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SUPPLEMENT ARTICLE

Mycoplasma genitalium From Basic Science to Public Health: Summary of the Results From a National Institute of Allergy and Infectious Disesases Technical Consultation and Consensus Recommendations for Future Research Priorities

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This article lays out the research priorities for *Mycoplasma genitalium* research agreed upon by the participants in a 2016 National Institutes of Allergy and Infectious Diseases–funded Technical Consultation focused on this organism. The state of current knowledge concerning the microbiology, epidemiology, clinical manifestations of infection, treatment, and public health significance of *M. genitalium* reviewed at the meeting is described in detail in the individual articles included in this supplemental edition of the *Journal of Infectious Diseases*. Here we summarize the points made in these articles most relevant to the formulation of the research priorities listed in this article. The most important recommendation resulting from this Technical Consultation is the initiation of clinical trials designed to determine definitively whether screening for and treatment of *M. genitalium* infections in women and their sexual partners improve reproductive health in women and/or prevent human immunodeficiency virus transmission.

Keywords. *Mycoplasma genitalium*; clinical trials; antibiotic resistance; HIV infection; diagnosis.

Mycoplasma genitalium (Mg) is now firmly established as the second most common cause of nongonococcal urethritis (NGU) after *Chlamydia trachomatis*. Although less common than the *C. trachomatis*, Mg infection is the more difficult to manage clinically due to the plasticity of its genome, which facilitates the development of antibiotic resistance. Forty to sixty percent of Mg strains identified in men with NGU worldwide are now resistant to the macrolide class of antibiotics, including azithromycin, which is the most common of these drugs used for the treatment of NGU. Compounding this problem is the observation made years ago that 60%–80% of Mg infections fail to respond to the tetracycline class of antibiotics (most commonly doxycycline or minocycline), which are used in many parts of the world as primary treatment for NGU. Thus, Mg is the major cause of NGU treatment failure, which greatly complicates the management of this syndrome, as reviewed in the article by Horner and Martin [1]. Commercial diagnostic tests for Mg are becoming available and will be essential to improving management of men with urethritis. European Conformity (CE) marked assays are now available in Europe for clinical use, but there are no US Food and Drug Administration–cleared Mg tests in the United States, although a few commercial laboratories have met the Clinical Laboratory Standards Amendments requirements for providing clinical Mg testing using analyte-specific reagents for the Aptima assay (Hologic, San Diego, CA). Assays that also identify the presence of the Mg gene mutations confering resistance to azithromycin would further improve NGU management, and 1 such assay (ResistancePlus, SpeeDx, Sydney, Australia) has recently been approved for clinical use in Australia. Advances in Mg diagnosis are discussed in detail in the article by Gaydos [2].

Certain members of the quinolone antibiotic class appear to be effective for macrolide- and tetracycline-resistant strains of Mg, but, unfortunately, there is recent evidence of emerging resistance to quinolones as well. Moreover, quinolone drugs such as moxifloxacin that are active against Mg are expensive, and as a class, quinolones have toxicity profiles that dictate they be used only when clearly needed. The only other drug in clinical use that has promise in the treatment of Mg infections is pristinamycin, a member of the streptogramin class of antibiotics. However, pristinamycin is only available in some parts of the world and not in the United States. Clearly new drugs are going to be required in the future for the management of Mg infections. The article by Bradshaw and colleagues [3] provides a comprehensive review of drugs in the research and

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development pipeline that have potential for use in treating Mg infections.

Unfortunately, it is not likely that significant investment in the further development of Mg diagnostic tests and new drugs effective for treating macrolide/tetracycline-resistant Mg infections will be forthcoming if the only problem to be addressed is NGU treatment failure. Although distressing for the man with persistent, untreatable urethritis and disconcerting for the healthcare provider caring for him, this condition is relatively uncommon among the myriad chronic conditions afflicting human populations, and its effect on the public's health in general is, at worst, minimal. Definitive proof that Mg, like *C. trachomatis* and *Neisseria gonorrhoeae*, has a significant effect on reproductive health in women will be needed to move this agenda forward.

Wiesenfeld and Manhart [4] summarize the evidence that Mg causes pelvic inflammatory disease (PID), infertility, and preterm birth. These data strongly suggest that Mg plays a role in the pathogenesis of these conditions. Furthermore, despite the dramatic advances in human immunodeficiency virus (HIV) treatment and prevention with the advent of highly active antiretroviral therapy and pre-exposure prophylaxis, the synergistic relationships between bacterial sexually transmitted infections and HIV infection remain key drivers of the HIV epidemic. There is now evidence that Mg infection increases HIV transmission risk. *Mycoplasma genitalium* has been clearly linked to HIV infection in cross-sectional studies, and a meta-analysis of 19 of these studies published in 2009 demonstrated a 2-fold increased risk of HIV infection among individuals infected with Mg (summary odds ratio (OR) = 2.01; 95% confidence interval (CI) = 1.4–2.8) [5]. More convincing evidence that Mg infection might enhance susceptibility to HIV infection comes from 2 longitudinal studies that demonstrated 2–2.5-fold increases in risk of acquiring HIV infection in Zimbabwean and Ugandan women with Mg [6, 7].

In addition to increased susceptibility to HIV infection, there is also evidence suggesting that HIV-positive individuals with Mg infection may be more likely to transmit HIV to their uninfected sex partners. Although a study among women in the Southern United States did not demonstrate an association between presence of Mg and detection of HIV RNA [8], Kenyan HIV-positive women with high Mg organism burdens were nearly 3-fold more likely to have HIV DNA detected in the genital tract than women without Mg [9]. *Mycoplasma genitalium*–infected Zimbabwean women had a similarly elevated likelihood of HIV RNA detection, although this latter relationship was not statistically significant [10]. In vitro studies by Dehon and colleagues demonstrated a possible mechanism for this observed increase in HIV shedding among Mg-infected individuals. Chronic cervical Mg infection in HIV-positive women was associated with elevated proinflammatory cytokine secretion and enrichment of HIV target cells, and these signs of inflammation cleared after successful eradication of Mg [11]. Although the relationship between Mg and HIV shedding in men who have sex with men (MSM) has not been explicitly evaluated, presumably the biologic mechanism for such a relationship would be the same. As such, MSM with Mg that are not on HAART may be at higher risk of transmitting their HIV infection, and targeted Mg testing in this high-risk population may be warranted.

Are the data summarized in the Wiesenfeld and Manhart [4] or that summarized above concerning the associations between Mg infection and HIV transmission adequate to support initiation of broad-based public health efforts to decrease the prevalence and incidence of Mg infection? The answer is probably not, given the high recurring cost of such programs. These costs would be borne by governmental agencies for the most part, although philanthropic organizations likely also would contribute. However, there is only so much money available for all public health programs, and this decision is not one to be taken lightly. This issue is addressed in detail in the article by Golden and colleagues [12]. What is required are prospective studies in high-risk populations designed to definitively determine whether screening for and treatment of Mg infections in women and their sexual partners improve reproductive health in women and/or prevent HIV transmission. It is unlikely that additional retrospective or even prospective studies of the association of Mg and adverse reproductive health outcomes will move the public health agenda forward. Only clear proof that intervention works will do that. The cost of these studies will be very high but is justified in terms of the impact the results would have on cost-effective allocation of future public health resources and defining the appropriate aims of future Mg research.

In light of the above, our consensus recommendations for future Mg research priorities are as follows.

1. Although Mg is associated with a number of significant clinical syndromes in men and women as summarized in this article, it is important to remember that these represent only a small proportion of the infected population. As is the case with many infectious diseases, including those transmitted sexually, the vast majority of Mg infections are asymptomatic and it is these infections that may result in adverse outcomes such as preterm deliveries, infertility, and enhanced risk of HIV infection. Therefore, it is critical that we determine whether or not screening for asymptomatic Mg in high-risk populations and successful treatment results in at least 1 of the following:
   a. Reduction in adverse pregnancy-associated neonatal and maternal outcomes. A pregnancy outcome study would be feasible but still would be expensive.
   b. Decrease in the incidence of HIV infection. An HIV prevention study in women would probably have to be done

in Africa, whereas a study in MSM could be done in developed countries.

c. Decrease in the incidence of infertility. Achievement of this study will be difficult if not impossible due to the huge sample size needed and length of follow-up that would be required to adequately assess the outcome.

d. Reduction in the incidence of clinical PID. This is a more controversial goal. The main assumption underlying such a study would be that PID is a precursor to tubal factor infertility, although some might argue that the morbidity of the syndrome itself justifies funding of population-based prevention programs. These issues require further analyses, as pointed out in the article by Golden et al [12].

2. There is a need for more effective and safe antibiotics for the treatment of Mg-related NGU in men and cervicitis and PID in women, regardless of whether or not widespread screening and treatment of Mg-infected women is recommended in the future. Research priorities in this area include:

a. Conduct of clinical trials designed to satisfy worldwide regulatory body requirements for the approval of pristinamycin for treatment of Mg infections in men and women.

b. Investigation of combined treatment with available drugs (ie, doxycycline and azithromycin or moxifloxacin and azithromycin). Combined treatment has the potential for improving cure rates and preventing the emergence of resistance at a low cost. Clinical studies to test this hypothesis are feasible now.

c. Conduct of phase 2 clinical trials of new drugs such as lefamulin and zoliflodacin for the treatment of Mg infections. These drugs have promising in vitro activity against Mg and are currently undergoing clinical trials for other infections.

d. Development of standardized in vitro testing using protocols panels of Mg strains with representative antibiotic susceptibility profiles for use in screening new antibiotics for anti-Mg activity. Such an assay conceivably also could be used to test for synergy between antibiotics, and the results could be used to guide clinical trials of combination treatment.

3. It is likely that the commercial availability of Mg testing in the United States will continue to be very limited until it is recommended by medical societies, national public health organizations, and/or governmental agencies. In anticipation of this happening at some point in the future, research priorities in this area include:

a. Development of assays that detect both the organism and the presence of resistance genes in order to improve patient management. Such an assay would be useful in clinical practice now.

b. Use of high-throughput sequencing of antibiotic-resistant Mg strains to identify additional Mg antibiotic resistance genes that could be included in resistance gene detection panels.

c. Development of point-of-care Mg assays.

4. Mg has the smallest genome of any known free-living organism and, as such, will continue to be the subject of basic research regardless of its clinical significance, as summarized in the article by McGowin and Totten [13]. Assuming that Mg eventually will be definitively proven to be a human pathogen important to women's health, translational basic research priorities include the following:

a. Better understanding of the mechanisms used by the organism to accomplish *mgpBC*/MgPar recombination. This could lead to the development of methods to interfere with this process, which appears to be essential to the organism's long-term survival in the human genital tract. If these recombination events could be blocked, the host immune system should be able to readily clear the infection.

b. Better comprehension of the natural history and basic life-cycle of Mg in reproductive tract tissues. This could similarly facilitate the development of therapeutic interventions and/or methods to prevent colonization and long-term survival.

c. Characterization of essential surface antigens. This could lead to the development of a vaccine for the prevention of Mg infection.

In summary, research over the last 35 years has clearly established Mg as a pathogen in the human genitourinary tract, but as yet these data have not resulted in the initiation of public health programs designed to prevent Mg infections in high-risk populations. It appears that the available data are not yet sufficient to move the Mg public heath agenda forward. A major goal of our 2016 National Institutes of Allergy and Infectious Diseases–funded Mg Technical Consultation, the proceedings of which are reviewed in this supplemental edition of the *Journal of Infectious Diseases*, was to generate discussion of this issue. We believe that the resulting research priorities listed herein succinctly summarize the way forward, and it is our hope that they will prove useful to investigators, research funding agencies, and public health planners.

Notes

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