PROFILE OF SYPHILIS COMPLIANCE AND SUCCESS OF THERAPY AT DERMATOLOGY AND VENEREOLOGY CLINIC RSUD DR. SAIFUL ANWAR MALANG: A DESCRIPTIVE STUDY

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ABSTRACT

Syphilis is a chronic progressive sexually transmitted infection, that causes a life-threatening condition if left untreated. In lower-middle-income countries, the burden of disease might appear to be lower due to a lack of reports. This study aimed to report the epidemiological profile, the profile of compliance, and the success of therapy of syphilis at the Dermatology and Venereology Outpatient Clinic in RSUD dr. Saiful Anwar Malang, Indonesia. This study used a descriptive approach using secondary data from the medical records of newly diagnosed syphilis patients at Dermatology and Venereology Clinic RSUD dr. Saiful Anwar Malang from January 2021 - December 2021. Sample collection was using a total sampling technique. Eighteen medical records met the inclusion criteria. The majority of samples were men (77.8%), aged 17-25 years (44.4%) and 26-35 years (44.4%), had a high school education (55.6%), HIV positive (50%) and HIV negative (50%). All 18 patients got intramuscular injections of a single 2.4 million U or 7.2 million U Benzathine Penicillin G according to the syphilis stage. It was found that eight patients (44.4%) had a successful therapy, two patients (11.2%), experienced failure, and the remaining eight patients (44.4%) were unknown due to loss of follow-up. Several factors are associated with better patient compliance including older age, higher educational level, type of the disease, and lower complexity of treatment schedules. Overall, therapeutic compliance of syphilis patients is good, but monitoring compliance needs to be improved. Benzathine Penicillin G remains the drug of choice for syphilis and has a high success rate.

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INTRODUCTION

Syphilis is a chronic progressive sexually transmitted infection caused by the bacterium *Treponema pallidum*. Syphilis can be classified into active clinical spectrums (primary, secondary, tertiary) and an asymptomatic period called latency[1,2]. This disease will develop into various stages, causing life-threatening complications if left untreated[3].

Although the incidence of syphilis declined significantly worldwide and

managed to reach its lowest point five decades after the discovery of penicillin in the mid-1940s, the number of cases in the United States and Europe reported to the Centers for Disease Control and Prevention (CDC) increased by 81% from 2014 to 2018[4,5]. In 2020, there were 7.1 million new cases of syphilis globally in people aged 15-49 years[3]. In Southeast Asia, the trend of syphilis is also increasing with a total of 350,000 cases[2]. According to the Indonesian Ministry of Health in 2021 there were 13,505 cases of early syphilis and 3,775 cases of stage syphilis[6].

In lower-middle-income countries, the burden of disease might appear to be lower due to a lack of reports[7]. Therefore this study aimed to report the epidemiological profile, the level of compliance, and the success of therapy of syphilis at the Dermatology and Venereology Outpatient Clinic in RSUD dr. Saiful Anwar Malang, Indonesia from January 2021 to December 2021.

MATERIALS AND METHODS

This study used a descriptive approach to secondary data from the medical records of syphilis patients at the Dermatology and Venereology Clinic RSUD dr. Saiful Anwar Malang from January 2021 - December 2021. Sample collection was using a total sampling technique which included all patients who met the inclusion and exclusion criteria. The inclusion criteria were newly diagnosed syphilis patients at Dermatology and Venereology Clinic RSUD dr. Saiful Anwar Malang from January 2021 - December 2021. The diagnosis of syphilis was confirmed by laboratory examination; the finding of *T. pallidum* in dark field examination or a reactive (nontreponemal & treponemal) syphilis serological test. The exclusion criteria were syphilis patients who received syphilis management outside the Dermatology and Venereology Clinic RSUD dr. Saiful Anwar Malang. The parameters studied were gender, age, education, occupation, syphilis stage, HIV infection status, CD4+ level, therapeutic modalities, therapeutic compliance, monitoring compliance, and success of therapy. Therapeutic compliance is the patient's behavior to seek treatment regularly according to a set time. Monitoring compliance is the patient's behavior to come for re-evaluation according to a set time. Successful treatment of syphilis was defined as a fourfold decrease in nontreponemal titer (VDRL) within 3–24 months of syphilis therapy, no persistence/recurrence of symptoms, nor a fourfold increase in titer for >2 weeks[1,8]. The data obtained were presented in numbers and percentages descriptively, and subjected to univariate analysis using the Statistical Package for the Social Sciences (SPSS ver. 21, IBM®) application. The research protocol has been approved by the Medical Research Ethics Committee of RSUD Dr. Saiful Anwar Malang (Approval number: 070/036/102.7/IKKK/09/2022, Date: September 28th, 2022).

RESULTS

There were 18 medical records of syphilis at the Dermatology and Venereology Clinic RSUD dr. Saiful Anwar Malang from January 2021 - December 2021 which met the inclusion and exclusion criteria.

According to Table 1, the majority of samples were men (77.8%), HIV positive (50%), aged 17-25 years (44.4%) and 26-

35 years (44.4%), had a high school education (55.6%), and worked in the private sector (44.4%).

Table 1. Epidemiological Profile of Syphilis Patients at Dermatology and Venereology Clinic RSUD dr. Saiful Anwar Malang in January - December 2021

Parameters	HIV positive (n,%)	HIV negative (n,%)	Total
Gender			
Male	9 (100)	5 (55.6)	14 (77.8)
Female	0 (0)	4 (44.4)	4 (22.2)
Age (years old)			
17 – 25	4 (44.4)	4 (44.4)	8 (44.4)
26 – 35	5 (55.6)	2 (22.2)	8 (44.4)
36 – 45	0 (0)	3 (33.3)	2 (11.2)
Education			
Elementary School	0 (0)	1 (11.1)	1 (5.6)
Junior High School	0 (0)	0 (0)	0 (0)
Senior High School	5 (55.6)	5 (55.6)	10 (55.6)
Higher Education	2 (22.2)	1 (11.1)	3 (16.7)
Unknown	2 (22.2)	2 (22.2)	4 (22.7)
Occupation			
Student	3 (33.3)	3 (33.3)	6 (33.3)
Private Sector	3 (33.3)	5 (55.6)	8 (44.4)
Civil Servant	1 (11.1)	0 (0)	1 (5.6)
Entrepreneur	0 (0)	1 (11.1)	1 (5.6)
Unemployed	2 (22.2)	0 (0)	2 (11.1)

Table 2 shows that the majority of syphilis patients were diagnosed at the secondary stage (50%). All 18 patients got intramuscular Benzathine Penicillin G according to the stage. The level of CD4+ of those who were tested was mostly <200/µL (27.7%).

All 15 (100%) early syphilis patients underwent a Benzathine Penicillin G 2.4 million U single dose intramuscular injection and all three (100%) late syphilis (tertiary and late latent) patients underwent a complete series of IM Benzathine Penicillin G 2.4 million U once a week for three consecutive weeks (shown in Table 3).

Table 2. Stage, Therapeutic Modalities, and CD4+ Level of Syphilis Patients

Stage	Frequency (n)	Percentage (%)
Primary	3	16.7
Secondary	9	50.0
Tertiary	0	0
Early Latent	3	16.7
Late Latent	3	16.7
Total	18	100
Therapeutic modalities		
IM Benzathine Penicillin G (2.4 million U)	15	83.3
IM Benzathine Penicillin G (7.2 million U)	3	16.7
PO Doxycycline (2 x 100 mg)	0	0
Others	0	0
Total	18	100
CD4+ level		
< 200/µL	5	27.7
200 – 349/µL	1	5.6
350 – 499/µL	0	0
≥ 500/ µL	0	0
Unknown	12	66.7
Total	18	100

Table 3. Therapeutic Compliance of Syphilis Patients

Therapeutic Compliance	Frequency (n)	Percentage (%)
Early Syphilis		
Full compliant	15	100
Non-compliant	0	0
Late Syphilis		
Full compliant	3	100
Non-compliant	0	0
Total	18	100

Table 4. Monitoring Compliance of Syphilis Patients

Monitoring Compliance	Month						
	1	3	6	9	12	18	24
Primary & Secondary stage without HIV co-infection							
Compliant (n, %)	1 (20)	2 (40)	2 (40)	0 (0)	1 (20)	0 (0)	0 (0)
Non-compliant (n, %)	4 (80)	3 (60)	3 (60)	5 (100)	4 (80)	5 (100)	5 (100)
Primary & Secondary stages with HIV co-infection							
Compliant (n, %)	3 (42.8)	2 (28.6)	2 (28.6)	1 (14.3)	1 (14.3)	0 (0)	0 (0)
Non-compliant (n, %)	4 (57.2)	5 (71.4)	5 (71.4)	6 (85.7)	6 (85.7)	7 (100)	7 (100)
Early & Late Latent stage without HIV co-infection							
Compliant (n, %)	1 (25)	2 (50)	1 (25)	1 (25)	2 (50)	0	0
Non-compliant (n, %)	3 (75)	2 (50)	3 (75)	3 (75)	2 (50)	4 (100)	4 (100)
Early & Late Latent stage with HIV co-infection							
Compliant (n, %)	0 (0)	2 (100)	1 (50)	0 (0)	0 (0)	0 (0)	0 (0)
Non-compliant (n, %)	2 (100)	0 (0)	1(50)	2 (100)	2 (100)	2 (100)	2 (100)
Total (n)	18	18	18	18	18	18	18

According to Table 4, the majority of syphilis patients came for re-evaluation in the 3rd month. However, the number of non-compliant patients was higher than the number of compliant. Of the 18 patients, five patients came for re-evaluation in the 1st month, eight patients in the 3rd month, six patients in the 6th month, two patients in the 9th month, and four patients in the 12th month. No patient came for re-evaluation at the 18th and 24th months.

Table 5. The Success of Therapy for Syphilis

Success of therapy	Frequency (n)	Percentage (%)
Success	8	44.4
Failed	2	11.2
Unknown	8	44.4
Total	18	100

Table 2 showed eight patients (44.4%) had a successful therapy defined as a four-fold decrease in nontreponemal titer (VDRL) within 3–24 months of syphilis therapy, no persistence/ recurrence of symptoms, nor a fourfold increase in titer for >2 weeks. Two patients (11.2%) experienced failure and the remaining eight patients (44.4%) were unknown due to loss of follow-up.

DISCUSSION

Syphilis is a sexually transmitted infection that requires therapy and follow-up within a certain time frame. The Centers for Disease Control and Prevention (CDC) recommends Benzathine Penicillin G as the first-line treatment for all stages of syphilis with the dose and duration of treatment depending on the stage. In early syphilis (primary, secondary, early latent) intramuscular 2.4 million units of Benzathine penicillin G was given as a single dose. In late syphilis (tertiary and late latent) intramuscular 2.4 million units of Benzathine penicillin G was given three times at one-week intervals. There is no difference in dosage and method of administration in both HIV patients and non-HIV patients. For the patient who is allergic to penicillin, an alternative such as doxycycline, tetracycline, or azithromycin can be given[1,8]. In this study, follow-up in primary and secondary syphilis was carried out at 6 and 12 months after treatment. Follow-up in HIV co-infected syphilitic patients was carried out more frequently, at 3, 6, 9, 12, and 24 months after treatment. In latent syphilis, follow-

up was carried out at 6, 12, and 24 months after treatment. Whereas, in latent syphilis with HIV co-infection, the follow-up is carried out more frequently, at 6, 12, 18, and 24 months after treatment[1]. The efficacy of a single dose of Benzathine penicillin via intramuscular injection for early syphilis has been validated due to its cost-effectiveness and favorable adherence. However, there are some drawbacks including the pain caused by a high-dose deep injection into the muscles, potential drug allergies, the need for disposable injection equipment, requisite personnel training, and the risk of transmitting bloodborne disease pathogens[9]. Replacing part of the diluent with the same volume of 1% lidocaine solution may reduce the pain associated with injection and may improve compliance with the second and third injections in late syphilis[10].

Compliance is the exactness of individual behavior in following medical advice. Therapeutic compliance is the patient's behavior to seek treatment regularly according to a set time. Monitoring compliance is the patient's behavior to come for re-evaluation according to a set time[11,12]. Successful treatment of syphilis is marked by a four-fold decrease in nontreponemal titer (VDRL or RPR) generally within 6–12 months after treatment in primary and secondary syphilis or within 12-24 months after treatment in latent syphilis[1]. Some patients in remission have low levels of reactive VDRL and RPR throughout their lives. This condition is referred to as the zero fast condition, in which the patient doesn't respond to repeated therapy anymore[13]. Treatment failure is defined as the absence of a four-fold decrease in nontreponemal titers (VDRL or RPR) within the expected time, persistence, or reappearance of symptoms, or a fourfold increase in titer for >2 weeks[14]. Patient compliance is influenced by several factors which can be grouped into patient factors, the complexity of treatment/ monitoring schedules, type of disease, nature of the doctor-patient relationship, and social and environmental factors. Older age, higher education level, higher socioeconomic status, and retirement and marriage are known to be associated with better compliance[11,15]. Compliance is not different between genders[16]. Lack of parental supervision, biological maturity, and lack of knowledge, may increase risky sexual behavior in adolescence[17]. Based on the data obtained, the majority of syphilis patients were diagnosed at early stages (primary, secondary, early latent) and 16.7% of patients were diagnosed at late stages of syphilis (tertiary and late latent). In this study, all patients showed good therapeutic compliance since intramuscular Benzathine Penicillin G was given only once for early stages and once a week for three weeks for late stages. However, monitoring compliance still needs to be improved because the success of therapy cannot be evaluated if the patient has never undergone a re-evaluation at least once. In this study, the majority of syphilis occurred in adolescents or working young adults with a lower educational stage which may be related to the tendency of being non-compliant for re-evaluation. Based on the data obtained, the majority of syphilis patients came for re-evaluation in the 3rd month. The long period of follow-up might also lead to poor monitoring compliance.

Syphilis is commonly co-infected with HIV, and the incidence is increasing

over time, especially in the Male Sex Male (MSM) group. Symptoms of syphilis with HIV positive are generally similar to non-HIV, but HIV patients are at risk of atypical and more aggressive syphilis, such as neurosyphilis[1,18]. HIV co-infection in syphilis can lead to increased disease progression, ineffective treatment results, overlapping symptoms, multiple chancre lesions, impaired serological response, false-negative, and delayed seroreactivity[19]. Based on the data obtained, 44.4% of patients experienced successful therapy and 11.2% of patients experienced failure, who were HIV positive. Serologic failure is common in HIV co-infection or late syphilis. Factors leading to treatment failure in syphilis are low serological titers (RPR<1:16), previous history of syphilis, and CD4+ levels <350cells/mL[14]. The majority of samples in this research who got tested had a <350cells/mL CD4+.

Studies from the 1950s onward have focused on Benzathine Penicillin G and demonstrated favorable cure rates. A randomized controlled trial in 2010 including 517 patients compared oral azithromycin with benzathine penicillin; 79% of benzathine penicillin recipients achieved serological cure within six months[20]. Another retrospective study showed a high success rate of a single dose of benzathine penicillin for early syphilis. *Treponema pallidum* remains extremely susceptible to penicillin, an antimicrobial agent targeting bacterial cell wall synthesis[21]. However, the use of benzathine penicillin cannot prevent the progression of neurosyphilis in HIV-coinfected patients. Neurosyphilis is a frequent complication of syphilis in the central nervous system, especially in HIV-positive patients. Neurosyphilis may be asymptomatic, or manifest as syphilitic meningitis, meningovascular syphilis, and ocular syphilis. In patients with HIV co-infection, the risk of developing neurosyphilis increases three to five times, and it can occur since the primary stage[14]. Patients who failed the treatment should be re-treated with intramuscular 2.4 million U Benzathine Penicillin G once a week for 3 weeks, re-evaluated for the HIV status, performed cerebrospinal fluid (CSF) examination to detect neurosyphilis[1,13].

The limitation of this descriptive study was it only provided an overview of variables without analyzing the correlation of each. Future correlational studies are needed to gain a more comprehensive understanding of the cause and effect of the phenomena under investigation.

CONCLUSION

Data at the Dermatology and Venereology Polyclinic RSUD Dr. Saiful Anwar Malang from January 2021 - December 2021 showed that syphilis was more common in men, aged 17-36 years, who had a high school education, who worked as private employees, diagnosed at the secondary stage, and might be co-infected with HIV. All subjects showed good therapeutic compliance, but monitoring compliance was lacking might be due to the patient's age, educational level, or socioeconomic factor. Almost half of the subjects were successfully treated with Benzathine Penicillin, but the success of therapy could not be evaluated in the other half of the subjects who did not come for re-evaluation. Failure of treatment shown in 11.2% of subjects

might be influenced by several factors such as HIV co-infection and CD4+ level.

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CONFLICT OF INTEREST

All authors have no conflict of interest regarding this research publication.

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AUTHOR CONTRIBUTION

All authors have contributed to all processes in this research, including preparation, data gathering, analysis, drafting, and approval or publication of this manuscript.

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