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What is the Evidence for the Sexual Transmission of Syphilis from Asymptomatic Persons?

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Clinicians have been diagnosing syphilis since (at least) the 15th century. Yet, hundreds of years on, we continue to gain new insights into the clinical manifestations and pathogenesis of this disease. A recent case report described primary syphilis as a cause of non-gonococcal urethritis in an initially seronegative man.[1] Another recent study of 183 men with primary syphilis showed that over one third had multiple anorectal lesions and that in nearly 50 percent, the lesions were painful.[2] These findings stand in contradistinction to the single painless lesion that most clinicians have been taught to anticipate in early syphilis. Now, in this issue of *Sexually Transmitted Diseases*, the topic of asymptomatic syphilis is highlighted by two new reports.

The first, (Allan-Blitz et al.) describes the case of a 50-year-old HIV-infected gay man who was incidentally discovered to have syphilitic proctitis on routine screening colonoscopy. Immunohistochemical stains with a specific monoclonal antibody identified *T. pallidum* in a biopsy taken from nodular areas in the distal rectum. A reactive serum RPR titer of 1:256 helped to confirm the diagnosis. In the second report (Godornes et al.), the authors conducted quantitative PCR targeting the *tp0574* gene on the semen and urine of three male patients: two with secondary and one with early latent syphilis. Samples from two patients were negative. However, one patient with secondary syphilis was found to have *T. pallidum* in the semen despite having no sores or other visible lesions in the urogenital region. That patient also had a concomitant negative urine sample.

As syphilis rates across the United States continue to rise unabated,[3] these reports raise questions about the relative importance of asymptomatic infections in fueling sexual transmission.

What do we know about the sexual transmission of syphilis? The lesions classically considered to be infectious include the chancre of primary and the mucous patches and condyloma lata of secondary syphilis. Studies of transmission between sexual partners (while fraught with considerable uncertainty regarding the exact stage during which

transmission occurred and the identity of the index partner) have estimated transmission rates that range between 9 and 64%. [4, 5] These investigations are principally based on identified contacts of patients with primary or secondary syphilis. Case series from von Werssowetz [6] and Clark [7] suggested that patients with early latent syphilis might be infectious; however, both studies have been criticized for having loose definitions of early latent syphilis and lack of clarity regarding whether contacts might have been exposed during earlier stages of disease. [4, 5] While uncertainties remain, transmission of latent infection has generally been considered to be limited to vertical transmission, though patients in early latency who relapse into primary or secondary stages may again become sexually infectious.

It is difficult to know with certainty what percentage of infectious lesions in primary and secondary syphilis (i.e. chancres, mucous patches, condyloma lata) are “asymptomatic”-in that they go unnoticed by the patient. Given that they are often painless, however, it is reasonable to assume that a significant proportion of these lesions when located in difficult to visualize areas (e.g. rectum, cervix) may fall into this category. For instance, in one case series, up to 44% of primary chancres in women were located on the cervix and patients with cervical primary chancres were noted to “seldom” present for treatment. [8] Complicating matters further is the issue of reinfection. Some studies have suggested that clinical manifestations may be attenuated in persons who are reinfected [9] although that is still a matter of some debate.

Asymptomatic lesions aside, are there other reservoirs in early syphilis that may be contributing to ongoing sexual transmission? As noted by Gordones et al, whether semen could be a vehicle for transmission of *T. pallidum* was a topic of considerable interest in the first half of the 20th century. In 1938, Kemp compiled the results from his own and other contemporaneous studies assessing the infectivity of semen. He found that in a total of 144 patients 20 percent of early cases (predominantly secondary or relapsed syphilis) had infectious organisms in the semen (mostly established by the rabbit infectivity test (RIT)) while only 1 of 52 late cases was found to have infectious organisms. The author suggested accordingly that infectiousness of semen was related to the presence of mucosal lesions in the urogenital tract rather than to excretion by a glandular structure (e.g. the seminal vesicles). [10] In 1942, a more rigorous study concluded that semen in patients with primary and secondary syphilis, in the absence of contamination from genital lesions, was not infectious. [11] Considerable energy was also devoted to assessing whether saliva, in the absence of intraoral lesions, can transmit syphilis. In one study, [12] saliva was obtained directly from the parotid duct of seven patients with florid secondary syphilis but was not found to contain infectious organisms using the RIT, leading the authors to conclude that the infectivity of saliva in patients with syphilis is probably due to contamination from intraoral lesions. Finally, the infectiousness of vaginal secretions and menstrual blood of syphilitic women were assessed. Based on the RIT, menstrual blood could harbor infectious organisms but vaginal secretions, in the absence of lesions, did not appear to do so. [13] While the RIT is considered the gold standard to determine infectiousness, its sensitivity is far from perfect - so a negative RIT may be the result of limited sensitivity of the test rather than lack of infectiousness. A positive RIT, however, is usually considered conclusive evidence of infectiousness.

Both articles in this issue of the journal shared a significant limitation: Neither one could demonstrate conclusively that the organisms they detected were infectious as neither study performed a RIT. In the Gordones study, it was also not possible to know with certainty whether the patient may have had an intraurethral lesion that was poorly visualized on physical examination. That lesion, rather than the semen itself, may have been the source of the spirochetes. The question of whether a patient with no recognizable lesions of any kind may still transmit syphilis through semen is still unanswered.

While it would be of scientific interest to confirm whether there are asymptomatic reservoirs of infection, practically, how would that change the way we manage syphilis? It's unlikely that the diagnostic approach would change. Serology is likely to remain the mainstay of diagnosis. Likewise, treatment will likely be unaffected. With most other STDs, clinicians are well aware that the majority of infected patients are asymptomatic. Perhaps it would allow us to conclusively add syphilis to that list. But is it necessary for us to wait for conclusive data? Though uncertainties persist, we would argue that it is reasonable to assume that asymptomatic patients are important contributors to the ongoing syphilis epidemic through active sexual transmission. Consequently, clinicians should focus on obtaining a history of exposures when performing a sexual history and should promote aggressive serological screening of all people at risk.

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