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PELVIC INFLAMMATORY DISEASE SUPPLEMENT

Gonococcal Pelvic Inflammatory Disease: Placing Mechanistic Insights Into the Context of Clinical and Epidemiological Observations

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While infection by *Neisseria gonorrhoeae* is often asymptomatic in women, undetected infections can ascend into the upper genital tract to elicit an inflammatory response that manifests as pelvic inflammatory disease, with the outcomes depending on the intensity and duration of inflammation and whether it is localized to the endometrial, fallopian tube, ovarian, and/or other tissues. This review examines the contribution of *N. gonorrhoeae* versus other potential causes of pelvic inflammatory disease by considering new insights gained through molecular, immunological, and microbiome-based analyses, and the current epidemiological burden of infection, with an aim to highlighting key areas for future study.

Keywords. *Neisseria gonorrhoeae*; gonorrhea; pelvic inflammatory disease (PID); cervicitis; endometrial infection; endometritis; salpingitis; oophoritis; neutrophil.

Gonorrhea has long plagued humans, although it was not until 1879 that *Neisseria gonorrhoeae* was determined as the infectious cause [1]. Gonococcal pelvic inflammatory disease (PID) is a complication of cervical infection that has substantial immediate and long-term consequences for women, including chronic pain, ectopic pregnancy, and infertility. PID is an umbrella term describing inflammation of the female upper genital tract (UGT), including salpingitis, endometritis, oophoritis, tubo-ovarian abscess, pelvic peritonitis, and perihepatitis [2], and it has been used to generally encompass these conditions in any combination. For the purposes of this review, we will focus on acute PID (≤30 days), because chronic PID (>30 days) is not typically associated with gonococcal infection [3].

PID is a result of microbes ascending the UGT, triggering host inflammation and subsequent tissue damage. Because sampling of the UGT and laparoscopy are not routinely performed due to the invasive nature of such procedures, many PID diagnoses make the supposition that *N. gonorrhoeae* is the cause if pelvic or lower abdominal pain is accompanied by gonococcal recovery from the cervix or urine. We will refer to such cases as "*N. gonorrhoeae*–associated PID" when it is not explicit that *N. gonorrhoeae* was isolated from the UGT.

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HOW DOES *N. GONORRHOEAE* CONTRIBUTE TO PID?

While Koch's postulates have been fulfilled for gonococcal urethritis in men [4] and *Chlamydia trachomatis* salpingitis in female monkeys [5], this has not been the case for gonococcal PID. The reasons for this include the difficulty of modeling PID in animals, because *N. gonorrhoeae* is a very fastidious and human-specific pathogen, and because it is highly unethical to infect a woman with *N. gonorrhoeae* owing to the risk of severe sequelae. However, *N. gonorrhoeae* has long been suspected of causing PID. In 1886, shortly after the discovery of *N. gonorrhoeae*, gonococci were isolated from the fallopian tubes (FTs) of a woman with acute salpingitis [5], leading to the conclusion that *N. gonorrhoeae* was the etiological agent for PID. Later, salpingitis cases became subcategorized as gonococcal or nongonococcal in origin. *N. gonorrhoeae* has since been isolated from the endometrium, FTs, and peritoneal fluid of women with PID [6–17]; notably, UGT recovery is not always accompanied by detectable cervical infection in these studies.

Aside from classic sexually transmitted infections (STIs), respiratory pathogens and anaerobes can also be detected in the UGT of women with PID, suggesting that the clinical outcome may be a general response to ascending infection, and there may be a polymicrobial cause [6]. In this context, the fact that STIs are strongly associated with PID and account for the majority of cases [3] may be a matter of infection location and opportunistic spread into the UGT, rather than a site-specific tropism. This is muddled by the uncertain role that bacterial vaginosis plays in PID development [18], as well as the ongoing uncertainty regarding the existence of a normal UGT microbiome [19]. It is therefore clear that bacterial seeding of the uterus is more commonplace than once

assumed, but it remains difficult to make conclusions about the relative contribution of bacteria other than *N. gonorrhoeae* and *C. trachomatis* to pathogenesis without more comprehensive PID-focused microbiome analysis.

Aside from the microbial composition, the factors that determine whether they are tolerated or drive inflammation within the UGT remain unknown. It has been proposed that salpingitis could be temporally polymicrobial—with *N. gonorrhoeae* or another inflammatory STI first ascending and triggering damage that "primes" the tissue, so that it may be colonized by anaerobic or other opportunistic bacteria [20]. However, this hypothesis has not been subjected to rigorous examination and thus remains an important focus for future study.

HOW DOES *N. GONORRHOEAE* ENTER THE UGT?

Since no experimental model can recapitulate all aspects of gonococcal disease, we must learn from studies using different systems. *N. gonorrhoeae* and host factors responsible for the establishment of lower genital tract colonization have been expertly reviewed elsewhere [21, 22]. Here we discuss ascending infections and UGT-specific findings.

Fulminant abdominal pain during, or shortly after, menses has classically indicated PID [18]. While this is often correlated with *N. gonorrhoeae*–associated PID [23, 24], it is not gonococcal specific [25]. Bacterial recovery is most common in the follicular/proliferative phases [2, 24, 25], which coincide with estrogen-controlled changes in mucus viscosity and uterine contractions that move fluid upward [2, 26]. These normal physiological changes, in additional to sexual intercourse and retrograde menstruation, can provide opportunities for *N. gonorrhoeae* and other microbes to ascend, with the outcome dependent on the load and virulence of the microbe as well as the resulting immune response [2, 26]. Figure 1 shows the canalicular flow of infection after gonococcal colonization of the endocervix.

Ascending infections occur in approximately 20% of estradiol-treated, wild-type mice infected with *N. gonorrhoeae* vaginally [34]. Because mice do not express epithelial receptors required for *N. gonorrhoeae* attachment, this supports the premise that basic physiological processes can carry the bacteria upward, even in the absence of more specialized virulence factors. The utility of this lower genital tract infection model to study ascending infection is unclear because the original study had only 2 mice with recoverable bacteria in the UGT [34]. Another study detected uterine bacteria in all infected mice, although this protocol described a large volume injected against the cervix, which may reflect a direct uterine inoculation [35]. However, no other model has been described to model bacterial ascent, and it remains to be seen whether transgenic mice expressing human factors that facilitate *N. gonorrhoeae* infection show increased ascent of *N. gonorrhoeae* into the UGT after their introduction into the vagina.

WHAT HAPPENS WHEN NGO REACHES THE UGT?

The endometrial epithelia represents a critical line of defense against infections [36]. In vitro cell culture model systems of human endometrium epithelial cells, including organ cultures and 3-dimensional cell models [27, 37], have demonstrated proinflammatory responses to *N. gonorrhoeae* infection. Notably, endometrial cells can differentiate between bacterial species since they produce inflammatory cytokines in response to *N. gonorrhoeae* infection but not commensal *Lactobacillus crispatus* or even bacterial vaginosis–associated *Gardnerella vaginalis* [27]. Therefore, there are clearly pathogen-specific cues with the potential to trigger inflammation and, potentially, development of PID. A cell culture model system, combining epithelial cells and neutrophils to study *N. gonorrhoeae*–induced neutrophil transcytosis across the epithelia, demonstrated coordinated eicosanoid-driven signaling between these cell types to enact the characteristic robust inflammation [28]. This work reinforced the observation that neutrophils have a self-perpetuating feedback loop that drives the *N. gonorrhoeae* immunopathogenic response [29]. Future work must aim to understand whether these effects contribute to the infiltration of neutrophils and plasma cells into the endometrium, since this typifies acute endometriosis in humans [13] (Figure 1, inset).

To put these in vitro findings into physiological context, mouse modeling can be used to study the onset of endometritis by directly infecting the uterus. Transcervical infection of progestin-treated mice leads to a rapid proinflammatory cytokine response and massive purulent influx of neutrophils into the uterine lumen, disrupting the epithelial layer and causing tissue damage [30]. Transcriptomic analysis reveals that infections in both estrus and diestrus stages of the reproductive cycle result in up-regulation of similar host response pathways, although diestrus infection has neutrophil-related signals that are magnitudes higher [38]. Interestingly, *N. gonorrhoeae* infection of mice expressing human carcinoembryonic antigen–related cell adhesion molecule 1 (CEACAM1) during estrus resulted in greater bacterial association and penetration of endometrial tissue than in wild-type mice, although tissue invasion did not affect bacterial clearance nor was there increased tissue damage [39].

To date, no animal model has described gonococcal FT involvement or postinfection sequelae such as tissue scarring or infertility, perhaps attributable to the specific adaptation of *N. gonorrhoeae* for humans. Interestingly, the Pelvic Inflammatory Disease Evaluation and Clinical Health (PEACH) clinical trial also failed to find a connection between endometritis and infertility in the absence of salpingitis [8]. This suggests that murine uterine infection may remain a valid model for studying acute endometritis and the onset of host inflammatory responses in the uterus.

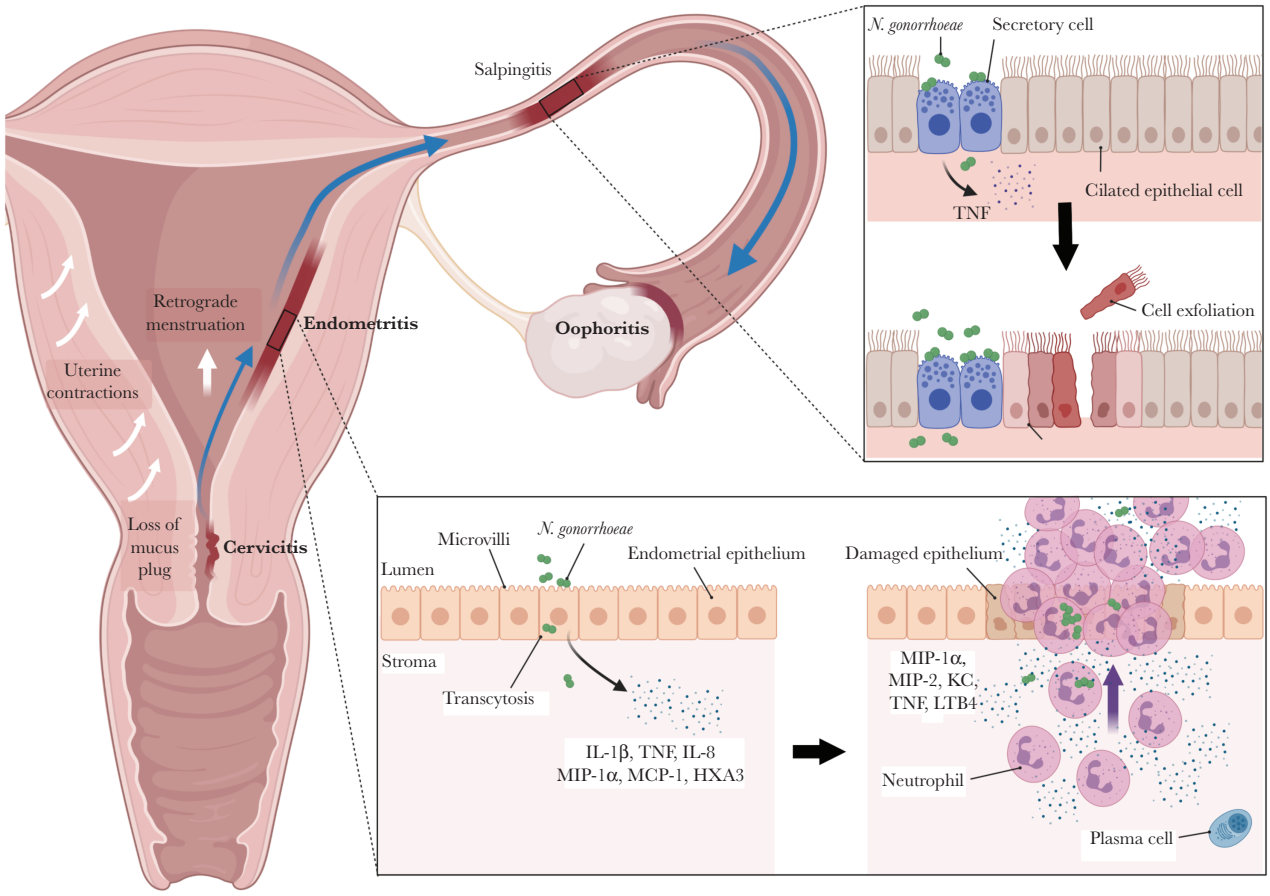

Figure 1. Ascending infection and mechanisms of inflammatory damage leading to pelvic inflammatory disease after endocervical infection by *Neisseria gonorrhoeae*. Endocervical infection by *N. gonorrhoeae* may or may not manifest as cervicitis. After infection is established, host physiological and physical factors, including hormone-controlled loss of the mucus plug, uterine contractions, sexual intercourse, and retrograde menstruation, can lead to ascent of bacteria into the endometrium [2, 26]. *N. gonorrhoeae*–specific virulence factors may also be involved, although their actual role during ascent have yet to be demonstrated in an appropriate model. Infection and subsequent inflammation of the endometrium (endometritis), fallopian tubes (FTs) (salpingitis), or ovaries (oophoritis) can occur. *Inset* (*bottom*), Endometrial damage occurs when *N. gonorrhoeae* interacts with the epithelial lining, leading to bacterial transcytosis and epithelial responses including release of proinflammatory cytokines interleukin 1β (IL-1β) and tumor necrosis factor (TNF); neutrophil chemokine interleukin 8 (IL-8), and the eicosanoid hepoxilin A3 (HXA3) [27, 28]. On recruitment to the site of infection, neutrophils enter a positive feedback loop by producing additional neutrophil chemotactic factors, including leukotriene B4 (LTB4), KC, and macrophage inflammatory protein (MIP) 2 (unpublished observations) [28, 29]. This results in a secondary wave of neutrophil migration into the uterine lumen, resulting in tissue damage [30]. Abbreviations: KC, keratinocyte-derived chemokine; MCP, monocyte chemoattractant protein. *Inset* (*top*), *N. gonorrhoeae* binding to nonciliated secretory cells and release of peptidoglycan and lipo-oligosaccharide fragments stimulate a potent inflammatory response from the epithelia of the FTs [31, 32]. The TNF produced leads to death and sloughing of ciliated cells [33], which can lead to irreversible scarring, deciliation and impaired fertility. (Illustration created using BioRender.com.)

HOW DOES GONORRHEA CAUSE TISSUE DAMAGE AND PID SEQUELAE?

PID morbidity arises primarily as a result of the tissue repair process after infection-triggered inflammatory damage to epithelium. Of particular importance to fertility are the ciliated cells of the FTs, which are crucial to transferring the ovum to the uterus [40]. Fibroblast replacement of damaged cells results in scarring, tubal occlusions, deciliation, pelvic adhesions and, potentially, irreversible tubal function loss, which can lead to ectopic pregnancy and infertility [2].

Unlike mouse infection with *Chlamydia*, *N. gonorrhoeae* uterine infection does not result in the development of hydrosalpinx [41], so an animal model for gonococcal salpingitis and sequelae is lacking. Experiments using human FT explants have shown that ciliated cells are particularly susceptible to *N. gonorrhoeae*–induced death, despite the fact that *N. gonorrhoeae* primarily interact with nonciliated secretory cells [40, 42]. Because *N. gonorrhoeae* have no cytolytic toxins to cause direct cell death, ciliated cells instead undergo tumor necrosis factor–induced apoptosis as a result of host detection of peptidoglycan monomers and lipo-oligosaccharide, both of which are abundantly released by growing *N. gonorrhoeae* [31–33, 40].

Pain, a common PID morbid effect, can also be caused by inflammation. Lipid mediators produced by neutrophils, such as prostaglandin E2 and leukotriene B4, are important mediators in models of inflammatory hypernociception [43, 44]. Neutrophils produce leukotriene B4 [28] and dendritic cells

produce prostaglandin E2 in response to *N. gonorrhoeae* in vitro [45], and elevated levels of both mediators have been found in the peritoneal fluid of women with acute PID [46]. It is enticing to consider that *N. gonorrhoeae*–induced neutrophilic responses could be the source of pain in women with PID, and that targeting these responses could help provide pain relief. The trigger for these lipid mediator–based responses remains unclear. However, when considered along with the cytokine and neutrophil responses, it seems clear that the exuberant response to *N. gonorrhoeae* infection, rather than a direct effect of the bacteria itself, leads to the tissue damage that typifies PID.

WHY IS PID SO DIFFICULT TO STUDY?

Clinical manifestations of PID vary widely, making diagnoses challenging and surveillance data difficult to interpret. A PID diagnosis is based on clinical evidence but cannot be made from the results of any single or specific physical, laboratory, or patient history finding [47]. It typically depends on pelvic pain and signs of lower genital tract infection, which can be subtle, vague, or asymptomatic. Laparoscopic visualization of salpingitis is considered the reference standard for diagnosis, although it may miss early signs of inflammation or endometritis. In addition, it is an expensive and invasive procedure, with variable user interpretation, and is not available in all healthcare settings [3]. Furthermore, the treatment of PID is dependent on accurate and timely detection of microbes, but *N. gonorrhoeae* has historically been considered short-lived in the FT and peritoneal cavity [5], making it difficult to distinguish from other triggers.

WHAT IS THE IMPACT OF ASYMPTOMATIC *N. GONORRHOEAE* INFECTION AND SUBCLINICAL PID?

Asymptomatic rates of gonorrhea are thought to be high, especially in women, although data remain sparse and depend on the population studied. Random sampling revealed more cases of untreated gonorrhea than cases diagnosed and reported [48], while another US study estimated 45% of gonorrhea cases to be asymptomatic [49]. This study also found that most cases of untreated gonococcal infections were due to a lack of symptoms [49]. More recently, Detels et al [50] found that 67%–100% of *N. gonorrhoeae*–infected individuals reported no symptoms in some populations. However, the reason why some infections remain asymptomatic while others are pathogenic remains poorly understood.

The concept of subclinical PID (also called atypical or silent PID) is that uncomplicated or asymptomatic cervical infection can be accompanied by inflammation of the UGT, without incurring symptoms of acute PID. A cohort of women with subclinical PID, defined by histological endometritis, had a significant risk of infertility compared with women with normal histological findings. Importantly, cervical infection with either *C. trachomatis* or *N. gonorrhoeae* without UGT involvement was not itself a risk factor for infertility [51]. However, up to half of women with apparently uncomplicated *N. gonorrhoeae* or *C. trachomatis* cervicitis have histological signs of subclinical PID [52], and women with infertility due to bilateral tubal occlusion were frequently found to have serological evidence of past *N. gonorrhoeae* or *C. trachomatis* infection despite not having a clinical history of salpingitis [53].

Early PID diagnosis is imperative to prevent sequelae, because delayed treatment is linked to worsened fertility outcomes [54]. This may explain why endometritis in subclinical PID (for which women do not seek medical attention) is linked to decreased fertility, unlike symptomatic endometritis in mild to moderate acute PID cases [8]. The varying sequelae, even among clinically inapparent infections, make it difficult to reveal a causal link between discrete attributes of infection and disease, particularly when considering the diversity among gonococcal strains that might also contribute to the outcome.

HOW HAS GONOCOCCAL-ASSOCIATED PID PREVALENCE CHANGED OVER THE YEARS?

Table 1 lists select studies conducted in the last 5 decades, indicating the proportion of acute PID associated with *N. gonorrhoeae*. These clinical studies reveal enormous variations in *N. gonorrhoeae*–associated PID, ranging from 1% to 74% of all patients with acute PID, making interpretations difficult. Certainly, some of these differences can be explained by the geographic location (eg, Israel having a low prevalence of gonorrhea [55]) and the time period (eg, gonorrhea epidemic in industrialized countries in the 1960s and 1970s [47]). However, small study sizes, variance in sampling and culture methods, differences in access to technology, and variation in clinical case definitions heavily affect the estimates of *N. gonorrhoeae*–associated PID. The results of several large-scale and long-term studies from different countries are briefly summarized below.

The 2 largest and longest running studies on gonococcal-associated PID come from Sweden. Both cohorts of approximately 2500 patients, staggered by 10 years, showed similar rates of *N. gonorrhoeae*–associated PID (48.7% in Lund [56] and 42% in Örebro [16]) at the start of each study period, followed by a steady decline over the following 25 years. In the United States, the PEACH trial examined mild to moderate PID from multiple US sites between 1996–1999; a total of 831 patients were enrolled in this study, with 20% being *N. gonorrhoeae* associated [57]. A large retrospective ecological study was performed in a cohort of Australian women from 2009 to 2014. Of the total 14 271 PID admissions, only 0.1% were *N. gonorrhoeae* related, while 5.3% were *C. trachomatis* related, suggesting that *N. gonorrhoeae* was a minor cause of PID in this population. However, it should be noted that 22.6% of these admissions were categorized as chronic PID, and 65.8% were considered unspecified PID [58]. For the latter, it is unknown whether another

Table 1. Prevalence of *Neisseria gonorrhoeae*–Associated Acute Pelvic Inflammatory Disease in Selected Studies by Country and Year

Country	Site of Specimen Collection	Laparoscopy-Confirmed PID	Patients With *Neisseria gonorrhoeae*–Associated PID, No. (%)		Years of Study	Authors (Year of Publication)
			LGT and UGT[a]	UGT Only[b]		
Denmark	LGT	No	9/166 (5)	NA	1979–1980	Møller et al (1981) [76]
Denmark	LGT and UGT	Yes	8/46 (17)	Unclear		Kristensen et al (1985) [64]
Sweden	LGT and UGT	Yes	5/65 (5)	0/65 (0)		Gjønnaess et al (1982) [77]
Sweden	LGT	Yes	41/209 (20)	NA	1979–1980	Osser and Persson (1982) [78]
Finland	LGT and UGT	Yes	18/72 (25)	7–9/72 (10–13)[c]	1983–1988	Heinonen and Miettinen (1994) [15]
USA	LGT and UGT	No	91/204 (45)	7/54 (13)	1972–1974	Eschenbach et al (1975) [6]
USA	LGT and UGT	No	133/197 (68)	12/197 (6)	1976	Cunningham et al (1977) [7]
USA	LGT	No	41/83 (49)	NA		McCormack et al (1977) [23]
USA	LGT	Retrospective, unspecified	70/114 (61)	NA	1978–1979	Tavelli (1986) [79]
USA	LGT and UGT	Yes	11/23 (48)	6/23 (26)	1982–1983	Wasserheit et al (1986) [11]
USA	LGT	No	27/42 (64)	NA		Dodson and Faro (1986) [80]
USA	LGT and UGT	Yes	23–30/46 (50–65)[d]	22/46 (48)	1982–1986	Kiviat et al (1990) [13]
USA	LGT	No	69/93 (74)	NA	1985–1988	Golden et al (1989) [81]
USA	LGT and UGT	Yes	55/82 (67)	41/78 (53)	1982–1988	Eschenbach et al (1997) [17]
USA	LGT	Retrospective, unspecified	24/343 (7)	NA	2007–2010	Burnett et al (2011) [82]
USA	LGT	No	27/271 (10)	NA	2012–2016	Trent et al (2019) [83]
USA	LGT and UGT	No	17/233 (7)	12/233 (5)	2010–2015	Wiesenfeld et al (2021) [9]
Canada	LGT	No	15/43 (35)	NA	1978–1980	Bowie and Jones (1981) [84]
Canada	LGT and UGT	Yes	21/50 (42)	9/50 (18)	1983–1987	Brunham et al (1988) [12]
Canada	LGT	No	19/100 (19)	NA	2004–2014	Chen et al (2018) [73]
United Kingdom	LGT and UGT	Yes	7/23 (30)	2/23 (9)	1984–1987	Stacey et al (1992) [14]
Israel	UGT	Yes	NA	0/40 (0)	1987–1989	Dan et al (1993) [55]
Kenya	LGT and UGT	Yes	83/133 (62)	Unspecified	1994–1996	Cohen et al (1998) [85]
Cameroon	LGT	No	1/70 (1)	NA	2013–2014	Nkwabong and Dingom (2015) [86]

Abbreviations: LGT, lower genital tract; NA, not available; PID, pelvic inflammatory disease; UGT, upper genital tract; USA, United States of America.

[a]Including coinfections and any LGT sites (cervical, vaginal, rectal, and urinary tract).

[b]UGT sites included endometrium, fallopian tubes, and peritoneal fluid. Percentages represent the percentage of all PID cases.

[c]Data were reported as numbers of patient with *N. gonorrhoeae* isolated from fallopian tubes or endometrium but without specifying whether any patients had *N. gonorrhoeae* isolated from both sites.

[d]An additional 8 women had cervical *N. gonorrhoeae* and/or *Chlamydia trachomatis* infection without UGT infection, but numbers were not delineated further.

etiological agent (such as *Mycoplasma genitalium*) is prevalent, or whether diagnoses were simply miscategorized, since this study did not link to test results for *N. gonorrhoeae* or *C. trachomatis*.

These studies support an overall consensus that *N. gonorrhoeae*–associated PID rates have dropped in industrialized countries since their peak in the 1960s and 1970s but that rates differ significantly between populations. More recent studies suggest that *N. gonorrhoeae*–related PID have remained below their former high levels, and overall rates of PID have been observed to decrease in the United Kingdom, the United States, and Australia [59]. These results have been attributed to aggressive public health campaigns that not only educate but also actively screen for *N. gonorrhoeae* and *C. trachomatis*, higher adoption rates of safe sex practices in response to human immunodeficiency virus, and the practice of treating infected partners to reduce PID recurrence [59–61]. Whether they begin to escalate again with recent increases in *N. gonorrhoeae* infection rate remains to be seen.

DO GONOCOCCI STILL CAUSE A SIGNIFICANT BURDEN OF PID?

The global decrease in *N. gonorrhoeae*–related PID begs the question of whether *N. gonorrhoeae* is still an important cause of PID. *C. trachomatis* infection remains the most prevalent bacterial STI worldwide, and is responsible for a higher proportion of PID cases than *N. gonorrhoeae*. There is also growing concern about the role of *M. genitalium* or other bacteria that are not monitored [3].

However, *N. gonorrhoeae* clearly remains a substantial problem. There is a strong correlation between gonorrhea prevalence and negative reproductive outcomes, with secondary and tertiary waves of PID and ectopic pregnancy following increases in gonorrhea incidence [47, 60, 62]. Meta-analysis shows that gonococcal infections are many times more prevalent in infertile populations than in the general population [63]. Patients with *N. gonorrhoeae*–associated PID are more febrile and ill than those with nongonococcal PID [23, 64, 65], consistent with the PEACH trial finding that women with

N. gonorrhoeae–associated PID sought care more quickly than women with *C. trachomatis* or *M. genitalium* infections [66]. An Australian study also found that hospitalization rates are higher for *N. gonorrhoeae*–associated than for *C. trachomatis*–associated PID [67], suggesting increased disease severity.

Unfortunately, gonococcal surveillance indicates that incidence rates are growing around the world [68–71]. It is suggested that 10%–20% of untreated gonococcal infections develop into PID [1, 60]. However, a small study from 1983 found rates as high as 47% in women who contracted gonorrhea from their infected partners [72], while a more recent Canadian study from 2004–2014 found PID complications in only 1.5% of gonorrhea cases [73]. A 2012 study alarmingly found that after treatment for *C. trachomatis* or *N. gonorrhoeae*, acute PID still developed in 13% of patients [74]. The recent emergence of gonococcal resistance to last-line antibiotics raises new concerns relevant to the PID discussion. The first reported case of ceftriaxone-resistant case of *N. gonorrhoeae* in Canada was asymptomatic and was discovered only because of STI screening [75]. The combination of increasing incidence rates and the possibility of untreatable gonococcal infections makes for a particularly urgent issue.

CONCLUSIONS

Because PID primarily strikes sexually active women during their reproductive years, it represents a terrible personal, economic, and societal burden. Public health–based interventions to reduce *N. gonorrhoeae* infection rates are clearly effective at reducing PID incidence. Indeed, preventing cervical infection in the first place, either by safe sex barrier methods or vaccines once they become available, will remain the most effective way to avoid the consequences of PID. However, beyond this, progress is beginning to be made toward understanding the intimate relationship between *N. gonorrhoeae* and humans. While this stealthy pathogen can persist undetected, the vigorous immunopathogenic response once it is recognized suggests that therapeutic immune modulation may help clear the infection and help suppress the emergence of sequelae. Given the inherent difficulties in studying gonococcal PID in humans, future work must aim to use clinical studies and primary cell or mouse-based modeling to reveal what processes drive the immunopathology associated with PID, so that new approaches to mitigate this damage can be developed.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases online*. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Owing to the restriction on references allowable, references 51–86 are cited but provided as supplementary content.

Notes

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