Persistent Gonococcal DNA: Artifact or Real? Further Insights Into the Biology of a Remarkable Pathogen

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(See the Major Article by Bissessor et al on pages 557–63.)

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In this issue of Clinical Infectious Diseases, Bissessor and colleagues [1] present data that are intriguing and that, in the face of resurgent gonorrhea, especially in men who have sex with men (MSM) [2], have critical public health implications. The seeds of this debate were planted in observations from >40 years ago. Their key finding was that in MSM with rectal and/or pharyngeal infection treated with ceftriaxone/azithromycin, persistence of a positive nucleic acid amplification test (NAAT) 2 weeks later was associated with higher minimum inhibitory concentrations to these antibiotics; the patients all had negative cultures. These results raise a series of intriguing questions on the pathogenesis and treatment of rectal and pharyngeal gonorrhea.

One potential explanation for the persistent NAAT-positive tests, which was considered by the authors, is that this represents persistent DNA but not viable organisms. However, prior reports [3, 4] strongly suggest that gonococcal DNA is cleared rapidly within days after anogenital infection. Furthermore, Bissessor et al’s analysis clearly showed that persistence was not random, but rather was associated with reduced susceptibility to the provided treatment. These data strongly suggest that there may be subpopulations that persist, but below the threshold inoculum required for culture in standard specimens. In terms of transmission and public health importance, it is unclear whether these are microbial populations that will persist, whether they ultimately resolve, and whether these are transmissible. For the sake of argument, let us assume that Bissessor et al’s data suggest a persistent subpopulation. If correct, it would be supported by a series of clinical and laboratory observations.

In 1972, Kilpatrick [5] observed in an editorial review of rectal gonorrhea that “rectal infections tend to persist after treatment more frequently than the genital infections. Resistance to penicillin, low tissue and intracellular concentrations of antibiotics, and the luminal concentration of the organism are important factors compromising antibiotic therapy.” Shortly thereafter, Klein et al [6] reviewed contemporaneous treatment studies and found that “results of therapy [of rectal gonorrhea] in men are discouraging, with failure rates ranging from 7% to 35%.”

Microbiological studies over the last 40 years consistently find that gonococcal isolates from MSM overall have reduced susceptibility to antimicrobials [7, 8], and even in 1980, distinct subpopulations were defined by auxotyping. Over time, these population differences became clearly manifest. In North America and Western Europe, the emergence of both quinolone resistance and cefixime resistance was first observed in MSM populations [2, 9]. DNA sequencing techniques clearly confirmed the clonal derivation of isolates circulating in MSM communities [10]. Interestingly, the clones found in MSM overwhelmingly have reduced antimicrobial susceptibility patterns.

Early efforts to explain this microbial-clinical relationship focused on innate organism characteristics. For example, Morse et al [11] suggested that the cell membrane from rectal isolates had reduced permeability to hydrophobic molecules as a survival strategy for the rectal environment, which in turn resulted in decreased macrolide resistance. I posit that recent observations strongly implicate pharyngeal and rectal biofilms as a basis for reduced susceptibility at rectal and pharyngeal sites.

Biofilms are matrices of bacteria and polysaccharides that occur at mucosal surfaces. Biofilm-associated bacteria have reduced antimicrobial susceptibility,
and have metabolic profiles that are markedly different from planktonic bacteria [12, 13]. Neisseria gonorrhoeae clearly forms biofilm in the cervix, and this has been hypothesized to cause asymptomatic carriage [14]. Studies of gonococci in a biofilm matrix [15, 16] have found that metabolism is anaerobic, and there is a complex interplay between the organism and its environment, both of which likely also reduce susceptibility to antimicrobials. Furthermore, gonococcal biofilms also actively secrete DNA, which in turn leads to enormous opportunities for genetic exchange and potential transfer of resistance determinants [17].

There is a clear need for research into understanding the natural history of N. gonorrhoeae in the rectal and pharyngeal environment, and its implications for therapy. We need to fully understand how the organism is cleared from these mucosal sites, which will require carefully conducted longitudinal studies. There has been little research in treatment strategies for these infections. In a recent large clinical trial for anogenital gonorrhea that compared cefixime/azithromycin to ceftriaxone, among 401 subjects, there were only 6 rectal and 25 pharyngeal infections [18].

However, these data may also suggest new approaches to treatment. We should consider developing and evaluating treatment approaches that are effective under anaerobic conditions. If biofilm is confirmed as a major factor in gonococcal pathogenesis, then newer approaches such as quorum-sensing inhibitors may need to be considered [19]. In any event, the gonococcus will continue to challenge and surprise us.

Notes

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