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The Immunopathogenesis of *Mycoplasma genitalium* Infections in Women: A Narrative Review

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Abstract

Mycoplasma genitalium is a common, predominately asymptomatic, and often undiagnosed sexually transmitted infection (STI) that is associated with inflammatory urogenital and reproductive tract disease syndromes of men and women. Without programmatic screening in the United States, and with increasing resistance to antibiotics used in empiric STI management, undiagnosed *M. genitalium* infections put many women at risk for cervicitis and pelvic inflammatory disease (PID). Chronic infection may also lead to tubal-factor infertility, adverse pregnancy outcomes in expectant mothers, and is a risk-factor for acquisition and transmission of HIV. This review details the dynamics of *M. genitalium* infection, and then examines the potentially deleterious role of host immunity in reproductive tract disease pathogenesis and enhanced HIV acquisition/transmission.

Keywords

Mycoplasma genitalium; immunopathogenesis; sexually transmitted infection; inflammation; reproductive tract

INTRODUCTION

Sexually transmitted infections (STIs) remain a significant public health concern in the United States (US). For example, despite several largely successful nationwide screening initiatives, we observed the highest combined annual number of chlamydia, gonorrhea, and syphilis cases to date in 2015 (1). *Mycoplasma genitalium*, an emerging cause of STIs worldwide, was first isolated from men with nongonococcal urethritis (NGU) in 1980 and has since been associated with several reproductive and urogenital syndromes. Although this review is focused on the immunopathogenesis of infections in women, *M. genitalium*

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infection is an established etiology of urethritis in men, accounting for approximately 30% of recurrent/persistent NGU (2). The inflammatory nature of *M. genitalium* infections has been substantiated experimentally through urethral inoculation of male chimpanzees, which resulted in acute signs of urethritis similar to those observed in infected men (3, 4). In women, *M. genitalium* has been associated epidemiologically with several inflammatory syndromes including cervicitis, pelvic inflammatory disease (PID), and preterm birth (5, 6). Having recognized the associations with female reproductive tract disease, the CDC recently included guidance for *M. genitalium* infections associated with cervicitis and PID in the 2015 Sexually Transmitted Diseases Treatment Guidelines (7), albeit of limited utility since we still lack a test that is cleared by the Food and Drug Administration (FDA) for use in the US.

The prevalence of *M. genitalium* in low- and high-risk populations, averaged across several studies, is 2.0 and 7.3%, respectively (6). With increasing resistance to currently-available antibiotics (8), including those used commonly for empiric treatment of STIs, many *M. genitalium* infections are ineffectively treated thereby placing women at risk for the inflammatory syndromes associated with chronic infection. Although clearly able to persist in the female reproductive tract despite local and peripheral immune responses, the underlying mechanistic links between *M. genitalium* infection and clinical disease are largely unknown. Presented as an evidence-based timeline, this review first details the early events of *M. genitalium* infection, and then examines the available evidence for whether host immunity plays a deleterious role in pathogenesis and chronic reproductive tract disease in women, including enhancement of HIV transmission risk.

ESTABLISHMENT OF INFECTION

With unequivocal evidence, it is clear that *M. genitalium* is transmitted through heterosexual contact (9–15). In the context of *M. genitalium* transmission from a male to female partner, receptive vaginal intercourse results in primary inoculation of lower tract tissues via the vaginal and/or cervical mucosa. Although we still lack a clear understanding of whether tissue tropisms exist, and which cell types are capable of supporting productive *M. genitalium* infection, *in vitro* studies have demonstrated the ability of *M. genitalium* to rapidly attach to the epithelial cells that line the lumen of the vagina, ectocervix, and endocervix (16, 17). With mucin-binding proteins that specifically and preferentially bind vaginal and cervical mucin (18), *M. genitalium* may utilize secreted extracellular components of the lower tract mucosa to aid in attachment and colonization. Paradoxically, antimicrobial peptides (AMPs) and other antimicrobial factors are common constituents of cervical mucus (19) and hypothetically should have antimicrobial activity against *M. genitalium* as the organism lacks a cell wall. Although no studies to date have addressed the activity of AMPs, defensins, or other antimicrobial factors on *M. genitalium*, it appears that the organism can indeed reach the epithelial surface documented by electron microscopy of specimens from infected women (20). However, the mechanisms by which *M. genitalium* is able to maintain infection within the stratified squamous epithelia of the vagina and ectocervix despite normal sloughing of the apical-most layers remains unknown. Similar to several other mycoplasmas, *M. genitalium* possesses a specialized tip structure for motility and adherence to host cells (21, 22). Several proteins are involved in the development of the

terminal organelle, including P140 (MgPa adhesin), P110 (also called P114), the proline-rich P65 protein, the DnaJ-like protein MG200, the protein encoded by the MG491 gene (ordered locus designation), HMW2, HMW1, and HMW3 (23–25). The interactions between adhesins and the host cell membrane are reversible (26) and rapid, with attachment of *M. genitalium* to cultured human reproductive tract epithelial cells occurring as early as 30 minutes after inoculation (16). Subsequent invasion of host epithelial cells appears to be a common and rapid phenomenon *in vitro* (16, 21, 27). If rapid epithelial invasion occurs similarly *in vivo*, this may be an evolved mechanism to evade the early acute phase innate responses including chemokine-mediated leukocytosis at the site of infection.

In the absence of a cell wall, *M. genitalium* encodes a substantial number of genes for lipid associated membrane proteins (LAMPs) (28) that likely have prolonged contact with the epithelial surface during acute and chronic infection. As described in more detail below, these LAMPs play a role in innate immune activation of both epithelial cells and resident immune cells through binding of highly-expressed pattern recognition receptors (PRRs) (29), ultimately resulting in the activation of cellular host defense pathways, secretion of pro-inflammatory cytokines, and perpetuation of the local inflammatory response as described below.

ACUTE IMMUNE RESPONSES TO INFECTION

With strong binding affinity to epithelial surfaces, inoculation of cultured human vaginal and cervical epithelial cells results in secretion of pro-inflammatory cytokines and chemokines including IL-6, IL-8, MCP-1, MIP-1 β , G-CSF, and GM-CSF (16, 30, 31s). This is mediated, at least in part, by LAMPs binding TLRs 1, 2, and 6, and CD14 (29, 32s–35s). *M. genitalium* LAMPs have also been shown to induce expression of human beta defensin-2 (HBD-2) in cultured endocervical epithelial cells, likely a downstream effect of TLR2/6 binding and MyD88/NF- κ B pathway activation. Cytokine responses to acute *M. genitalium* infection have been similarly observed in studies of transcriptional activity as well (17). In fact, the profile of cytokine/chemokine responses to *M. genitalium* infection of reproductive tract epithelial cells has been remarkably consistent among studies, and mirrors closely what is observed in cervical secretions from women with chronic infections lasting more than one year (36s). Genome-wide transcriptional profiling using a 3-dimensional (3-D) cervical epithelial cell model showed that cellular pathways of host defense and inflammation are the most upregulated of all cellular pathways upon acute *M. genitalium* infection (31s). Interestingly, the intensity of cytokine responses to infection is reduced in studies of 3-D compared to conventional 2-D epithelial cell cultures of the same cell type (31s). This suggests that secreted factors from 3-D cells may impair access of *M. genitalium* to the epithelial cell surface, or that 3-D cells may produce antimicrobial factors that reduce the viability or capacity of *M. genitalium* to stimulate the epithelial cell. Nonetheless, these findings suggest that epithelial cells play an important role in the mucosal immune response to infection, and also validate the use of epithelial cell models to study mucosal responses to infection (36s).

With clear *in vitro* evidence that *M. genitalium* can stimulate pro-inflammatory responses from the infected epithelium, the next obvious consideration is whether these responses

direct the recruitment of leukocytes to establish and perpetuate the local immune response. Several key chemokines, namely IL-8 and MCP-1, are consistent components of the epithelial cell response to acute and chronic infection *in vitro* (17, 31s), and are also observed in cervical secretions of chronically infected women (36s). Unfortunately, very few studies have directly characterized the profile of leukocyte response to *M. genitalium* infection of lower reproductive tract tissues, and none have specifically addressed the acute response in humans. In the single study to investigate acute lower tract responses to *M. genitalium* infection, female chimpanzees inoculated intravaginally showed elevated levels of polymorphonuclear leukocytes (PMNL) in the vagina, which were highest 2–4 weeks following infection (4). Additionally, human epidemiological studies of cervicitis have shown that *M. genitalium* is associated with infiltration of PMNLs measured either directly from cervical gram stains (microscopic cervicitis) or inferred from the presence of cervical discharge on clinical exam (5, 6). Using a ratio of pan leukocytes to epithelial cells in liquid-based cytology specimens, two studies (one of low-risk and one of high-risk HIV-positive women) have reported an approximately three-fold increase in leukocytosis compared to women testing negative for *M. genitalium* and other common STIs (36s, 37s). Interestingly, subjects with *M. genitalium* infection showed the highest mean level of leukocytosis compared to other prevalent STIs, including *C. trachomatis*, *N. gonorrhoeae*, and *T. vaginalis* (37s). Although neither the epidemiological nor clinical studies have differentiated between acute and chronic infection, leukocyte recruitment appears to be a common outcome of *M. genitalium* infection and is compatible with the inflammation observed in epithelial cell and animal modeling. Interestingly, *M. genitalium* infection is more often associated with cervicitis when microscopic criteria are used as opposed to overt clinical signs of disease (i.e. cervical discharge and/or friability), suggesting that *M. genitalium* induces chronic leukocytosis without overt signs of disease on pelvic exam (6, 38s). Thus, *M. genitalium* infections may be under-diagnosed despite adherence to the CDC guidelines for empiric management of cervicitis, thereby providing further rationale for screening at-risk populations. Collectively, strong evidence-based links exist between the basic mechanics of mucosal infection and epithelial cell-mediated cytokine/chemokine responses, ultimately resulting in inflammation of the cervix.

CHRONIC REPRODUCTIVE TRACT INFECTION

Since *M. genitalium* infections are asymptomatic in 40–75% of women (9, 10), not routinely screened for in the US, and are commonly resistant to antibiotics used currently for empiric STI treatment (8), infections often persist leading to chronic inflammatory syndromes (5, 6). Several studies using laboratory animals, non-human primates, and human subjects have unequivocally demonstrated that *M. genitalium* is able to persist in female reproductive tract tissues (4, 15, 36s, 39s–45s). It is hypothesized that persistence in lower tract tissues increases the risk of ascending infection of the upper reproductive tract, which leads to an increased risk for PID, tubal-factor infertility, and adverse pregnancy outcomes. A recent Meta-analysis by Lis and colleagues reported that *M. genitalium* infection was associated with an approximately 2 to 2.5-fold increase in the risk for PID, tubal-factor infertility, and preterm birth (5). Unfortunately, the pathogenesis of upper tract disease syndromes associated with *M. genitalium* infection remains poorly understood. Due largely to the

inherent difficulties in collecting upper tract tissues for research, our evidence for *M. genitalium* as an etiology of upper tract disease comes predominately from epidemiological investigations that inherently lack mechanistic insight.

Although persistence is well documented in humans, the natural history and clearance rate of *M. genitalium* is understudied and largely unknown. Nonetheless, infection appears to be associated with chronic inflammation at lower genital tract sites as evidenced *in vitro* by significant secretion of IL-6, IL-7, IL-8, GM-CSF, and MCP-1 from chronically infected endocervical epithelial cells (30). Similarly, but in the clinical setting, HIV-positive women with chronic *M. genitalium* infection showed marked signs of cervical leukocytosis and significantly increased levels of IL-1 β , IL-6, IL-8, MCP-2, and MDC in cervical secretions compared to women testing negative for *M. genitalium* and other common STIs (36s). Interestingly, women with acute *M. genitalium* infection in the same cohort did not show similar increases in secreted cytokines/chemokines, suggesting long-term infection may be necessary to elicit detectable increases in mucosal inflammation (36s). Importantly, leukocyte infiltrates were absent following cure of *M. genitalium* infection (36s) implying that screening and treatment may indeed mitigate the associated inflammatory sequelae.

Unfortunately, only a few studies have assessed how infiltrating leukocytes interact with *M. genitalium*, how effective these cell types are at killing the pathogen, or whether associated local immune responses are deleterious to reproductive tract tissues. Although neutrophils represent the most common leukocyte type observed during chronic infection of the human cervix (36s), no studies to date have specifically addressed the interaction of *M. genitalium* with neutrophils. Considering the elevated cervical neutrophil responses observed for up to two years among chronically infected women (36s), and knowing that oxidants and hydrolytic enzymes released by stimulated neutrophils induce tissue damage (46s, 47s), it is highly likely that chronic infection and neutrophil infiltration has immunopathogenic consequences. In addition to hydrolytic enzymes, neutrophils secrete high concentrations of several pro-inflammatory cytokines and chemokines (47s, 48s) capable of perpetuating the local inflammatory response. Additionally, several studies have shown that exposure of *M. genitalium* to monocytes/macrophages results in activation, differentiation, and/or potent pro-inflammatory cytokine responses (16, 32s, 35s, 49s–51s), confirming that exposure to several relevant leukocyte types perpetuates the inflammatory response. Clearly, additional studies are warranted to understand the immunopathogenic role of recruited leukocytes given the smoldering microenvironment of inflammation involving both the epithelial cells and infiltrating leukocytes during chronic infection. Undetected chronic inflammation may have deleterious effects on mucosal health, may increase the risk of HIV acquisition as described in more detail below, and should be a significant factor as we consider the need for *M. genitalium* screening in the US.

EVASION OF HOST IMMUNE RESPONSES

Despite the seemingly clear picture of inflammation during chronic infection, *M. genitalium* possesses mechanisms to evade local immune responses and persist. In the presence of local antibodies (52s), observed cellular infiltrates (36s, 37s), and a local pro-inflammatory milieu as described above, two key mechanisms likely facilitate survival in human reproductive

tract tissues: [1] intracellular localization within epithelial cells; and [2] a complex, highly evolved genomic system for diversifying outer membrane immunogens. Intracellular localization of *M. genitalium* was first observed in cultures of infected Vero cells (21), and appears to occur as early as 30 minutes after inoculation (27). Once inside the cell, organisms are protected from gentamicin exposure (an antibiotic that does not efficiently enter eukaryotic cells and is used commonly to assess intracellular localization of bacteria; (16)), and commonly localize to membrane-bound vacuoles adjacent to the nucleus of cultured human cells (16, 21, 27). Previous *in vitro* studies suggest that intracellular organisms are also protected from direct phagocytosis (16) and, as macrophages are common residents of reproductive tract mucosae (53s–55s), epithelial cell invasion is likely a critical strategy to evade cellular immune responses. Importantly, we still lack conclusive evidence for the importance of complement and/or antibody-mediated opsonization of *M. genitalium* or its components for phagocytic uptake and killing by either macrophages or neutrophils. Nonetheless, evading phagocytosis during acute infection, and certainly in the inflamed mucosal environment during chronic infection, seems to be imperative for long-term survival.

Despite the fact that little is known about antibody-mediated opsonization, *M. genitalium* infection can indeed elicit strong humoral antibody responses in both men and women (56s, 57s). Antibody responses in humans and laboratory animals have been predominately observed against two major immunogenic outer membrane proteins encoded within the MgPa operon, MgpB and MgpC (56s). Importantly, reactive IgG and IgA antibodies are also detected in cervicovaginal secretions of experimentally-infected pig-tailed macaques (44s, 45s) and women (52s). *M. genitalium* has evolved a sophisticated and efficient multi-locus system for antigenic variation of the MgpB and MgpC proteins as described in detail elsewhere (39s, 58s–60s). In short, the genes encoding MgpB and MgpC, numbered loci MG191 and MG192, respectively, undergo homologous recombination with nine repetitive, non-coding chromosomal sequence islands termed MgPars. The MgpB and MgpC proteins are each prominent surface antigens that, due to recombination, have several regions of hypervariability that seem to be the clear result of antibody-mediated immune pressure (39s, 44s, 61s, 62s).

Survival in the dynamic environment of the lower reproductive tract necessitates the ability to evade both the innate and adaptive responses to infection. Considering the apparent capacity to induce inflammation in several epithelial and leukocytic cell types of the reproductive tract, *M. genitalium* clearly has a highly evolved capacity to persist. With inefficient natural clearance, chronic inflammation is the resultant consequence of untreated infections for many patients, most of who are asymptomatic and lack overt signs of disease that would normally direct STI screening and/or empiric therapy.

A ROLE FOR ENHANCED HIV TRANSMISSION

Considering the observed capacity to establish chronic infections associated with inflammation in lower reproductive tract tissues, *M. genitalium* has been identified as an established risk factor for HIV acquisition. In this context, the importance of *M. genitalium*-associated inflammation extends beyond the impacts on reproductive tract health. Two

longitudinal studies have assessed the association of *M. genitalium* in HIV acquisition, and both found that *M. genitalium* infection increases the risk of HIV acquisition by approximately 2–3 fold (63s, 64s). Additionally, as for enhancement of HIV transmission, two clinical studies have observed a significant association between *M. genitalium* infection and the frequency of HIV RNA (65s) or proviral DNA (66s) detection in the endocervix. In turn, several epidemiological studies (mostly cross-sectional) have shown associations of *M. genitalium* and HIV infection, with the prevalence of *M. genitalium* in HIV-positive individuals ranging between 11–33% (67s). Although we still lack a detailed, evidence-based explanation, the most plausible mechanisms by which *M. genitalium* enhances HIV acquisition and transmission are [1] HIV target cell enrichment and activation in reproductive tissues where HIV acquisition commonly occurs; and [2] disruption of the epithelial barrier in reproductive tract tissues, either via *M. genitalium* directly or as a consequence of neutrophil influx and local inflammation.

As detailed above, *M. genitalium* infection is associated with chronic leukocyte infiltrates and pro-inflammatory secretions in the cervix. Importantly, the profile of pro-inflammatory cytokines and chemokines, observed in both *in vitro* models and in CVL samples of *M. genitalium*-infected women, have been associated with increased HIV shedding as well as enhanced HIV acquisition (68s–76s). Additionally, pro-inflammatory cytokines observed during *M. genitalium* infection, including IL-6, IL-8, and/or IL-1 β , are known to predict a higher viral load set point, an early marker of rapid HIV disease progression (69s, 73s, 74s, 77s). IL-8, released in response to *M. genitalium* infection, is a potent chemokine for neutrophils, which appear to be the predominant infiltrating cell type in cervical *M. genitalium* infections (36s). Neutrophils have a well-defined role in immune activation, pro-inflammatory cytokine secretion, and ultimately recruitment and activation of HIV target cells (47s, 48s). Additionally, neutrophils release cytokines known to induce NF- κ B activation in HIV-infected cells, which binds the long terminal repeat (LTR) of HIV and enhances viral replication (47s, 48s, 71s, 72s). Macrophages are a common resident immune cell type in the cervix that appear to be enriched via MCP-1 and/or MCP-2 during *M. genitalium* infection (16, 30, 36s), and are HIV target cells thought to play an important role in the establishment of founder virus populations, ultimately facilitating a productive HIV infection (78s). Because tissue macrophages survive for extended periods of time, they may also serve as a reservoir for latent virus (78s, 79s) and contribute to HIV shedding and transmission to an uninfected partner. In addition, the potent capacity of macrophages to secrete pro-inflammatory cytokines suggests that this cell type may also play a role in HIV target cell recruitment and activation, further contributing to enhanced local HIV infection and replication (78s, 80s–82s).

Impairment of the epithelial barrier in lower reproductive tract tissues is a well-established mechanism to enhance HIV acquisition (83s). Indeed, *M. genitalium* infection of cultured endocervical epithelial cells (cultured on three-dimensional transwell inserts) has been shown to enhance the crossing of HIV across the barrier (84s). In addition to barrier impairment by *M. genitalium* directly, the inflammatory microenvironment of the infected mucosa, namely through recurrent neutrophil infiltration, may also damage the epithelium (46s, 47s) and enhance the ability of HIV to access underlying target cells. Collectively, the epidemiological and mechanistic associations of *M. genitalium* with HIV are striking, with

the local inflammatory response being the logical mediator of these immunopathogenic outcomes. To this end, and with substantial public health implications, the significant burden of HIV infections among adolescent girls and young women demand that we explore strategies to reduce *M. genitalium* infections.

CONCLUSIONS AND IMPLICATIONS FOR THE FUTURE

Dovetailed with the substantial body of epidemiological data, the pathobiological findings reviewed herein not only provide compelling evidence for *M. genitalium* as a female reproductive tract pathogen, but also spotlight the immunopathogenesis of this emerging STI. Our current understanding is that *M. genitalium* can persist and lead to lower tract inflammation that appears to manifest most commonly as cervicitis. Importantly, these conclusions rely in part on *in vitro* models of infection and/or studies of laboratory animals that should be substantiated in the clinical setting where possible. Nonetheless, without effective treatment, chronic *M. genitalium* infections in women may result in colonization of upper tract tissues leading to more severe disease including PID, endometritis, and tubal-factor infertility. Unfortunately, we still lack data from randomized controlled trials on whether screening and treatment of *M. genitalium* infections reduces female reproductive tract disease, but evidence-based rationale now exists to conduct such treatment trials. It is critically important that we consider not only the reduction of common STI-associated disease syndromes, but also consider the public health impact for HIV infections and adverse pregnancy outcomes. It is only with the data from such trials and the availability of FDA-approved molecular diagnostic tests that we can we can informatively manage *M. genitalium* infections, reduce the associated disease burden, and further explore the feasibility of a national prevention program in the United States.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SHORT SUMMARY

A comprehensive review of the immunopathogenic responses underlying *Mycoplasma genitalium* infections and associated reproductive tract diseases in women.