

Clinical and Epidemiological Characteristics of Patients with Syphilis: 5 Year-Case Study from Thailand

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Background: Syphilis has been increasing dramatically worldwide since 2000, especially among men who have sex with men (MSM), and in those with human immunodeficiency virus (HIV) infection. However, most previous reports studied about prevalence and risk factors of syphilis in MSM population without statistical comparison with non-MSM population.

Objective: The present study aimed to describe epidemiological trends, clinical manifestations, laboratory investigation, treatment, and HIV co-infection in patients diagnosed with syphilis, including statistical evaluation these data between MSM and non-MSM, as well as HIV and non-HIV populations.

Material and Method: This was a retrospective medical records review of patients diagnosed with syphilis who attended Sexual Transmitted Diseases (STD) clinic between January 2008 and December 2012. Demographic data, clinical manifestations, HIV status, VDRL titer, and treatment regimens were collected.

Results: Of the 922 patients that attended the STD clinic, 143 syphilis patients were recruited with an overall prevalence of 15.5%. Twenty-six patients were MSM and 31 were HIV infected patients. Prevalence rate of syphilis in MSM and HIV infected patients were 2.8% and 3.4%, respectively. Prevalence had upward trend that started from 2008 and reached peak in 2011. When taking MSM into account, MSM significantly had younger age than non-MSM. Early stage of syphilis, VDRL titer higher than 1:32 at diagnosis, and MSM population were significantly associated with HIV-positivity among syphilis patients. Regarding treatment of syphilis, median time to cure syphilis was 117 days (95% confidence interval = 93-141). Treatment regimen, MSM, and HIV co-infection did not significantly show influence on duration to cure.

Conclusion: Prevalence of syphilis has been continuously increasing. MSM with syphilis significantly associated with younger age. Moreover, early stage of syphilis, VDRL titer higher than 1:32, and MSM population were significantly related with HIV infection. Treatment regimen, MSM, and HIV co-infection did not significantly show influence on duration to cure.

Keywords: Syphilis, Men who have sex with men (MSM), Human immunodeficiency virus (HIV)

J Med Assoc Thai 2014; 97 (9): 963-8

Full text. e-Journal: <http://www.jmatonline.com>

Syphilis is a sexual transmitted infection (STI) caused by *Treponema pallidum*. Despite significant decrease in cases of syphilis in the 1990s, syphilis incidence has raised dramatically since 2000. In Canada, cases of syphilis increased from 0.6 per 100,000 in 2000 to 5.0 per 100,000 in 2009⁽¹⁾. Overall, the higher number of syphilis cases occurred among men, especially men who have sex with men (MSM), who have been strongly associated with high rates of human immunodeficiency virus (HIV) co-infection and high-risk sexual behaviors⁽²⁻⁶⁾. In China, meta-analysis demonstrated that HIV-syphilis co-infection in MSM increased from 1.4% between 2005 and 2006 to 2.7% between 2007 and 2008⁽⁷⁾.

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In Thailand, syphilis has been considered to be a major STI. Previous report described syphilis prevalence among 4,762 MSM clients in Bangkok between 2005 and 2011 was 9.8%. Between 2005 and 2011, significant increased occurred in the annual prevalence of syphilis from 5.0% to 12.5%⁽⁸⁾. Another previous study among HIV-infected MSM attending a public STD clinic in Bangkok between 2005 and 2007 reported 21% of HIV infected MSM had reactive syphilis serology and high-risk sexual behaviors⁽⁹⁾. However, most previous reports studied the prevalence and risk factors of syphilis in MSM population without statistical comparison with non-MSM population^(2,4-7).

The present retrospective study aimed to describe epidemiological trends and clinical manifestations, laboratory investigations, treatment, and HIV co-infection in patients diagnosed with syphilis. Moreover, statistical evaluation of these data

between MSM and non-MSM, as well as HIV and non-HIV populations was studied.

Material and Method

Subjects

This was a retrospective medical records review of all patients diagnosed with syphilis between January 2008 and December 2012 at Sexual Transmitted Diseases (STD) clinic. Demographic data (including age, sex, marital status, MSM status, sexual behavior, and history of STI), clinical manifestations, neurological symptoms, cerebrospinal fluid characteristics, and treatment regimens were collected. Laboratory examination including serology for Venereal Disease Research Laboratory (VDRL) titer, *Treponema pallidum* haemagglutination (TPHA) titer, HIV infection, CD4 cell count, hepatitis B and C infection and serial follow-up of VDRL titers at 3, 6, 9, 12, and 24 months were also included.

Definitions

The diagnosis and stages of syphilis are based on the sexually transmitted diseases treatment guidelines 2010 of Centers for Disease Control and Prevention (CDC). Early syphilis includes primary, secondary, and early latent syphilis. Late syphilis includes late latent and tertiary syphilis. Treatment success is defined as a fourfold decline of VDRL titers. If an initial test titer is less than 1:4, treatment success will be considered when the titer returns to non-reactive. Treatment failure is defined as a patient who does not achieve a fourfold serologic decline within one year after treatment in case of early syphilis, and within two years in case of late syphilis.

Statistical analysis

Chi-square test was used to compare differences in categorical data and Independent t-test for continuous variables. According to VDRL titer, the statistical analysis was performed in all VDRL titer level. Multivariate analysis was performed with logistic regression. A 2-tailed p -value <0.05 was considered statistically significant. The estimated duration to cure between penicillin-treated and doxycycline-treated patients were compared using Kaplan-Meier curves and the Breslow test. All the statistical calculations were performed using the Statistical Package for the Social Sciences (SPSS) for Windows (Version 18.0; Chicago, IL, USA).

Results

Between 2008 and 2012, 922 patients attended STD clinic. One hundred forty three patients diagnosed with syphilis were included in the present study. The overall prevalence rate of syphilis was 15.5%. The mean age of the patients was 41.4 ± 15.1 years old, of which 26 (18.2%) were MSM and 31 (21.7%) were HIV-infected patients. Of the 922 patients attending STD clinic, prevalence of syphilis in MSM and HIV infected patients were 2.8% and 3.4%, respectively. Prevalence of syphilis in overall patients, MSM, and HIV patients experienced an upward trend, which started in 2008 and reached a peak in 2011. Overall syphilis prevalence increased from 13.2% in 2008 to 15% in 2011. Prevalence in MSM and HIV population increased from 0.7% and 1.7% in 2008 to 3.5% and 3.5% in 2011, respectively.

Eighty-four percent of the overall subjects had risky sexual behaviors. Of MSM group, 96.2% had at least one unsafe sex behavior. The determined risks were having sex without a condom (60.1%), prostitute contact (32.9%), multiple sex partners (30.1%), sex partner had syphilis (7.7%), and intravenous drug use (1.4%). Twenty-seven percent of the patients have prior history of STI such as syphilis (10.1%), gonococcal urethritis (7.9%), herpes simplex infection (2.9%) and genital wart (2.2%). Among these 143 patients, 42 (29.4%) patients presented with early syphilis, two and 40 patients presented with primary and secondary syphilis, respectively. The remaining 101 (70.6%) patients presented with late latent syphilis. Sixty-seven patients (46.9%) were diagnosed by the screening program, 29 patients (20.3%) were detected in blood donor screening, and the remaining 47 patients (32.9%) presented with symptoms and signs of syphilis. Regarding treatment of syphilis, the overall median times to cure was 117 days (95% confidence interval = 93-141).

Considering the difference between the MSM and non-MSM patients, MSM significantly was younger age and had more HIV co-infection than non-MSM (Table 1). However, MSM did not significantly influence overall duration to cure.

In multivariate analysis between HIV and non-HIV groups, MSM, early stage of syphilis, and VDRL titer higher than 1:32 at diagnosis were significantly associated with HIV-positive syphilis patients. Age, maculopapular eruption, and anti-HCV antibody were excluded from multivariate analysis because of a lack of statistical significance from the final model (Table 2). In the same way as MSM, HIV

co-infection did not significantly show influence on duration to cure.

Most of the patients (73.4%) were treated with benzathine penicillin according to their syphilis stages. Thirty-eight patients (26.6%) were treated by doxycycline twice daily because penicillin injections were out of stock due to the flood crisis in 2011, or because the patients were allergic to penicillin. Clinical

and laboratory data of penicillin and doxycycline groups were not statistically different. There was no statistically significant difference of time to serological responses after treatment between patients receiving penicillin and those receiving doxycycline (113 and 133 days, respectively, Breslow test, p -value = 0.946). Overall, ten patients had treatment failure, nine of them were in late latent and one of them was in

Table 1. Demographic and clinical characteristics of patients with syphilis infection

Factors	Univariate		p -value
	MSM (n = 26)	Non-MSM (n = 117)	
Age (mean, year) (SD)	27.4 (8.1)	44.5 (14.5)	<0.001 ^a
HIV	15 (57.7%)	16 (13.8%)	<0.001 ^b
Stage of syphilis			
Early	18 (69.2%)	24 (20.5%)	<0.001 ^b
Late	8 (30.8%)	93 (79.5%)	
Presence of chancre	3 (11.5%)	6 (5.1%)	0.210 ^b
Presence of maculopapular eruption	14 (53.6%)	17 (14.5%)	<0.001 ^b
Presence of papulosquamous eruption	2 (7.7%)	6 (5.1%)	0.637 ^b
Presence of moth eaten alopecia	1 (3.9%)	5 (4.3%)	1.000 ^b
VDRL titer at diagnosis higher than 1:32	12 (46.2%)	19 (16.2%)	0.001 ^b
Anti-HCV positive	2 (7.7%)	3 (2.6%)	0.224 ^b
HBsAg positive	3 (11.5%)	3 (2.6%)	0.115 ^b

MSM = men who have sex with men; HCV = hepatitis C virus; HBsAg = hepatitis B surface antigen

^a Independent t-test, ^b Chi-square test

Table 2. Factors correlated with the HIV-infection in 143 syphilis patients

Factors	Univariate			p -value	Multivariate	
	HIV (n = 31), %	Non-HIV (n = 112), %	Crude odds ratio (95% CI)		Adjusted odds ratio** (95% CI)	p -value
Age (mean, year) (SD)	30.8 (7.9)	44.4 (15.3)	0.9 (0.8-0.9)	<0.001 ^a		
MSM	15 (48.4)	11 (9.8)	8.6 (3.3-22.1)	<0.001 ^b	4.6 (1.6-13.5)	0.006
Stage of syphilis						
Early	21 (67.7)	21 (18.8)	9.1 (3.7-22.1)	<0.001 ^b	3.2 (1.1-9.6)	0.039
Late	10 (32.3)	91 (81.3)	1			
Presence of chancre	2 (6.5)	7 (6.3)	1.0 (0.2-5.3)	1.000 ^b		
Presence of maculopapular eruption	17 (54.8)	14 (12.5)	8.5 (3.5-20.9)	<0.001 ^b		
Presence of papulosquamous eruption	3 (9.7)	5 (4.5)	2.3 (0.5-10.2)	0.371 ^b		
Presence of moth eaten alopecia	3 (9.7)	3 (2.7)	3.9 (0.7-20.3)	0.116 ^b		
VDRL titer at diagnosis higher than 1:32	17 (54.8)	14 (12.5)	8.5 (3.5-20.9)	<0.001 ^b	3.7 (1.2-11.2)	0.021
Anti-HCV positive	4 (12.9)	1 (0.9)	16.4 (1.8-153.1)	0.008 ^b		
HBsAg positive	2 (9.5)	4 (7.8)	1.3 (0.2-7.3)	0.569 ^b		

MSM = men who have sex with men; HCV = hepatitis C virus; HBsAg = hepatitis B surface antigen

^a Independent t-test, ^b Chi-square test, ** Adjusted for MSM, stage of syphilis and VDRL titer at diagnosis higher than 1:32

secondary stage. Only one patient with late latent syphilis treated with doxycycline had treatment failure.

Of the 143 patients, none had neurological, otological, and ophthalmologic signs or symptoms. Eight HIV infected patients had CD4 cell counts less than 350 cell/ μ L or VDRL titer higher than 1:32, but did not obtain the lumbar puncture. Seven patients were successfully treated without any complication. The other one lost to follow-up.

Discussion

After a steady decrease for many decades, the rates of syphilis have been resurgent since 2000. Syphilis has been rising rapidly in the past decade. Previous studies have shown a growing trend in the prevalence of syphilis in developed and developing countries^(1,7,10). In Thailand, previous study showed the prevalence of syphilis was 8% of all patients with sexually transmitted disease in 2011, which has been increasing from 2010⁽¹¹⁾. The present study demonstrated a similar changing trend for syphilis, so syphilis remains a major problem in Thailand.

Previous studies demonstrated that the prevalence of syphilis in male gender and MSM were on the rise^(12,13). Among MSM in Thailand in other study, the prevalence of syphilis was 9.8% and the incidence was 3.6 per 100 person-year between 2005 and 2011⁽⁸⁾. In the present study, the prevalence of MSM syphilis patients was similar and had a rising trend.

Increasing of the rate of syphilis among MSM may come from a decrease in safe sex behaviors that had been reported previously⁽¹⁴⁻¹⁷⁾. The present study found that 96.2% of MSM group had at least one unsafe sex behavior. In addition, the prevalence of syphilis in previous study was independently associated with history of treated syphilis infection and MSM⁽¹³⁾. The present study found that 11.2% of patients had a previous history of syphilis infection. This represents poor awareness and education about syphilis prevention in the MSM and treated patients.

Study about clinical manifestation compared between MSM and non-MSM was limited. This present study demonstrated MSM were younger age that might be in sexually active periods and higher HIV co-infection lead to greater spread of syphilis and HIV in MSM group. Thus efficient preventive education and intervention for this disease, especially in MSM group, are necessary.

HIV-syphilis co-infection was rising especially in MSM group^(1,18). The present study supported that prevalence of this co-infection was increasing. Farhi et al, also demonstrated that, among 279 syphilis cases in their retrospective cohort study, the HIV infection was significantly associated with MSM and early syphilis⁽¹⁹⁾. The present study also had similar result. Moreover, the present study found that a VDRL titer higher than 1:32 was found to be associated with HIV-syphilis co-infected patients. Similarly, results from study in Brazil found that VDRL-positive patients had a higher chance to have HIV infection⁽²⁰⁾. A previous study demonstrated that syphilis seems to be an early determinant for HIV diagnosis and care in MSM⁽²¹⁾. From the present study, the presence of early syphilis and VDRL titer high than 1:32 in MSM syphilis patients indicated the need for awareness of HIV infection to promote earlier HIV diagnosis and prevention.

Doxycycline is preferred alternative agent in syphilis patients whom the penicillin cannot be given. Ghanem KG et al study found no patient had serological failure in the doxycycline-treated group⁽²²⁾. Wong T et al study correspondingly supported that the serological response rates were similar between penicillin and doxycycline-treated groups in primary syphilis patients⁽²³⁾. The present results were concurrent with the findings of these studies.

Conclusion

Prevalence of syphilis has been continuously increasing. MSM with syphilis significantly associated with younger age. Moreover, early stage of syphilis, VDRL titer higher than 1:32 and MSM population were significantly related with HIV infection. Treatment regimen, MSM, and HIV co-infection did not significantly show influence on duration to cure.

Limitations

There were some limitations of the present study. First, the present study dealt with mostly male patients. Only seven women (4.9% of all subjects) were included because women with syphilis are usually treated by gynecologists. As a consequence, the data were insufficient to be analyzed for female. Second, 53 patients (37.1% of the subjects) were lost to follow-up; hence, these affected the follow-up serological data and treatment outcomes. Third, this retrospective chart review may have resulted in bias if the medical records were incomplete.

What is already known on this topic?

Prevalence of syphilis has been increasing. MSM is the high-risk group.

What this study adds?

MSM is significantly younger age than non-MSM. The presence of early syphilis and VDRL titer higher than 1:32 in MSM syphilis patients indicated the need for awareness of HIV infection.

Potential conflicts of interest

None.

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ลักษณะทางคลินิกและความชุกของผู้ป่วยโรคซิฟิลิสในประเทศไทย: การศึกษาย้อนหลัง 5 ปี

จรัสศรี พียาพรรณ, สุขุม เจียมตน, นันทิดา ประเสริฐวรนนท์, พิทยา มณีประสพโชค, วิบูลย์ อ่ำเจริญ

ภูมิหลัง: ความชุกของโรคซิฟิลิสเพิ่มสูงขึ้นทั่วโลกตั้งแต่ พ.ศ. 2543 โดยเฉพาะกลุ่มชายรักชายและผู้ติดเชื้อเอชไอวี อย่างไรก็ตาม รายงานก่อนหน้านี้น่าสนใจมากศึกษาเกี่ยวกับความชุกและปัจจัยความเสี่ยงของโรคซิฟิลิสในประชากรชายรักชายโดยไม่มี การเปรียบเทียบทางสถิติกับประชากรที่ไม่เป็นชายรักชาย

วัตถุประสงค์: การศึกษาแนวโน้มความชุก ลักษณะทางคลินิก การตรวจทางห้องปฏิบัติการ การรักษา และการติดเชื้อเอชไอวีร่วมในผู้ป่วยโรคซิฟิลิส รวมถึงการศึกษาเปรียบเทียบทางสถิติข้อมูลเหล่านี้ในประชากรที่เป็นชายรักชายและที่ไม่เป็นชายรักชาย รวมถึงประชากรที่ติดเชื้อเอชไอวีและไม่ติดเชื้อเอชไอวี

วัสดุและวิธีการ: การศึกษานี้เป็นการศึกษาเวชระเบียนย้อนหลังของผู้ป่วยโรคซิฟิลิสที่ได้รับการตรวจที่คลินิกโรคติดต่อทางเพศสัมพันธ์ ระหว่างเดือนมกราคม พ.ศ. 2551 ถึง ธันวาคม พ.ศ. 2555 เก็บข้อมูลเกี่ยวกับข้อมูลพื้นฐาน ลักษณะทางคลินิก การติดเชื้อเอชไอวี ระดับ VDRL และการรักษา

ผลการศึกษา: จากผู้ป่วยทั้งหมด 922 ราย ที่มาคลินิกโรคติดต่อทางเพศสัมพันธ์ มีผู้ป่วยโรคซิฟิลิส 143 ราย คิดเป็นความชุกเท่ากับ 15.5% มีผู้ป่วย 26 ราย เป็นชายรักชาย และ 31 ราย ติดเชื้อเอชไอวี ความชุกของผู้ป่วยโรคซิฟิลิสที่เป็นชายรักชายและผู้ป่วยโรคซิฟิลิสที่ติดเชื้อเอชไอวีเท่ากับ 2.8% และ 3.4% ตามลำดับ ความชุกมีแนวโน้มเพิ่มสูงขึ้นตั้งแต่ พ.ศ. 2551 และสูงสุดใน พ.ศ. 2554 เมื่อมาพิจารณาในกลุ่มผู้ป่วยชายรักชาย พบว่า ผู้ป่วยโรคซิฟิลิสที่เป็นชายรักชายจะมีอายุน้อยกว่ากลุ่มที่ไม่ได้เป็นชายรักชายอย่างมีนัยสำคัญ ระยะต้นของโรค ระดับ VDRL สูงกว่า 1:32 และกลุ่มชายรักชายมีความสัมพันธ์อย่างมีนัยสำคัญกับการติดเชื้อเอชไอวีในผู้ป่วยโรคซิฟิลิส ด้านการรักษาพบว่า ระยะเวลามัธยฐานที่ผู้ป่วยมารักษาจนหายคือ 117 วัน (ช่วงความเชื่อมั่น 95% เท่ากับ 93-141) สูตรการรักษา การเป็นชายรักชายหรือการติดเชื้อเอชไอวีร่วมด้วยไม่มีผลต่อระยะเวลาการหายอย่างมีนัยสำคัญ

สรุป: ความชุกของโรคซิฟิลิสยังคงสูงเพิ่มขึ้น ชายรักชายที่มีการติดเชื้อซิฟิลิสจะมีความสัมพันธ์อย่างมีนัยสำคัญกับอายุน้อย นอกจากนั้น ระยะต้นของโรค ระดับ VDRL สูงกว่า 1:32 และกลุ่มชายรักชาย มีความสัมพันธ์อย่างมีนัยสำคัญกับการติดเชื้อเอชไอวี สูตรการรักษา การเป็นชายรักชายหรือการติดเชื้อเอชไอวีร่วมด้วยไม่มีผลต่อระยะเวลาการหายอย่างมีนัยสำคัญ
