred and twenty-seven male urethritis patients were included in this study with a mean age was 29.5 years. GU and NGU were found in 120 (52.9%) and 107 (47.1%) of patients, respectively. Overall prevalence of GU and NGU during the 8-year study period at STD Clinic, Siriraj Hospital, was 8.6% and 7.8%, respectively. Ninety-six patients (42.3%) were lost to follow-up. Recurrent urethritis was found in 23.8% of patients, and HIV infection was identified in 11.6%. Mean age of patients lost to follow-up was 29 years. Compared with patients who attended every scheduled follow-up visit, men who have sex with men had a significantly lower rate of loss to follow-up ($P = 0.012$). **Conclusion:** Almost half of patients with GU or NGU were lost to follow-up, and one-quarter had recurrent urethritis. Fast and easy access to services that provide accurate diagnostic testing and effective treatment should be a public health priority to prevent complications and reduce rates of disease transmission.

Key words: Compliance, male, sexually transmitted disease, urethritis

INTRODUCTION

Urethritis in males that is caused by sexual transmission is a major health-care concern worldwide. Gonococcal urethritis (GU) is a common sexually transmitted disease (STD) that is caused by *Neisseria gonorrhoeae*. Common signs and symptoms in males are purulent discharge from the urethra with dysuria, perimeatal erythema, and edema. Positive test for intracellular Gram-negative diplococci from urethral

discharge establishes definitive clinical diagnosis of GU.^[1] In contrast, non-GU (NGU) is a nonspecific infection of the urethra with many infectious etiologies. NGU is confirmed in symptomatic men when staining of urethral secretions indicates inflammation without Gram-negative diplococci.^[2] GU and NGU coinfections are common.^[1]

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According to the 2014 annual epidemiological surveillance report on sexually transmitted infection conducted by the Bureau of Epidemiology, Ministry of Public Health, Thailand, 6,184 (17.6%) of 35,073 patients with STDs were diagnosed with gonococcal infection. The male-to-female sex ratio was 1:0.26. Age ranges of STD-infected individuals were as follows: 15–24 years (57.9%), 25–34 years (18.8%), and 35–44 years (8.7%).^[3] The percentage of infection in 15–24 years age group continues to grow on a year-over-year basis. As a result, GU and NGU are of increasing concern to physicians and public health officers in Thailand.

Antimicrobial resistance in GU and NGU is currently found worldwide. In 2012, the Gonococcal Isolate Surveillance Project from the United States reported 0.3%, 0.4%, 1.1%, 13.5%, and 22.5% of gonococcal isolates resistant to ceftriaxone, azithromycin, cefixime, ciprofloxacin, and tetracycline, respectively.^[4] The Gonococcal Resistance to Antimicrobials Surveillance Program from England and Wales reported 0.2%, 0.8%, 5.7%, 2.2%, 25.2%, and 75.0% of gonococcal isolates resistant to those same five antibiotics, respectively.^[5] Antimicrobial resistance affects treatment outcomes. Loss to follow-up and poor compliance rates among GU and NGU patients are an increasingly serious problem in Thailand. These two factors could result in an increase in the prevalence of antimicrobial resistance as well as an increase in the spread of infection to sexual partners.

Studies regarding treatment outcomes and loss to follow-up rate in GU and NGU in Thailand have been limited. This information is essential for policy and strategic planning regarding diagnostic tools and treatment regimens. Accordingly, the aim of this study was to determine treatment outcomes and loss to follow-up rate of male patients with GU and NGU at an STD clinic at Thailand's largest university-based tertiary care hospital. Clinical manifestations, risk behavior, laboratory investigations, and treatment were also evaluated between GU and NGU patients.

METHODS

This retrospective chart review of male patients diagnosed with GU and/or NGU during January 2007 to December 2014 study period at STD Clinic, Siriraj Hospital, Thailand, was approved by the Siriraj Institutional Review Board. Data regarding prevalence, clinical manifestations, risk behavior, laboratory investigations, and treatment were collected and evaluated.

GU was diagnosed based on urethral swab that found ≥ 5 intracellular Gram-negative diplococci per oil-immersion field. NGU was diagnosed from urethral swab with white blood cell ≥ 5 per oil-immersion field but without Gram-negative diplococci. Nucleic acid amplification testing (NAAT) was not routinely used for diagnosis in our center's STD clinic.

Treatment outcome in our study was based on clinical signs and symptoms of patients when they visited for follow-up. Normally, patients were appointed to follow-up at 2 weeks after treatment to check for treatment adherence and symptoms. Retest or urethral swabs were performed only in persistent symptomatic or suspected recurrent patients.

Statistical analysis

Descriptive statistics, such as mean \pm standard deviation (SD), median and range, and number and percentage, were used to describe demographic data, clinical characteristics, laboratory investigations, medications, outcome of treatment, and loss to follow-up rate. Chi-square test or Fisher's exact test was used to compare categorical variables. Continuous variables with and without normal distribution were analyzed by Student's *t*-test and Mann-Whitney U-test, respectively. Multivariate analysis was performed using logistic regression model. A $P \leq 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS Statistics version 18.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Two hundred and twenty-two male urethritis patients were included in this study. Mean age (SD) was 29.5 (11.6) years, with a range of 15–82 years. There were 29 (12.2%) patients that were men who have sex with men (MSM) and 10.6% were HIV-infected patients. History of sexual behavior risk was collected in 173 patients. Of these cases, 59% had multiple sex partners, 37.6% had engaged in sex with a prostitute within the previous 5 years, and 2.3% worked as a commercial sex worker. Sixty-nine percent of urethritis patients reported never using a condom. Regarding clinical characteristics, 73.1% presented with urethral discharge, of which 62.1% had purulent discharge, 4.4% had mucoid discharge, and 6.6% had clear fluid discharge. Regarding other symptoms, 7.5% had regional lymphadenopathy and 1.8% had associated fever.

Concerning diagnosis, 120 (52.9%) patients were diagnosed as GU and 107 (47.1%) as NGU. Overall

prevalence of GU and NGU among total patients in the STD clinic during the study period was 9.1% and 8.1%, respectively. The prevalence of GU and NGU was 11.0% and 9.7% in 2007, 10.9% and 8.7% in 2008, 9.6% and 7.2% in 2009, 7.9% and 10.8% in 2010, 6.2% and 8.7% in 2011, 7.8% and 4.5% in 2012, 7.6% and 8.6% in 2013, and 11.8% and 7.7% in 2014, respectively. Concomitant gonococcal conjunctivitis was found in two patients. No patients in either group presented with disseminated gonococcal infection. Almost all GU patients were diagnosed by Gram stain of intracellular Gram-negative cocci organism. Collection of intraurethral discharge for aerobic culture was performed in 45 of 120 (37.5%) GU patients depending on patient's health insurance coverage and aimed to determine drug resistance organism. Thirty-six (80%) patients were positive for *N. gonorrhoeae* that was sensitive to ceftriaxone and resistant to ciprofloxacin, penicillin, and tetracycline. For the other 20%, the result of culture was no growth. Only one culture specimen demonstrated beta-lactamase-negative *N. gonorrhoeae* with sensitivity to ceftriaxone, penicillin, and tetracycline but resistance to ciprofloxacin.

Regarding treatment, GU patients were prescribed with dual therapy consisting of ceftriaxone 250 mg intramuscular in a single dose with doxycycline 100 mg orally twice a day for 7 days for 102 patients (85%), ceftriaxone intramuscular alone for ten patients (8.3%), ceftriaxone intramuscular with azithromycin 1 g orally in a single dose for three patients (2.5%), azithromycin orally

alone for two patients (1.7%), doxycycline 100 mg orally twice a day for 7 days for one patient (0.8%), azithromycin with doxycycline orally for one patient (0.8%), and azithromycin with ciprofloxacin 500 mg orally a day for 7 days for one patient (0.8%). For NGU, patients were treated with doxycycline 100 mg orally twice a day for 7 days for 67 patients (62.6%), ceftriaxone 250 mg intramuscular 250 mg in a single dose with doxycycline orally for 27 patients (25.2%), ciprofloxacin 500 mg orally a day for 7 days for six patients (5.6%), azithromycin 1 g orally in a single dose for three patients (2.8%), ceftriaxone intramuscular alone for two patients (1.9%), and ceftriaxone intramuscular with azithromycin orally for two patients (1.9%). Among patients who complied with all follow-up instructions and scheduling, the cure rate was 96.2%. Average time to cure for both GU and NGU (SD) was 13.3 (6.6) days.

Ninety-six patients (42.3%) were lost to follow-up as shown in Table 1. All patients who reported for follow-up visits had taken all prescribed medications. Recurrent urethritis developed in 23.8% of total patients. Mean age of loss to follow-up patients was 29 years. Among these patients, the rate of HIV infection was 11.6%. Compared to patients that came to follow-up as appointed, MSM patients had a significantly lower rate of loss to follow-up ($P = 0.012$).

Demographic and clinical characteristics of GU and NGU patients are presented in Table 2. Shorter median time to onset, more purulent discharge, more

Table 1: Comparison of demographic data and clinical characteristics between male patients who were lost to follow-up and patients with good compliance

Demographic data	Patients lost to follow-up (n=96)	Patients with good compliance (n=131)	P
Mean age (years, SD)	29.0 (11.8)	29.9 (11.6)	0.548
Undergraduate education (%)	20/32 (62.5)	37/79 (46.8)	0.135
Risk factors (%)			
MSM	6 (6.3)	23 (17.6)	0.012*
Multiple sex partners	43/71 (60.6)	59/102 (57.8)	0.720
Prostitute contact in 5 years	29/71 (40.8)	36/102 (35.3)	0.458
Commercial sex worker	0/71 (0)	4/102 (3.9)	0.145
HIV infection*	5/43 (11.6)	12/117 (10.3)	0.778
Median time to onset (days, min, max)	7 (1, 180)	7 (1, 365)	0.824
Presenting symptoms (%)			
Urethral discharge	73 (76)	93 (71)	0.397
Purulent discharge	63/73 (86.3)	78/93 (83.9)	0.805
Mucoid discharge	4/73 (5.5)	6/93 (6.5)	0.794
Clear fluid discharge	6/73 (8.2)	9/93 (9.7)	0.745
Dysuria	66 (68.8)	94 (71.8)	0.624
Recurrent infection	21 (21.9)	33 (25.2)	0.562

*Statistical significance ($P \leq 0.05$). Data presented as number (%) or median and range unless otherwise specified. SD=Standard deviation; MSM=Sex with men

Table 2: Comparison of demographic data and clinical characteristics between patients with gonococcal and nongonococcal urethritis

Demographic data	Gonococcal urethritis (n=120)	Nongonococcal urethritis (n=107)	P
Mean age (years, SD)	28.2 (10.9)	40.0 (12.3)	0.075
Undergraduate education (%)	25/60 (41.7)	32/51 (62.7)	0.027*
Risk factors (%)			
Men who have MSM	20 (16.7)	9 (8.4)	0.063
Multiple sex partners	48/88 (54.5)	54/85 (63.5)	0.230
Prostitute contact in 5 years	22/88 (25.9)	43/85 (50.6)	0.001*
Commercial sex worker	2/88 (2.3)	2/85 (2.4)	1.000
Occasional condom use	32 (26.7)	27 (25.2)	0.806
HIV infection (%)	11/81 (13.6)	6/79 (7.6)	0.219
Median time to onset (days)	5 (1, 90)	14 (1, 365)	<0.001*
Presenting symptoms (%)			
Urethral discharge	116 (96.7)	50 (46.7)	<0.001*
Purulent discharge	113/116 (97.4)	28/50 (56)	<0.001*
Mucoid discharge	1/116 (0.9)	9/50 (18)	<0.001*
Clear fluid discharge	2/116 (1.7)	13/50 (26)	<0.001*
Dysuria	92 (76.7)	68 (63.6)	0.031*
Pruritus	2 (1.7)	16 (15)	<0.001*
Orchitis	6 (5)	4 (3.7)	0.753
Lymphadenopathy (%)	12 (10)	5 (4.7)	0.128
Systematic symptoms (%)			
Fever	4 (3.3)	0	0.124
Conjunctivitis	2 (1.7)	0	0.499
Median time to cure (days, min, max)	14 (7, 20)	14 (5, 50)	0.078
Lost to follow-up (%)	53 (44.2)	43 (40.2)	0.545
Recurrent infection (%)	23 (19.2)	31 (29)	0.083

*Statistical significance ($P \leq 0.05$). Data presented as number (%) or median and range unless otherwise specified. PMNS=Polymorphonuclear cells; MSM=Sex with men

dysuria, and more inguinal lymphadenopathy were found in GU patients than in NGU patients. Mean age of NGU patients tended to be higher than that of GU patients, but the difference was not statistically significant. Mucoid discharge, clear fluid discharge, and pruritus were presenting symptoms more often in NGU patients than in GU patients.

DISCUSSION

Urethritis is an important health problem in Thailand and worldwide. A 2013 study conducted in men in the United States reported the number of gonorrhea and chlamydia urethritis cases to be 19.8% and 17.2%, respectively.^[6] From a 2011 study conducted in India, the prevalence of GU and NGU in an STD clinic was 5.97% and 4.97%, respectively.^[7] In Thailand, study of young Thai men in Northern of Thailand reported percentage of GU and NGU among STDs in 1993–1995 was 20.2% and 15.2%, respectively.^[8] The present study identified increases in the prevalence for both GU and NGU over the 8-year study period in Thailand.

Antimicrobial resistance in *N. gonorrhea* is increasing and is becoming a public health crisis. A previous

survey of *N. gonorrhea* antibiotic susceptibility in six Southeast Asian countries from 2009 to 2012 reported that 84%, 59.5%, and 87% of *N. gonorrhea* isolates were resistant to penicillin, tetracycline, and ciprofloxacin, respectively.^[9] In the present study, almost all *N. gonorrhea* isolates (97.2%) produced beta-lactamase and were resistant to penicillin, tetracycline, and ciprofloxacin. All isolates, however, were susceptible to ceftriaxone.

Poor patient compliance regarding medication use increases the development of antimicrobial resistance. In addition, the patient loss to follow-up decreases a physician's ability to evaluate treatment outcomes. If the prescribed treatment protocol fails, the spread of infection (especially resistant strains) to sex partners becomes a major concern. Almost half of urethritis patients in this study were lost to follow-up. MSM had significantly lower rates of loss to follow-up. This may be due to a higher awareness of health-care problems among MSM. Education that focuses on the importance of follow-up is necessary. Moreover, clinical management, including timely and accurate diagnosis and effective treatment, remains a challenge in resource-limited countries.

As a result, diagnostic tests that are sensitive and that provide an accurate and rapid result are a necessary tool in an STD unit setting. However, Gram-stain test for urethritis in males still has an essential role due to its high specificity, with interpretable results available within a few minutes to a few hours.^[10] Furthermore, the cost of Gram-stain testing is very low and is available in every hospital. However, because of its lower sensitivity, a negative Gram stain should not be considered sufficient for ruling out infection in asymptomatic men. Additional testing to identify etiology is recommended to prevent complications, reinfection, and transmission because definitive diagnosis improves treatment compliance, delivery of risk reduction interventions, and partner notification. NAAT is preferred for detection of *Chlamydia trachomatis* and *N. gonorrhoeae*, with urine being the preferred specimen in males.

Treatment modalities in our clinic were subject to physicians' decisions according to uncertainty treatment guideline and patient's history of drug allergy. Appropriate treatment is becoming more challenging due to increasing antimicrobial resistance, particularly in gonorrhea and *Mycoplasma genitalium* infections. Poor compliance and low regulation of antibiotic treatment increase the risk of antimicrobial resistance. Having acknowledged the increase in antibiotic resistance, the effectiveness of antibiotic treatment remains high. By way of example, a previous study reported that only 0.3% of *N. gonorrhea* isolates in Thailand were resistant to azithromycin. The current 2015 Centers for Disease Control and Prevention treatment guideline recommends ceftriaxone 250 mg intramuscular in a single dose plus azithromycin 1 g orally in a single dose. This dual therapy is considered to be the first-line regimen for GU treatment. From the findings of our study, the high loss to follow-up rates should raise awareness regarding the importance of patient compliance. Azithromycin provides more compliance advantage and convenience as compared to doxycycline. Moreover, because of the higher rate of gonococcal resistance to tetracycline and high rate of azithromycin susceptibility of *M. genitalium*, the use of azithromycin should be encouraged in Thailand. To maximize compliance with recommended therapies, the administration of medications should be directly observed in the clinic or at least the first dose should be dispensed on site and directly observed in patients prescribed with multidose regimens. Direct observation of single-dose therapy with azithromycin should be considered the first best choice in patients for whom adherence to multiday dosing is a concern.

Almost half of patients with GU or NGU were lost to follow-up, and one-quarter had recurrent urethritis. According to cure rate, even though high cure rate was demonstrated in patients who came to follow-up, we could not assume good outcomes in patients who lost to follow-up. Good counseling at the first visit is essential to enhance the patient's education and to improve the compliance. Fast and easy access to services that provide accurate diagnostic testing and effective treatment should be a public health priority to prevent complications and reduce rates of disease transmission.

CONCLUSION

Almost half of patients with GU or NGU were lost to follow-up, and one-quarter had recurrent urethritis. Fast and easy access to services that provide accurate diagnostic testing and effective treatment should be a public health priority to prevent complications and reduce rates of disease transmission.

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Conflicts of interest

There are no conflicts of interest.

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