BRIEF REPORT

Dilemmas in the Management of Syphilis: A Survey of Infectious Diseases Experts

Deborah Dowell,[1,2] Philip M. Polgreen,[4] Susan E. Beekmann,[4] Kimberly A. Workowski,[2,3] Stuart M. Berman,[2] and Thomas A. Peterman[2]

[1]Epidemic Intelligence Service, Office of Workforce and Career Development, and [2]Epidemiology and Surveillance Branch, Centers for Disease Control and Prevention, and [3]Department of Infectious Diseases, Emory University, Atlanta, Georgia; [4]Department of Internal Medicine, University of Iowa Carver College of Medicine, Iowa City, Iowa

(See the editorial commentary by Gross, on pages 1530–1.)

We surveyed infectious diseases consultants to determine how they manage syphilis when there are insufficient data to guide management or when guidelines cannot be followed because of a lack of available definitive diagnostic tests. Most providers did not have access to dark-field microscopy. We found variation in management of syphilis, especially for patients with human immunodeficiency virus infection.

Areas of uncertainty exist in the clinical management of syphilis, because of the limited data available for some aspects of management. The *Sexually Transmitted Diseases Treatment Guidelines, 2006* [1], published by the Centers for Disease Control and Prevention, are based on systematic reviews of peer-reviewed journal articles and published abstracts, and are widely regarded as the authoritative source on sexually transmitted disease management and treatment worldwide. However, some guidelines are based on observational data and not on results from randomized studies. Diagnostic testing for primary syphilis can be challenging, because the sensitivity of serologic tests for primary syphilis is low (70%–80%) [2], and definitive methods for diagnosing primary syphilis, such as dark-field microscopy or direct fluorescent antibody testing, may be unavailable. Management of syphilis for patients who are allergic to penicillin may also be difficult because of the limited data available on alternative treatments. In addition, penicillin skin testing is impractical in most outpatient clinical settings, in part because of the lack of availability of skin-test reagents [1]. Human immunodeficiency virus (HIV) infection can modify the presentation and progression of syphilis, including more rapid progression to neurosyphilis [3, 4]), decreased correlation between the serum rapid plasma reagin test and the cerebrospinal fluid venereal disease research laboratory test [5], and changes in serologic response to treatment [6, 7] without clear evidence of changes in clinical response to treatment. There is also evidence that serologic responses to treatment may be modified by highly active antiretroviral therapy [8]. We sought to determine how infectious diseases experts manage syphilis in circumstances in which there is limited availability of definitive diagnostic tests for primary syphilis or in which definitive guidelines are lacking as a result of limited data.

Methods. We developed a survey to determine what decisions were being made by infectious diseases experts to diagnose and treat syphilis, focusing on areas for which there is limited evidence to guide patient management. Topics included availability and use of diagnostic testing for suspected primary syphilis, treatment of early syphilis for patients coinfected with HIV, threshold nontreponemal test titer for retreatment or lumbar puncture among patients with an unchanged titer after treatment, and lumbar puncture among HIV-infected persons with early syphilis and no neurologic or ophthalmologic signs or symptoms.

From November to December 2008, Web-based surveys were distributed to the 1007 members of the Emerging Infections Network who reported seeing adult patients with infectious diseases. The network is funded by the Centers for Disease Control and Prevention and sponsored by the Infectious Diseases Society of America. It is a sentinel network of infectious diseases consultants who regularly engage in clinical activity and who volunteer to participate [9]. Staff at the coordinating center of the Emerging Infections Network (in Iowa City, Iowa) sent the initial survey invitation by e-mail or facsimile, followed by 2 reminders. Statistical tests were performed using Excel (Microsoft) and SPSS, version 17.0 (SPSS). We used the χ^2 test to compare proportions; 2-sided P values of $<.05$ were considered to be statistically significant.

Results. Of the 1007 infectious diseases consultants who received our survey, 465 (46%) responded. Respondents and

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Reprints or correspondence to Dr Deborah Dowell, Epidemiology and Surveillance Branch, Centers for Disease Control and Prevention, 1600 Clifton Rd, NE, MS E-02, Atlanta, GA 30329 (gdo7@cdc.gov).

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nonrespondents were similar with respect to their geographic location, practice location (urban, suburban, or rural), and practice setting (hospital, academic, private, government, and military). Respondents were more likely than nonrespondents to teach (71% vs 56%; $P < .001$), perform research (52% vs 38%; $P < .001$), and practice general internal medicine (16% vs 11%; $P = .048$). Seventy-five respondents indicated they were not involved in the care of patients with syphilis and were excluded from further analysis, thus leaving only 390 respondents for our study.

Respondents who reported having experience managing patients with syphilis had practiced a median of 15 years since completion of an infectious diseases fellowship program. Practice settings were private practice (32% of respondents), medical school or university (31%), hospital (27%), government (7%), and military (2%). The number of patients seen who had syphilis within the past year was as follows: >20 patients for 6% of the respondents, 6–20 patients for 27% of respondents, 1–5 patients for 59% of respondents, 0 patients for 8% of respondents (Table 1). Most of the respondents (ie, 87%) had been consulted about patients with syphilis within the past year. A majority (56% of respondents) had seen >50 patients with HIV infection within the past year.

Dark-field microscopy was unavailable to 81% of the respondents, and only 11% of the respondents actually used dark-field microscopy. In deciding whether to treat for primary syphilis, 56% of the providers responded that they send a rapid plasma reagin test to the laboratory and treat presumptively for syphilis, 18% responded that they send a rapid plasma reagin test to the laboratory and repeat the test (if the test result was negative) before deciding to treat, 17% responded that they send the rapid plasma reagin test to the laboratory and treat only if the test result is positive, and 2% responded that they treat presumptively without sending a rapid plasma reagin test to the laboratory. Neither the availability of dark-field microscopy nor the diagnostic approach to primary syphilis varied significantly by practice setting or number of patients with syphilis or HIV infection.

Most respondents (236 [63%] of 374) had been consulted about a penicillin-allergic HIV-positive patient with syphilis. Of these 236 respondents, 230 (97%) answered questions about desensitization. Of these 230 respondents, 181 (79%) had recommended desensitization. Of the 181 respondents who made this recommendation, 71 (39%) reported that desensitization was not always done when recommended. Thirty respondents provided reasons why desensitization was not done, which included patient refusal (15 [50%] of 30 respondents), difficulties in arranging a monitored setting (6 respondents [20%]), lack of availability (4 respondents [13%]), or the time or cost required (3 respondents [10%]).

Secondary syphilis among HIV-infected patients was more often treated with 3 doses of benzathine penicillin (each dose given by injection at 1-week intervals) than with 1 dose of benzathine penicillin by injection (62% vs 32% of respondents). One injection was used more often by respondents who had >5 patients with syphilis in the past year than by respondents who had ⩽5 patient with syphilis in the past year (42% vs 25%; $P = .005$). Treatment of secondary syphilis among HIV-infected patients did not vary significantly by number of HIV-infected patients or by practice setting. For secondary syphilis among HIV-positive patients without neurologic or ophthalmologic symptoms, 65% of providers responded that they would perform a lumbar puncture if the $CD4^+$ cell count were 150 cells/μL, and 44% of providers responded that they would perform a lumbar puncture if the $CD4^+$ count were 550 cells/μL. Providers who treated >5 patients with syphilis in the past year were less likely to perform a lumbar puncture than were providers who treated fewer patients with syphilis in the past year, both for patients with a $CD4^+$ count of 150 cells/μL (64% vs 77%, $P = .007$) and for patients with a $CD4^+$ count of 550 cells/μL (36% vs 50%; $P = .013$). The likelihood of performing a lumbar puncture did not vary significantly by number of HIV-infected patients seen or by practice setting.

For a patient with an unchanged nontreponemal titer 12 months after treatment for early syphilis and reporting no reexposure, more respondents would follow (retest periodically without retreatment or lumbar puncture) a titer >1:4 in an HIV-negative patient than in an HIV-positive patient (41% vs 30% of respondents). For an HIV-negative patient, willingness to follow an unchanged titer >1:4 was greater for respondents with >5 patients with syphilis than for respondents with ⩽5 recent patients with syphilis (51% vs 36%; $P = .006$). Similarly, for an HIV-positive patient, willingness to follow an unchanged titer >1:4 was greater for respondents with >5 patients with syphilis than for respondents with ⩽5 patients with syphilis (39% vs 26%; $P = .009$). Differences between physicians by number of HIV-infected patients and by practice setting were not considered to be statistically significant.

Discussion. Definitive diagnosis of primary syphilis relies on direct testing [1], which includes the use of direct fluorescent antibody testing and dark-field microscopy. However, direct fluorescent antibody testing is rarely available [10]. We also found that dark-field microscopy was infrequently available. A presumptive diagnosis of syphilis using a serologic test is commonly made, but a serologic test may be falsely negative in 20%–30% of cases of primary syphilis [2]. We found that some consultants rely on serologic testing to decide whether to treat, an approach that may leave some patients with primary syphilis untreated, thus allowing for the ongoing transmission of the disease [11–13].

There is substantial variation in the management of syphilis in areas where limited evidence exists to guide the decision-

Table 1. Diagnosis and Management of Syphilis, by Number of Patients with Syphilis within the Past Year

Question, response	No. (%) of providers who responded that they treated patients with syphilis					
	Overall[a] (n = 390 respondents)	0 patients (n = 32 respondents)	1–5 patients (n = 226 respondents)	6–20 patients (n = 105 respondents)	>20 patients (n = 23 respondents)	P[b]
Use of dark-field microscopy						
Not available	304 (81)	14 (70)	190 (85)	77 (73)	20 (87)	.157
Unsure if available	24 (6)	3 (15)	12 (5)	9 (9)	0 (0)	
Available, but do not use	6 (2)	1 (5)	2 (1)	3 (3)	0 (0)	
Use it	41 (11)	2 (10)	19 (9)	16 (15)	3 (13)	
Diagnosis of primary syphilis						
Send RPR test to lab, treat patient	211 (56)	8 (42)	128 (57)	62 (59)	12 (52)	.828
Send RPR test to lab, repeat if negative before treating patient	69 (18)	6 (32)	41 (18)	18 (17)	3 (13)	
Send RPR test to lab, treat only if positive	62 (17)	3 (16)	38 (17)	14 (13)	6 (26)	
Treat, no RPR test	8 (2)	1 (5)	4 (2)	3 (3)	0 (0)	
Other	25 (7)	1 (5)	13 (6)	8 (8)	2 (9)	
Benzathine penicillin treatment for secondary syphilis for patients with HIV infection						
Once	118 (31)	1 (5)	61 (27)	43 (41)	10 (44)	.006
3 doses	233 (62)	16 (80)	150 (67)	53 (51)	13 (57)	
Other	24 (6)	3 (15)	13 (6)	8 (8)	0 (0)	
LP performed for asymptomatic secondary syphilis if $CD4^+$ cell count is 150 cells/μL						
No	93 (25)	1 (6)	46 (21)	34 (32)	11 (48)	<.001
Yes	242 (65)	16 (89)	145 (65)	68 (65)	11 (48)	
Uncertain	39 (10)	1 (6)	33 (15)	3 (3)	1 (4)	
LP performed for asymptomatic secondary syphilis if $CD4^+$ cell count is 550 cells/μL						
No	193 (54)	2 (11)	109 (52)	65 (64)	15 (65)	.002
Yes	157 (44)	15 (83)	95 (45)	37 (36)	8 (35)	
Uncertain	7 (2)	1 (6)	6 (3)	0 (0)	0 (0)	
Highest titer willing to follow for HIV-negative patient						
<1:4	88 (28)	7 (50)	51 (27)	24 (26)	6 (27)	.047
1:4	99 (31)	3 (21)	70 (37)	22 (24)	4 (18)	
>1:4	131 (41)	4 (29)	68 (36)	47 (51)	12 (55)	
Highest titer willing to follow for HIV-positive patient						
<1:4	135 (41)	11 (73)	85 (44)	29 (31)	8 (37)	.024
1:4	94 (29)	3 (20)	56 (29)	29 (31)	5 (23)	
>1:4	98 (30)	1 (7)	51 (27)	37 (39)	9 (41)	

NOTE. Some respondents did not answer all the questions, so the denominator (ie, total no. of patients who answered the question) changes for some of the questions. HIV, Human immunodeficiency virus; LP, lumbar puncture; RPR, rapid plasma reagin.

[a] There were 4 respondents who did not indicate the number of patients with syphilis seen within the past year.

[b] For difference, by number of patients with syphilis.

making process. Although there is no definitive evidence to support improved outcomes when >1 dose of benzathine penicillin is used for the treatment of HIV-positive patients with early syphilis [1, 6, 14], most respondents treat patients with 3 doses of benzathine penicillin. Respondents caring for a greater number of patients with syphilis were more likely to use 1 dose. This suggests that clinicians with less experience managing patients with syphilis may choose to err on the side of overtreatment.

Controversy exists regarding the use of lumbar puncture for HIV-positive patients with early syphilis and without neurologic or ophthalmologic symptoms [1, 14]. The clinical and prognostic significance of mononuclear pleocytosis and elevated protein among HIV-positive patients is unknown [1, 14]. Respondents who treated more patients with syphilis were less likely than those who treated fewer patients with syphilis to perform a lumbar puncture for an HIV-positive patient with secondary syphilis without neurologic or ophthalmologic symptoms. Such respondents were also more likely to follow (without lumbar puncture or retreatment) a nontreponemal titer >1:4 that was unchanged 12 months after treatment for early latent syphilis without reexposure. These findings suggest that increased experience managing syphilis may correlate with confidence that management according to established guidelines is sufficient to prevent adverse outcomes.

Our study has several limitations. Infectious diseases consultants from the Emerging Infections Network may not be representative of all clinicians managing patients with syphilis in the United States. Respondents may have had a greater interest in syphilis and may have been more aware of existing guidelines [1, 14], compared with nonrespondents. We conducted a survey and not an audit of actual practice. We limited the number of questions in order to increase the acceptability of our survey.

A definitive diagnosis of primary syphilis is challenging because of the limited availability of sensitive tests. A substantial minority of consultants rely on less sensitive tests to decide whether to treat for primary syphilis. There is an urgent clinical need for a rapid point-of-care test for the definitive diagnosis of primary syphilis. Clinicians should treat presumptively when syphilis is suspected on the basis of clinical presentation and epidemiologic circumstances [1]. More data are needed to determine whether early detection and treatment of asymptomatic cerebrospinal fluid abnormalities improves long-term outcomes for HIV-infected patients with syphilis.

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