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REVIEW

Management of Pelvic Inflammatory Disease in Clinical Practice

Hasiya Yusuf[1], Maria Trent[1,2]

[1]Department of Pediatrics, Johns Hopkins School of Medicine, Baltimore, MD, USA; [2]Department of Population, Family, and Reproductive Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Correspondence: Maria Trent, Bloomberg Professor of American Health and Pediatrics, Departments of Population, Family, and Reproductive Health Sciences and Pediatrics, Johns Hopkins University, 200 N. Wolfe Street #2056, Baltimore, MD, 21287, USA, Tel +1 443-287-8945, Fax +1 410-502-5440, Email mtrent2@jhmi.edu

Abstract: Pelvic inflammatory disease (PID) is a common reproductive health disorder among women of reproductive age. The treatment of PID has slowly evolved, reflecting changing antibiotic susceptibility and advancements in therapeutics and research; however, it has been largely unchanged over the last several decades. The most recent treatment recommendations consider the severity of infection, clinical presentation, and the polymicrobial nature of the disease. In addition, the role of novel organisms like *Mycoplasma genitalium* in PID is of emerging significance. PID treatment guidance offers oral and parenteral treatment options based on the patient's clinical status; however, deviations from the published guidelines are a general concern. Point of care (POC) testing for precision care, provision of adherence support, optimizing self-management and prevention strategies, and other alternative or synergistic approaches that maximize treatment outcomes will be instrumental for addressing the current challenges in PID diagnosis and management.

Keywords: pelvic inflammatory disease, treatment, *Neisseria gonorrhoeae*, chlamydia trachomatis, guidelines, sexually transmitted infection

Introduction

Pelvic inflammatory disease (PID) is a polymicrobial infection that predominantly affects sexually active young women.[1] According to the Centers for Disease Control and Prevention (CDC), more than one million women are diagnosed with PID annually, and approximately 2.5 million women of reproductive age have had a PID diagnosis.[2,3] PID affects the upper genital tract through the retrograde movement of microorganisms from the lower genital tract.[4,5] Other routes of infection, such as hematogenous and lymphatic transmission (eg, tuberculosis), have been described though less commonly encountered. Upper genital tract infection leads to inflammation, abscess formation, tubal scarring, or obstruction. Acutely, patients may present with endometritis, salpingitis, pelvic peritonitis, or tubo-ovarian abscesses.[4,6] PID is both a clinical and public health concern due to its potential to result in infertility in undiagnosed or poorly treated cases.[1] This complication affects one in every eight women with a history of PID.[7] Furthermore, PID is associated with other morbidities like chronic pelvic pain, ectopic pregnancy, and recurrence.[8]

In the past, *Chlamydia trachomatis* (*C. trachomatis*) and *Neisseria gonorrhoeae* (*N. gonorrhoeae*) were responsible for most PID diagnoses. The proportion of PID caused by *C. trachomatis* exceeded 30% for younger women, though lower for older women, who generally have less risk for PID.[9] However, other organisms such as anaerobes, respiratory and enteric bacteria, and those linked to bacterial vaginosis are increasingly implicated.[1,10] Approximately half of PID cases are polymicrobial in origin and involve enteric pathogens (*Escherichia coli, Bacteroides fragilis*, group B *Streptococci*), respiratory pathogens (*Haemophilus influenza, Streptococcus pneumonia, Staphylococcus aureus*), and pathogens responsible for bacterial vaginosis (*Peptostreptococcus* species, *Bacteroides* species).[1,11]

Knowledge of the role of novel organisms like *Mycoplasma genitalium (M. genitalium)* in the pathogenesis of PID has been evolving,[12–14] and some studies have reported that *M. genitalium* PID and cervicitis incidence rates are

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comparable to *C. trachomatis*.[15,16] *M. genitalium* is isolated from the upper genital tract of many women with PID.[17–19] Unlike chlamydial PID, *M. genitalium*-associated PID presents with less inflammatory markers, lower pain intensity, and less frequent mucopurulent vaginal discharge, leading to fewer diagnoses and a consequent higher risk of infertility.[14,15] In addition, the current recommended treatment for PID does not provide adequate antibiotic coverage against *M. genitalium*, and *M. genitalium* infections tend to persist or reoccur in patients treated for PID even after clearance of *N. gonorrhoeae* and *C. trachomatis*.[17]

Sexually transmitted infection (STI) screening partner notification and treatment have led to a decline in PID incidence rates.[5,20] These prevention efforts have also helped reduce the direct and indirect costs of PID and its sequela, estimated to exceed $2000 per-person lifetime cost.[21] Further, the management of PID is slowly evolving, and diagnostic, and treatment guidelines are revised to reflect advances in diagnostics, therapeutics, and clinical research outcomes. For example, the Pelvic Inflammatory Disease Evaluation and Clinical Health (PEACH) trial established the similarity in treatment outcomes between patients with mild to moderate PID managed in partial inpatient versus outpatient settings.[22] While patients still experienced significant adverse clinical outcomes (eg, recurrent STIs/PID, chronic pelvic pain, or tubal infertility) in both groups, this work informed the current recommendation for a more cost-effective outpatient management approach for women with mild-moderate disease.[22]

Current Management Practices

Diagnosis

PID management begins with a prompt and accurate diagnosis through a comprehensive history and physical examination. Laboratory investigations, while helpful, are not required for clinical diagnosis and treatment initiation.[1] Clinicians managing patients with probable PID often consider the clinical presentation in light of known patient risk factors. For example, PID is most prevalent in women ≤25 years, although older women may also be affected. Other risk factors include a history of STIs, having two or more sexual partners within the last year, inconsistent condom use, and having a new sexual partner or a sexual partner with symptoms or a known STI diagnosis.[5,23,24] The clinical presentation of patients with PID can vary widely from an asymptomatic or mild clinical picture to severe disease.

Consequently, a high index of suspicion is required to avoid missed diagnoses and ensure timely treatment initiation. Pelvic examination of patients with clinically evident disease typically demonstrates mucopurulent discharge, pelvic pain, and cervical motion tenderness on the bimanual examination component.[1] Patients may also report fever, metrorrhagia, urinary symptoms, or dyspareunia on review of systems.[23,25] Rectal pain in a patient with suspected PID suggests the presence of a pelvic abscess.[24] When complications are suspected, laboratory or radiological investigations may be helpful to guide management decisions and disposition (eg, ultrasound to assess for a tubo-ovarian abscess).[1] Clinical diagnosis of PID has a high positive predictive value among sexually active young women who attend STI clinics and in populations with high STI prevalence.[1,25]

Current guidelines recommend a high index of suspicion and a low threshold for diagnosing PID because of its associated sequelae.[1,7] Clinical suspicion based on history and examination findings of cervical motion tenderness or adnexal tenderness is usually sufficient for diagnosis. However, clinical diagnosis for PID presents a problem of low sensitivity and specificity.[1] In recognition of the non-specificity of the clinical signs, many treatment guidelines recommend supporting clinical diagnosis with laboratory investigations.[1,24,26,27] However, negative diagnostic tests are not a basis for excluding a clinical diagnosis, especially where there is a high index of suspicion. Pregnancy tests are essential to ensure the absence of an intrauterine pregnancy or an ectopic pregnancy that is a medical emergency requiring immediate intervention. Nucleic acid amplification tests (NAAT) for *N. gonorrhoeae* and *C. trachomatis* are recommended for all patients. Wet prep microscopy and testing for STIs, eg, *T. vaginalis*, the human immunodeficiency virus (HIV), and syphilis, should also be considered.[1,24] Other labs can often provide supportive information, though not required for diagnosis. Leukocytes are often present on wet prep saline microscopy of mucocervical secretions, and a urinalysis may be positive for leukocyte esterase and white blood cells. Serum markers of inflammation, such as erythrocyte sedimentation rates (ESR), C-reactive protein, and white blood cell counts, may also be elevated in patients with PID. Laparoscopy can provide a definitive diagnosis of PID, but it is invasive, costly, and rarely needed.

Treatment and Contact Tracing

The recommended treatment for PID is based on published treatment guidelines and considers the severity of infection, clinical presentation, and an understanding of the polymicrobial nature of PID. Current CDC management guidelines stipulate that mild to moderate infections be treated on an outpatient basis using a combination of oral and parenteral regimens.[1] Conversely, severe PID is to be treated on an inpatient basis with wholly parenteral regimens for at least 24–72 hours. The variance in treatment between mild to moderate and severe disease was adopted from the outcome of the PEACH study, which showed that mild to moderate PID can be treated on an outpatient basis without a consequent increase in the risk of sequelae (infertility, chronic pelvic pain).[22] Antimicrobial treatment is initiated immediately after the collection of specimens. According to the Centers for Disease Control and Prevention (CDC) STI treatment guidelines, mild to moderate PID should be treated with a single dose of intramuscular ceftriaxone or cefoxitin, twice-daily dosing of oral doxycycline, with or without metronidazole. (see Table 1). Other parental third-generation

Table 1 Selected Treatment Guidelines and Recommended Testing for PID Demonstrating Variations Across Regions

	CDC	CNGOF & SPILF	European Guidelines
Outpatient regimens	Single dose Ceftriaxone 250mg IM & Doxycycline 100mg orally twice daily for 14 days **with or without** Metronidazole 500mg orally twice daily for 14 days **Or** Single-dose cefoxitin 2g I.M. and Doxycycline 100mg orally twice daily for 14 days **with or without** Metronidazole 500mg orally twice daily for 14 days 1–2 doses of Azithromycin 500mg IV daily, then Azithromycin 250mg orally for 12–14 days **with or without** Metronidazole 500mg orally twice daily for 14 days *Levofloxacin 500mg orally once daily **Or** *Ofloxacin 400mg twice daily **Or** *Moxifloxacin 400mg orally once daily **with or without** Metronidazole 500mg orally twice daily for 14 days	Single-dose Ceftriaxone 1g I.M. and doxycycline 100mg orally twice daily and Metronidazole 500mg twice daily for 14 days **Or** Oral ofloxacin 200mg daily and metronidazole 500mg twice daily with or without single dose ceftriaxone IM **alternatives** oral levofloxacin 500mg daily and metronidazole 500mg twice daily for 10 days with or without single ceftriaxone 1g IM **Or** Oral moxifloxacin 400mg daily for 10 days **with or without** single dose ceftriaxone 1g I.M.	Single dose ceftriaxone IM 500 mg and oral doxycycline 100 mg twice daily with metronidazole 500 mg twice daily for 14 days **Or** Oral ofloxacin 400 mg twice daily and oral metronidazole 500 mg twice daily for 14 days (ofloxacin may be replaced by levofloxacin 500 mg once daily **Or** Oral moxifloxacin 400 mg once daily for 14 days
Inpatient regimens	Cefotetan 2g IV 12 hours and Doxycycline 100mg orally or IV 12 hours **Or** Cefoxitin 2g IV 6 hours and Doxycycline 100mg orally or IV 12 hours **Or** Clindamycin 900mg IV 8 hours and Gentamicin IV/IM loading dose at 2mg/kg, then dose 1.5mg/kg 8 hours or single daily dosing of 3–5mg/kg Ampicillin/Sulbactam 3g IV 6 hours and Doxycycline 100mg orally or IV 12 hours	Single dose ceftriaxone 1g IV & Oral/IV doxycycline 100mg and oral metronidazole 500mg twice daily for 10 days **Or** IV doxycycline 100mg and Cefoxitin 2g for twice daily **replaced by** doxycycline 100mg twice daily and metronidazole 500mg twice daily for 10 days **Alternative** Clindamycin 600mg and gentamicin 5mg/kg/day IV for 3 days, then clindamycin 600mg three times daily oral for 10 days	Ceftriaxone IV/IM 1g once daily and Oral/IV Doxycycline 100 mg twice daily and oral Metronidazole 500 mg twice daily for 14 days **Or** Clindamycin 900mg 3 times daily and Single daily dose gentamicin (3–6 mg/kg) and clindamycin 450 mg four times daily for 14 days **Or** Oral doxycycline 100mg twice daily and oral metronidazole 500 mg twice daily for 14 days

(*Continued*)

Table 1 (Continued).

	CDC	CNGOF & SPILF	European Guidelines
Diagnostic criteria or Tests	*Minimal criteria* Cervical motion tenderness Uterine tenderness Adnexal tenderness *Additional criteria* Oral temperature > 101°F or 38.3°C Cervical mucopurulent discharge Elevated ESR Elevated C-reactive protein Positive test for gonorrhoeae/ chlamydia *Specific criteria* Endometrial biopsy with histopathologic evidence of endometritis Transvaginal USS or MRI Laparoscopic evidence of PID	NAAT urogenital mycoplasma culture C-reactive protein Complete blood count Endocervical samples for microbiological diagnosis Swab for standard culture Pelvic USS -for signs of complication Abdominopelvic CT	NAAT/culture for gonorrhoeae, chlamydia and *M. genitalium* ESR C-reactive protein WBC Laparoscopy Ultrasound scanning Endometrial biopsy CT/MRI – to rule out other causes of peritonitis Endometrial biopsy pregnancy test
Notes	All three minimum criteria must not be present for a diagnosis of PID. The presence of one or more additional criteria improves the specificity of PID diagnosis	Regimen covering gonorrhoeae, chlamydia, and anaerobes, as well as gram-negative bacteria and streptococci, should be given for 24–48 h Abdominopelvic CT is recommended for diagnostic difficulty *M. genitalium* is considered a principal cause of STI and PID	Metronidazole is included in some regimens to improve coverage for anaerobic bacteria. It may be discontinued in patients with mild or moderate PID who cannot tolerate it Antibiotic coverage for *M. genitalium* with moxifloxacin is recommended.

Notes: *represent alternative oral or IM regimens. Adapted from these studies.[1,24,27]
Abbreviations: CDC, Centers for Disease Control and Prevention; CNGOF, French National College of Gynecologists and Obstetricians; SPILF, French-language Society for Infectious Diseases; USS, ultrasound scan; NAAT, nucleic acid amplification test.

cephalosporins in combination with doxycycline can also be used. Azithromycin or levofloxacin are recommended as alternatives in patients with known cephalosporin allergies.

In contrast, hospitalization and parenteral antibiotics are recommended for pregnant or severely ill patients (eg, high fever, vomiting, tubo-ovarian abscess), patients unable to follow or tolerate an outpatient treatment regimen, and patients whose symptoms persist after 72 hours of outpatient treatment.[1,23] The addition of metronidazole to treatment is often at the discretion of the managing physician and is based on clinical judgment and the result of laboratory test(s). Still, it is usually reserved for patients with bacterial vaginosis or severe disease with possible anaerobic involvement.[1] Discharging providers should highly consider adjunctive treatment with metronidazole in patients residing in *T. vaginalis* prevalent communities and for those with laboratory evidence of *T. vaginalis* infection at diagnosis. Re-testing at three months post-treatment is recommended for all women with PID who test positive for gonococcal or chlamydial infections.

Ideally, all sexual contacts within 60 days of PID diagnosis should be tested and treated for N. *gonorrhoeae* and *C. trachomatis*. Where sexual contact is longer than 60 days, only the most recent sexual partner is treated.[1] The utility of presumptive treatment in asymptomatic sexual partners has been questioned. A study conducted in Sydney, Australia, found that only a quarter of the sexual contacts of patients diagnosed with an STI tested positive for asymptomatic gonococcal infection.[28] Such low infection rates in sexual contacts have led to questions about the relevance of presumptive treatment of sexual contacts in light of rising antibiotic resistance.

Adherence to Treatment Guidelines

Generally, treatment guidelines like those established for managing patients with PID result from extensive clinical research, experiences from clinical practice, and expert opinions set to ensure the best standards of practice. Deviations from PID treatment guidelines are a general concern due to the risk of sequelae such as infertility, chronic pelvic pain, ectopic pregnancies, and the risk of fostering antibiotic resistance. Despite existing recommendations for PID management, many surveys report failure to adhere to these guidelines by some care providers. For example, a study of select US clinics that managed patients with PID demonstrated that, whereas a majority (68%) of patients were treated according to CDC guidelines, others received second-line medications or antibiotic combinations not recommended by the guidelines.[29]

In addition, many primary care physicians, one of the medical specialties most likely to see patients with PID, do not follow the recommended guidelines for treatment, as more than 50% reported non-adherence or lack of comprehensive knowledge of the older CDC guidelines.[30] Only 3% who reported adherence to the guidelines for PID management in the past year could correctly respond to questions testing their knowledge.[30] Poor adherence to treatment guidelines for PID management is not limited to adult women. Similar treatment patterns have been observed in adolescent girls treated for PID in emergency departments across the U.S.[31] Addressing non-adherence to guidelines is vital to reducing the morbidity associated with low-quality PID care to meet the United States Healthy People 2030 goals to reduce PID in young women and to promote the health and well-being of women.[32]

Variations in Treatment Guidelines

Treatment guidelines for PID widely recommend broad-spectrum antibiotics to cover the commonly implicated organisms (e,g, *C. trachomatis*, *N. gonorrhoeae*, and anaerobes). Though largely similar, guidelines for PID treatment tend to vary minimally by country, with recommended regimens primarily dependent on prevalent organisms, antibiotic susceptibility, and cost.[1,24,27] It is worth noting that the spectrum of organisms responsible for PID is similar across contexts. It accounts for similarities in treatment regimens with occasional differences based on the abovementioned factors. The US and French guidelines recommend using 3rd generation cephalosporins in addition to doxycycline and metronidazole as first-line treatment for mild to moderate PID.[1,24] Though similar, the guidelines differ in the recommended treatment duration (ten vs fourteen days) and the addition of metronidazole to treatment regimens (Table 1). Differences in treatment duration may result from country-based studies and concerns about antibiotic stewardship. Like the US, the French guidelines reserve the use of fluoroquinolones for patients with cephalosporin allergies or when no alternatives are available. The European guidelines for PID management have similar antibiotic recommendations.[27] All three guidelines recommend a combination of twice-daily dosing of ofloxacin as alternate first-line regimens in uncomplicated PID.[1,24,27]

In light of burgeoning antibiotic resistance, efforts to identify the most clinically efficacious and cost-effective approaches to PID treatment remain ongoing. The standardization of PID treatment regimens in these three examples reflects current practice in developed societies. In contrast, PID management is less standardized in low- and middle-income countries, and wide variations in antibiotic use exist due to limitations imposed by cost and underdeveloped healthcare systems.[33] Antibiotics known to be effective are rarely prescribed, and the majority of providers have never accessed treatment guidelines, while some are oblivious to their existence.[33]

Current Challenges in PID Management: Novel Organisms

M. genitalium is a diminutive pathogenic bacteria first isolated in 1981.[13,18] Early research findings were unclear on the association between this organism and PID. Still, more recent evidence has established an association between them, including the feared reproductive complication of fertility impairment.[14,15,17,18,34,35] In a meta-analysis conducted by Lis et al, *M. genitalium* infection caused a 2-fold risk of infertility and increased the risk for spontaneous abortions, preterm births, and PID in women.[36] In light of this evidence, many research studies have focused on understanding the incidence, prevalence, and disease burden of *M. genitalium* in populations.

While reports show gross variations in incidence and prevalence, and many infected women have no clinically evident disease,[12,15] findings from certain studies have aroused concern, particularly in persons at risk for PID. In

a survey of 1139 women with asymptomatic bacterial vaginosis recruited from five clinics across the US, one in five (20.5%) women were positive for *M. genitalium* at baseline. These rates were comparatively higher than the prevalence of *N. gonorrhoeae* (4.8%) and *C. trachomatis* (14.7%) and the highest for any reportable STI within the U.S.[19] The prevalence of *M. genitalium* was highest in younger women of reproductive age,[19] and the incident rate during the study was 36.6 per 100 person-years. A similar clinical picture was observed in another study. The prevalence of *M. genitalium* outpaced the more commonly known STIs, ie, *N. gonorrhoeae* and C. *trachomatis*, by more than twice.[18] Women infected with *M. genitalium* also have greater odds of having other STIs than women without *M. genitalium*.[37] *M. genitalium* may cause subclinical PID, as seen with some other causes of PID. Also, similar to *N. gonorrhoeae* and *C. trachomatis*, antibodies against *M. genitalium* were higher in women with infertility due to tubal inflammation than in women with infertility from other causes.[35]

Although *M. genitalium* is now duly recognized as one of the organisms that play a role in the pathogenesis of PID, limited testing capabilities and research data hinder proactive action toward its identification and treatment. PID due to *M. genitalium* is usually asymptomatic or mild, presenting with less severe pelvic pains, less mucopurulent cervical discharge, and fewer markers of inflammation.[16] Furthermore, antimicrobials used in PID treatment tend to cover a broad spectrum of organisms. Still, they are not fully effective against *M. genitalium*-associated infections, and antibiotics to which *M. genitalium* is most sensitive are absent from current treatment guidelines.[1]

Fortunately, recognizing the potential disease impact and advances in developing novel diagnostics for *M. genitalium* raise the potential to optimize care. In 2015, the CDC labeled *M. genitalium* a public health threat, and the FDA recently approved a laboratory test to detect the organism in endocervical, vaginal, and urine samples.[38] The test will better ensure physicians accurately diagnose and treat cases of PID caused by *M. genitalium*. Unfortunately, the sensitivity of *M. genitalium* to azithromycin is waning due to rising antimicrobial resistance to macrolides. However, the organism currently remains sensitive to moxifloxacin. Patients diagnosed with *M. genitalium* had persistent infection despite treatment with azithromycin and achieved cure after treatment with moxifloxacin.[39] Moxifloxacin remains the antibiotic most effective for treating *M. genitalium* infections, although using doxycycline as first-line treatment is recommended until antibiotic sensitivity results become available.[40] This staggered approach optimizes treatment outcomes and limits the overuse of moxifloxacin. Despite not being part of current guidelines, this is likely to change as more evidence of the role of *M. genitalium* in PID and infertility emerges.

Innovating Next Steps to Define Future Possibilities

Point of Care (POC) Testing and Precision Care

To effectively reduce STI prevalence and curtail transmission between infected persons, timely treatment initiation with appropriate antibacterial agents is needed. In turn, effective STI therapy depends on rapid and accurate diagnosis. Unfortunately, the time lag between sample collection and completion of laboratory tests to results availability leads to discontinuity in treatment, with many patients lost to follow-up before precision treatment is fully initiated. For example, in a randomized clinical trial of women diagnosed with PID who were followed longitudinally for STI reinfection, many patients failed to return for treatment despite being notified of their diagnosis and referral for no-cost treatment.[41] Failure to return for treatment can potentially be improved by implementing POC testing. Most women are willing to trade a short wait to receive their test in real-time, so treatment can be initiated if needed.[42] Development of STI POC testing will optimize timely treatment by reducing confirmatory diagnostic delays.

POC testing for *N. gonorrhoeae*, *C. trachomatis*, and *T. vaginalis* infections is now available, and others are in development. Commercially available POC tests for *C. trachomatis* and *N. gonorrhoeae* detect the presence of antibodies or specific antigens.[43] The WHO criteria for the ideal POC test include sensitivity, specificity, affordability, easy use, accessibility to the end-user, and rapidly producing results.[43] Many commercially available POC tests meet these criteria to varying degrees. Antigen detection tests have comparatively higher utility in STI diagnosis as they indicate active infection requiring treatment. Conversely, antibody detection is diagnostic of active disease or immunologic response to past infection(s). Compared to POC testing for *C. trachomatis, there are fewer* antigen detection tests for *N. gonorrhoeae and M. genitalium*. Despite being an emerging concern, POC tests to detect antibiotic resistance determinants for *M. genitalium* and *N. gonorrhoeae* remain limited.[43–45]

POC testing for STI during asymptomatic infection will allow early intervention and primary prevention of future reproductive sequelae. Efforts to develop rapid diagnostic tools in asymptomatic patients have seen some success. One such achievement is the development of a yet-to-be-approved genetic biomarker that identifies women with asymptomatic endometritis. The highly sensitive test can rule out non-STI endometritis with fairly high accuracy.[46] Other advancements in POC testing for STIs, such as diagnostic sticks that are compatible with mobile phones, are also ongoing.[43,47] POC testing tools are unarguably the next big thing in STI diagnosis, and expectations are high that they will revolutionize STI diagnosis and treatment, promote precision care, and potentially reduce the global burden of STI and PID.

Adherence Support and Optimization of Self-Management and Prevention

Antibiotic treatment is prescribed for ten to fourteen days to effectively treat PID.[1,24,27] Treatment adherence is challenging for many patients, including those with STIs and PID. Even when satisfied with the quality of clinical care received, less than 50% of women managed for PID report compliance with prescribed medications.[48] Non-adherence to treatment predisposes to the persistence of infection and raises the risk for complications and onward transmission. Hence, adherence support may be necessary to assist patients through treatment.

Our previous study showed that patients who received adherence support through text message reminders and home visits by community health nurses had higher clearance rates of both *N. gonorrhoeae* and *C. trachomatis* infections at 1- and 3-months post-PID diagnosis and treatment.[49] These patients were also more likely to report condom use during last sex, a correlate of improved self-care and STI risk-reducing behavior.[50] Thus, the provision of adherence support improves treatment adherence and affects other areas of STI treatment that can impact overall treatment outcome and risk of future STI acquisition. Adherence support intervention appears to be effective and acceptable as an alternative model of care for STI and PID management. Patients with a PID diagnosis have expressed a willingness to pay a percentage higher than their usual cost of treatment to access additional support services in the form of nursing health visits.[51]

Vaccination Against STIs

It is estimated that 10–15% of chlamydial PID progress to tubal factor infertility.[52] Chlamydial infections alone cost the US more than 500 million dollars in healthcare costs, and the burden is expectedly higher in low- and middle-income countries.[53] A vaccine against *C. trachomatis* serovars D-K, the chlamydial genotype responsible for PID, can potentially avert an estimated 1 million chlamydial-associated tubal factor infertility annually.[54] The search for a *C. trachomatis* vaccine began a century ago. Initial vaccine trials focused on finding effective vaccines against genotypes A-C, the causative agent of trachoma. However, trachoma posed a significant public health burden before strategies including antibiotic treatment, environmental and personal cleanliness, safe and potable water supplies, and vector control, culminating in reduced incidence in most parts of the world. Although efforts at finding a vaccine against the organism eventually failed due to disease exacerbation concerns in subjects exposed to the live vaccine, the few successes recorded were relevant to studies on vaccines against genital *C. trachomatis*.

Research among sex workers has shown that some natural immunity develops after a genital infection with *C. trachomatis*, given the higher frequency of infections in younger women, the decreased frequency of infections with age despite persistent exposure, and the correlation between resistance to chlamydial infection and the duration of sex work.[54,55] Nonetheless, natural immunity tends to be partial and insufficient to offset the risk of infertility.

Research into chlamydial vaccines has been conducted using animal models. Much of what is known about the feasibility and potential of a vaccine emerges from research on *Chlamydia muridarum* in mice.[56] Initial trials focused on whole-cell (mostly live attenuated) vaccine trials and used laboratory mice as surrogate models. Live attenuated and inactivated vaccines in mice produced robust immune responses and significantly decreased *C. trachomatis* infection and infertility.[54,56] However, these vaccines are not feasible for human use due to the risk of chlamydial disease, reversal to wild types, and the cost of production of whole vaccines.

Protein-based subunit vaccines against *C. trachomatis* were developed to address the challenges of whole vaccines.[56,57] Many bacterial subunits are being studied, but the most promising subunit vaccines contain Major Outer

Membrane Protein (MOMP). MOMP is a 40 kDa protein that makes up the greater part of the outer membrane of chlamydia and is the antigen primarily responsible for generating immune responses.[57] Cell-mediated immunity through type 1 helper T cells is robust and most important for preventing *C. trachomatis* infection, and MOMP can induce innate and adaptive immune responses.[58] Vaccine formulations containing MOMP were highly effective in preventing upper genital disease in mouse models, eliciting immune responses comparable to those produced by live inactivated vaccines.[57]

The preferred genital vaccines would ideally have mucosal penetration: nasal, oral, vaginal, or gastrointestinal, although vaccines that utilize multiple administration sites have been widely proposed.[54,57] For the first time in decades of research, a vaccine has reached the first phase of human trials.[59] Its success will mark the beginning of a tremendous primary prevention milestone in the fight against STIs and PID.

Vaccines effective against *N. gonorrhoeae* and *M. genitalium* are also in development and are currently at different stages of pre-clinical testing, trailing behind chlamydial vaccines.[60,61]

Novel Approaches to Treatment

Effective, broad-spectrum antimicrobial agents are the mainstay of PID treatment and the prevention of associated sequelae such as tubal factor infertility. However, the success of antimicrobials in PID management is threatened by rising antimicrobial resistance. For example, fluoroquinolones were discontinued for PID treatment due to reduced effectiveness against *N. gonorrhoeae* due to antimicrobial resistance. The third-generation cephalosporins have now replaced fluoroquinolones. There is also rising concern about the effectiveness of macrolides, a class of antibiotics with coverage against anaerobes.

Rising antibiotic resistance has become a driving factor in identifying alternative approaches to PID treatment, and novel treatment strategies that utilize non-pharmacological therapies are being considered. For example, the effect of Ozone therapy on inflammatory processes in PID has been assessed and shown to progressively decrease inflammation through a reduction in the concentrations of pro-inflammatory interleukin-6 and improvements in the sonographic features of PID.[62] These positive outcomes were observed in studies conducted on rats. While a long way from use in humans, these findings may represent the future of PID management and help overcome the challenges of growing antimicrobial resistance.

Conclusion

PID affects women of reproductive age across the globe. Prevention strategies such as asymptomatic screening have reduced PID prevalence, but non-adherence to treatment guidelines and antimicrobial resistance pose challenges for the management of affected women. POC testing to optimize precision care and adherence support to optimize self-management are critically important. Advances in bench science to produce anti-chlamydial vaccines and alternative antimicrobial therapies may be vital to overcoming these challenges moving into the future.

Disclosure

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