William Osler referred to syphilis as “The Great Imitator,” referring to the vast array of potential clinical presentations and morbidity associated with syphilis at the beginning of the 20th century. While the infection’s varied presentations remain a continuing source of confusion for clinicians, the challenges of syphilis management do not stop with diagnosis. The absence of readily available culture or other direct microbiologic tests for syphilis diagnosis, and the resulting dependence upon serological testing to evaluate response to therapy, regularly creates questions for clinicians.

For better and for worse, serological testing for syphilis diagnosis and monitoring response to therapy has been a mainstay of syphilis management since soon after 1906 when Wassermann and colleagues developed the first serological tests for syphilis [1]. Since then however, evolution of tests, testing methods, reagents, and test formats has not resolved fundamental questions or limitations of currently available tests. Syphilis is no longer common enough to be easily studied at a single institution in the numbers needed to provide conclusive answers to important management questions but it is common enough that questions regularly arise in management of syphilis patients. In the United States, rates of primary and secondary syphilis have been <5 per 100,000 population for >15 years [2] and rates are still lower in Western Europe. Nonetheless, questions regarding serological test interpretation continue to vex clinicians at all stages of syphilis management—diagnosis, staging, and response to therapy. Furthermore, the close links between syphilis and human immunodeficiency virus infection add to concerns because of the theoretical potential for coexistence of the 2 infections to modify the manifestations and management of each other. Common questions include: How long should it take for effective therapy to result in changes of serological tests and titers? Does the response to syphilis vary in persons with human immunodeficiency virus (HIV)? What is the best test for serological follow-up of infection? and What is the clinical significance of test titers that do not change following therapy? Generation of reliable answers to these questions is a challenge. Further, newer assays such as enzyme immunoassays and tests for IgM antibodies to Treponema pallidum likewise [3, 4] are badly in need of study.

In this issue of Clinical Infectious Diseases, Knaute and colleagues [5] report on their analyses of patterns of serological response to syphilis therapy among 192 of 456 patients diagnosed with syphilis at their institution over the decade from 1999 through 2008. Their data serve to confirm and expand findings from other studies which suggest that the serological response to syphilis tends to be more rapid and occurs more often in patients with early stages of infection [6]. The data also suggest that HIV coinfection has little significant impact on the serological response to therapy, other than for persons with primary syphilis or CD4 counts of <500 cells/μL. Nonetheless, as they acknowledge, their data are limited by constraints common to many retrospective studies. Analysis of data collected retrospectively from patients evaluated in a nonstandardized fashion are subject to limitations relating to loss to follow-up (records for 42% of syphilis patients seen during the study period could not be included in the analyses) as well as due to biases which include that the group of syphilis patients with coexistent HIV were followed more closely and were significantly more likely to be treated with multiple doses of penicillin than patients who were not HIV coinfected. Moreover, the authors’ analyses may have been impacted by other, less apparent nonstandardized variation in clinical assessments; it is noteworthy that 42% of their primary syphilis patients had negative Venereal Disease Research Laboratory (VDRL) tests, a figure...
that is about twice as high as the 20% figure more widely accepted [7]. Use of incompletely standardized criteria for ascertainment of syphilis diagnoses raised concerns as to whether or not all persons classified as having early syphilis were infected. Such biases make the study’s major conclusions, including the recommendation that the VDRL should not be recommended as a preferred syphilis diagnostic test, noteworthy and a logical starting point for further, prospective studies.

Many of the studies that contribute to current knowledge of syphilis management were conducted in the 1940s and 1950s and involved thousands of participants to clearly define the remarkable advance in syphilotherapy provided by penicillin [8, 9]. These studies, however, utilized study designs, penicillin formulations, and serological assays for evaluation of response to therapy that are no longer in use. There is a pressing need to address the questions studied by Knaute et al, as well as other pressing questions regarding other facets of the infection with more current and better data from prospectively conducted, multicenter studies of syphilis and the syphilis serologic response to therapy carried out in a variety of settings with patient groups.

Note

Potential conflicts of interest. Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References