

Correlation Between Changes in Syphilis Treatment and Jarisch-Herxheimer Reaction

YOUNG-MIN YANG¹, KATSUMI SHIGEMURA^{1,2}, REO ONISHI²,
KOKI MAEDA¹, SHIAN-YING SUNG³, KUAN-CHOU CHEN⁴,
SOICHI ARAKAWA⁵, and MASATO FUJISAWA¹

¹Department of Urology, Kobe University Graduate School of Medicine, Kobe, Hyogo, Japan.

²Department of International Health, Kobe University Graduate School of Health Sciences, Kobe, Hyogo, Japan.

³Ph.D. Program for Translational Medicine, Taipei Medical University, Taipei, Taiwan

⁴Department of Urology, Taipei Medical University Shuang Ho Hospital, Taiwan, Taiwan.

⁵Sanda City Hospital, Sanda, Hyogo, Japan

Received 29 March 2021 / Accepted 5 October 2021

Keywords: Syphilis; Sexual behavior; Asia; Antibiotic; Urology

The number of syphilis patients has significantly increased recently in Japan and worldwide. Previous reports, even in large institutions, may not accurately reflect the current situation in urological clinics. We therefore collected data from 11 urological clinics in Hyogo Prefecture, Japan over a 2-year period subdivided into 1) August 2016 to July 2017 and 2) August 2017 to July 2018 to compare changes in syphilis consults. We analyzed the patient data including a rapid plasma reagin test (RPR), *Treponema pallidum* (TP) antibody, clinical stage, therapy, and presence of Jarisch-Herxheimer reaction. In total, 45 patients presented for a first consultation, 22 in the first year and 23 in the second year. Almost all patients were male. Initial consolidation and hard chancre were the major symptoms. RPR values and TP antibody values did not change. The treatment period with amoxicillin was significantly longer in the first year ($p=0.006$). A Jarisch-Herxheimer reaction was seen in 13.6% in the first year and 60.9% in the second year ($p=0.001$). The duration of antibiotic treatments was more likely to be based on the guidelines for antibiotic use in the second year, but Jarisch-Herxheimer reactions increased. Further follow-up including recurrent patients is necessary to draw definitive conclusions.

INTRODUCTION

The significant resurgence of syphilis is a severe and problematic issue in the field of infectious disease [1]. Syphilis was common as recently as the 1960's but seemed to be eradicated in Japan by the 1990's, when Japanese statistical data demonstrated that syphilis was under control, with 500-800 cases annually from 1990 into the 2000's [2]. Unfortunately, the number of syphilis patients began to increase exponentially after 2010, reaching 4,546 cases in Japan in 2016 [3]. This reflected a general worldwide increase [4].

The current situation calls for measures to inhibit the spread of syphilis. The first step toward addressing the significant increase of syphilis is to gather and analyze the data on syphilis patients consulting with hospitals or clinics. Japan's increasing incidence of syphilis in recent years includes both men and young women [5]. The number of syphilis patients increased by a factor of 10 from 2003 to 2013 [6]. Japanese health authorities and medical professionals should undertake effective research and control measures for STI, not least because the Japanese government expects many foreign visitors for the 2021 Tokyo Olympic Games [7]. Investigation of the current situation in clinics, in addition to existing government data, is necessary to grasp the real situation.

Syphilis treatment issues should also be reconsidered. Currently the worldwide treatment of choice is benzathine penicillin G injection. Decades of clinical experience, clinical case studies, and laboratory studies support its effectiveness [8][9][10]. Also, the Jarisch-Herxheimer reaction, where patients experience shaking chills, a rise in temperature, and intensification of skin rashes within 24 hours after antibiotic treatment of the spirochetal infection, with the symptoms resolving a few hours later [11], has become unfamiliar to the present generation of urologists.

Japanese guidelines recommend oral benzathine penicillin G (not injection) or amoxicillin 1500 mg per day as the first choice [12] [13]. As a first step toward broader studies, we investigated syphilis patient consultations with urological clinics in Hyogo Prefecture, Japan, an urban area, comparing patients, diagnosis, symptoms and treatments to assess the changes over a 2-year period.

METHODS

1. Surveillance.

We asked for data on symptomatic syphilis patients from 11 of our university hospital-related clinics and hospitals in Kobe city. Six institutions replied with the requested data. No patients were excluded in this study. This study was approved by the Institutional Review Board of Kobe University School of Medicine as a multicenter study (No. 180103).

2. Syphilis patient characteristics.

We collected the patient data as follows: the number of patients presenting for a first consultation, the diagnostic date, age, gender, occupation, chance to be infected, nationality, duration of symptoms, nature of symptoms, RPR, TP antibody, clinical stage, therapy, and presence of Jarisch-Herxheimer reaction. Jarisch-Herxheimer reaction was diagnosed if there was a fever within 24 hours after the start of antibiotic administration. The stage classification was based on existing guidelines [12], as were the categories we examined.

3. Analyses and statistics.

The investigation was divided into 2 periods for comparison, August 2016 to July 2017 and August 2017 to July 2018. Statistical analyses were done by Fisher's exact tests. The second group starting in 2017 corresponds to the period when the number of people infected with syphilis began to increase rapidly [14]. The significance level was $p < 0.05$.

RESULTS

1. Patient characteristics.

Six clinics (54.5 %) provided enough data for evaluation. In total, 45 patients presented for a first consultation, 22 in the first year and 23 in the second year. Ages ranged from 19-79 (median: 33) in the first year and 17-70 (median: 38) in the second year. By gender 21 males and 1 female presented in the first year and 23 males and no females presented in the second year. By occupation, there were 11 office workers and 4 civil servants in the first year and 10 office workers, 4 civil servants and 3 managers in the second year. The details of chance to be infected were sorted as commercial sex workers (CSW) ($n=11$) and others ($n=11$) in the first year and CSW ($n=12$) and others ($n=11$) in the second year. All patients were Japanese in nationality in both years. There were no significant changes between the first and second year as to these categories ($p > 0.05$) (Table I).

2. Symptoms

Disease stages reported were first stage ($n=13$), second stage ($n=8$) and unknown ($n=1$) in the first year and first stage ($n=17$), second stage ($n=5$) and unknown ($n=1$) in the second year. The duration of symptoms was 10 days to 3 months in the first year and 10 days to 1 year in the second year. There were no significant changes between the first and second year as to these categories ($p > 0.05$) (Table I).

3. Laboratory tests for syphilis

The RPR value was 0.9-240 (median: 64) R.U. in the first year and 0.5-290 R.U. in the second year. TP antibody values were 12.9-20480 times in the first year and 16-10240 times in the second year. There were no significant changes between the first and second year ($p > 0.05$) (Table II).

4. Treatments

The treatment duration with amoxicillin 1500 mg was significantly different between the first and second year ($p=0.006$). Importantly, the treatments based on the guidelines [9] (amoxicillin or amoxicillin/clavulanate) were 11/15 (73.3%) (excluding unknown cases) in the first year and 22/23 (95.7%) in the second year ($p=0.07$) (Table II).

5. Adverse events

Jarisch-Herxheimer reaction was seen in 3 patients (13.6 %) in the first year and in 14 patients (60.9 %) in the second year, a statistically significant change ($p=0.001$). Drug eruption was seen in 1 case with amoxicillin 1500 x 2 weeks, which was then changed to minocycline 200 mg x 8 weeks (Table II). Jarisch-Herxheimer reactions were significantly more frequent in patients treated with 1500 mg amoxicillin ($p=0.002$) (Table III). The proportions of patients in stage 1 and stage 2 were comparable between the amoxicillin 1500mg group and the Others. (Table IV).

JARISCH-HERXHEIMER REACTION IN SYPHILIS TREATMENT

Table I. Patient demographics. First year: August 2016 to July 2017. Second year: August 2017 to July 2018. We analyzed the sex, age, occupation, nationality, infection route, time to birth, and symptoms of syphilis patients.

	First year	Second year	<i>p</i> -value
N	22	23	-
Gender			
Male	21	23	0.982
Female	1	0	
Age	19 – 79 (median 33)	17 – 70 (median 38)	-
Occupation			
Office worker	11	10	0.376
Civil servant	4	4	
Self-employed	0	3	
Others	7	6	
Chance to be infected			
Commercial sex worker: CSW	11	12	0.686
Others	11	11	
Nationality			
Japanese	22	23	-
Time until symptoms appear (days)	10-90 (median 30)	10-365 (median 60)	-
Symptoms (including patients with multiple symptoms)			
Initial consolidation	7	9	0.932
Hard chancre	7	8	
Inguinal lymph node swelling	7	5	
Syphilitic roseola	3	2	
Papular syphilid	2	2	

Table II. Laboratory tests, treatments and adverse effects. First year: August 2016 to July 2017, Second year: August 2017 to July 2018. We analyzed the antibody titer of syphilis patients, the antibacterial agents used for treatment, and the presence or absence of Jarisch-Herxheimer reaction.

		First year	Second year	<i>p</i> -value
N		22	23	-
RPR value (R.U.)		0.9-240 (median: 64)	0.5-290 (median: 29)	-
TP antibody value (times)		12.9-20480 (median: 1280)	16-10240 (median: 1280)	-
Treatments				
Amoxicillin 1500 mg	8 weeks	6	2	0.006
	7 weeks	0	1	
	6 weeks	0	5	
	5 weeks	0	3	
	4 weeks	1	7	
	2 weeks	1	0	
Amoxicillin 1000 mg	3 weeks	0	1	0.500
	1 week	1	0	
Amoxicillin 750 mg	4 weeks	0	1	-
Amoxicillin/ clavulanate 750mg	4 weeks	1	1	0.513
	3 weeks	1	0	
	2 weeks	1	1	
Cefcapen 300 mg	3 weeks	1	0	0.513
	2 weeks	1	1	
	1 week	1	0	
Minocycline 200 mg	8 weeks	1	0	-
unknown		6	0	-
Jarisch-Herxheimer reaction		3	14	0.001

Bold: statistically significant.

Table III. Correlation between drug selection and Jarisch-Herxheimer reaction. We excluded 6 patients with unknown treatment and analyzed the correlation between Jarisch-Herxheimer reactions and treatment with 1500 mg of Amoxicillin by Fisher's exact test.

Treatment	Amoxicillin 1500 mg	Others	<i>p</i> -value
Positive for Jarisch-Herxheimer reaction	61.5 % (16/26)	7.7 % (1/13)	0.002

Bold: statistically significant.

Table IV. Relationship between drug selection and stage of syphilis. We excluded 6 patients with unknown treatment and performed Mann-Whitney U test to analyze the relationship between stage of syphilis and treatment with 1500 mg of Amoxicillin.

Stage of syphilis	Treatment		<i>p</i> -value
	Amoxicillin 1500 mg	Others	
Stage 1	65.4% (17/26)	76.9% (10/13)	0.7129
Stage 2	34.6% (9/26)	23.1% (3/13)	0.7129

DISCUSSION

Though syphilis greatly declined after the adoption of penicillin treatment, recent trends in STI include the emergence of antimicrobial-resistant gonorrhoeae and a significant increase in syphilis worldwide, including Japan and Asian countries. Syphilis, a traditional infectious disease, was recently considered all but exterminated [1] [15] [16] [17]. Its rapid resurgence indicates the need for more research on the epidemiology of STI. STI research has increased but most similar studies are derived from institutional or national databases rather than clinical

JARISCH-HERXHEIMER REACTION IN SYPHILIS TREATMENT

settings. We designed this study to gather the data from urological clinics where syphilis patients actually consulted, and compared the annual data over a two-year period from 6 urological clinics in urban Japan.

We searched for any similar studies using key words such as “syphilis” and “urology”, and found a German nationwide study assessing all STI patients treated by urology departments. In general, only 0.03 % (n=110) of patients with urological disorders (n=347090) were recorded as having syphilis; the most frequent STI was anogenital warts (0.64%) (n=2216) [18]. The widespread resurgence of syphilis is recent. The current generation of urologists needs to be familiar with this disease, and we may ask whether patients know which departments they should consult with.

Our data showed no significant change in the number of patients, the details of diagnosis and treatments, and patient background, including the chance of becoming infected, symptoms and disease stages as shown in Table I. This study was based solely on symptomatic patients. As mentioned above, most studies of this kind are from research institutions and include asymptomatic and/or symptomatic patients with only minor symptoms, for instance only testing positive for RPR, or TPHA antibodies detected incidentally in blood tests such as HIV tests and preoperative screenings [19]. The value of this study is its focus on symptomatic patients treated by urologists, some of whom are not familiar with syphilis.

Significant changes over the two years covered by this study were more frequent treatment with amoxicillin or amoxicillin/clavulanate based on Japanese guidelines in the second year of the study and Jarisch-Herxheimer reactions more than four times as numerous as the first year of the study, a statistically significant change. To our knowledge, there are no similar reports from urologists or urological clinics focusing on year-to-year comparison.

The Jarisch-Herxheimer reaction manifests fever and malaise caused by the death of large amounts of causative bacteria in the body of a patient who has been given an antibacterial drug such as penicillin for syphilis treatment. The Jarisch-Herxheimer reaction is epidemiologically more likely to occur in adolescents, primary infections, and early syphilis, but no significant difference was reported between groups [20]. Reportedly, the Jarisch-Herxheimer reaction is likely to occur when penicillin is selected as an antibacterial drug [21]. In this study, Jarisch-Herxheimer reactions were significantly more frequent in patients treated with 1500 mg of amoxicillin (Table III). In the second year, significantly more patients were treated with this medicine compared to the first year (Table II) and Jarisch-Herxheimer reactions were more than 4 times as numerous in the second year. The distribution of syphilis medical treatment guides to general doctors in 2018 greatly influenced changes in antibiotic use. As mentioned above, these two significant changes may be due to the increasing familiarity of clinical urologists with the management of syphilis. The stage of syphilis was considered as a confounding factor, but the proportions of stage 1 and stage 2 were similar between the two groups. Therefore, it was considered that the effect of 1500 mg amoxicillin was related to the higher onset of Jarisch-Herxheimer reaction (Table IV).

One possible reason for potential underreporting of syphilis is that most syphilis patients are outpatients and consult with clinics. For instance, in Japan epidemiological research is most commonly done at the research institute or university hospital level, and clinic-level data does not tend to be reported. This study reports syphilis patient data from the daily clinic setting. Syphilis patients consult with dermatologists, emergency care and infectious disease departments as well as urologists [22].

In Hyogo prefecture, clinical data does not demonstrate any increase in syphilis patients over a two-year period. Though direct comparison is hard due to the small number of patients, detailed factors such as STI, diagnosis, and treatments were not different over the study period. Possible reasons include:

1) Patients may visit dermatological departments, not urologists. Guidelines do not specify whether dermatology or urology departments are more appropriate. 2) Urologists may not necessarily recognize syphilis, or may misdiagnose the symptoms.

Several study limitations need to be emphasized. First, the number of patients was small and the study was retrospective in nature. Second, recurrence and treatment outcomes were not assessed. Third, in some cases treatments were not based on the guidelines. Fourth, the examined categories were not broad enough for definitive conclusions. Fifth, we definite Jarisch-Herxheimer reactions by only a fever within 24 hours after the start of antibiotic administration. Sixth, some clinical data about RPR-value, stage of syphilis, and HIV infection were insufficient. These limitations will be addressed in future studies.

CONCLUSIONS

Our retrospective survey of symptomatic syphilis patient data from urological clinics in Hyogo Prefecture showed no significant change in the number of the syphilis patients over a 2-year period. The significant changes seen in these 2 years were 1) antibiotic treatments more often followed the guidelines in the second year and 2) Jarisch-Herxheimer reactions increased significantly in the second year. Further follow-up including recurrent patients will be necessary to draw further conclusions.

ACKNOWLEDGEMENTS

We would like to thank Dr. Nakano, Dr. Oka, Dr. Imanishi, Dr. Oda, Dr. Yamamichi and Dr. Matsumura for collecting and providing data for this study.

Conflicts of interest: The authors declare no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

REFERENCES

1. Sugishita, Y., Kayebeta, A., Soejima, K., et al. 2018. Rapid increase of syphilis in Tokyo: an analysis of infectious disease surveillance data from 2007 to 2016. *Western Pac Surveill Response J* **10**: 6-14.
2. Taniguchi, K., Hashimoto, S., Kawado, M., et al. 2007. Overview of infectious disease surveillance system in Japan, 1999-2005. *J Epidemiol* **17**(Suppl): S3-13.
3. Sugishita, Y., Yamagishi, T., Arima, Y., et al. 2016. Increase in Primary and Secondary Syphilis Notifications in Men in Tokyo, 2007-2013. *Jpn J Infect Dis* **69**: 154-157.
4. Kojima, N., and Klausner, J.D. 2018. An Update on the Global Epidemiology of Syphilis. *Curr Epidemiol Rep* **5**: 24-38.
5. Hook, E.W. 2017. Syphilis. *Lancet*. **389**: 1550-1557.
6. The Ministry of Health, Labour and Welfare. [in Japanese]. Available from URL: <http://www.mhlw.go.jp/topics/2005/04/tp0411-1.html>. (accessed 2 August 2017).
7. Tanimoto, T., Maeda, Y., Morita, T., et al. 2018. The increasing incidence of syphilis among young women in Japan is also concerning. *Intern Med J* **48**: 101-102.
8. Workowski, K.A., Bolan, G.A. and Centers for Disease Control and Prevention. 2015. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep* **64**: 1-137.
9. Kingston, M., French, P., Higgins, S., et al. 2016. UK national guidelines on the management of syphilis 2015. *International Journal of STD and AIDS*. **27**: 421-446.
10. Janier, M., Hegyi, V., Dupin, N., et al. 2014. 2014 European guideline on the management of syphilis. *J Eur Acad Dermatol Venereol* **28**(12): 1581-1593.
11. Butler, T. 2017. The Jarisch–Herxheimer Reaction After Antibiotic Treatment of Spirochetal Infections: A Review of Recent Cases and Our Understanding of Pathogenesis. *Am J Trop Med Hyg* **96**: 46-52.
12. Kiyota, H. 2016. Sexually Transmitted Infections diagnosis · treatments guideline. *Japanese Journal of Sexually Transmitted Infections* **27** (Suppl): S48-52.
13. Spiteri, G., Unemo, M., Mårdh, O., et al. 2019. The resurgence of syphilis in high-income countries in the 2000s: a focus on Europe. *Epidemiol Infect* **147**: e143.
14. National Institute of Infectious Diseases. [In Japanese]. Available at < <https://www.niid.go.jp/niid/ja/syphilis-m-3/syphilis-idwrs/7816-syphilis-data-20180105.html> > (accessed at 29 June 2021)
15. World Health Organization, Department of Reproductive Health and Research. The global elimination of congenital syphilis: rationale and strategy for action. Available at < <https://www.who.int/reproductivehealth/publications/rtis/9789241595858/en/> > (accessed at 19 August 2021).
16. Patton, M.E., Su, J.R., Nelson, R., et al. Centers for Disease Control and Prevention (CDC). 2014. Primary and secondary syphilis—United States, 2005–2013. *MMWR Morb Mortal Wkly* **63**: 402-406.
17. European Center for Disease Prevention and Control. Sexually transmitted infections in Europe 2011. Available at < <https://www.ecdc.europa.eu/en/publications-data/sexually-transmitted-infections-europe-2011> >. (accessed 19 August 2021)
18. Jacob, L., Duse, D.A., and Kostev, K. 2018. Prevalence and treatment of sexually transmitted infections in men followed by urologists in Germany - a cross sectional study with 347,090 men. *Ger Med Sci* **16**: Doc03.
19. Blonde, L., Khunti, K., Harris, S.B., et al. 2018. Interpretation and Impact of Real-World Clinical Data for the Practicing Clinician. *Adv Ther* **35**: 1763-1774.
20. Yang, C.J., Lee, N.Y., Lin, Y.H., et al. 2010. Jarisch–Herxheimer Reaction after Penicillin Therapy among Patients with Syphilis in the Era of the HIV Infection Epidemic: Incidence and Risk Factors. *Clin Infect Dis* **51**: 976-979.
21. Arando, M., Fernandez, C., Mota, M., et al. 2018. The Jarisch–Herxheimer reaction in syphilis: could molecular typing help to understand it better? *J Eur Acad Dermatol Venereol* **32**: 1791-1795.
22. Cossman, J.P., and Fournier, J.B. 2017. Frequency of Syphilis Diagnoses by Dermatologists. *JAMA Dermatol* **153**: 718-719.