Newest Approaches to Treatment of Pelvic Inflammatory Disease: A Review of Recent Randomized Clinical Trials

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(See the editorial commentary by Eschenbach on pages 961–3)

Treatment of pelvic inflammatory disease (PID) should provide high rates of clinical and microbiological cure for a range of pathogens and should ultimately prevent reproductive morbidity. Between 1992 and 2006, 5 randomized clinical trials of moxifloxacin (1 trial), ofloxacin (1 trial), clindamycin-ciprofloxacin (1 trial), and azithromycin (2 trials) treatment among women with mild to moderate PID were found to have clinical cure rates of 90%–97%. Trials of ofloxacin and clindamycin-ciprofloxacin reported rates of cure of Neisseria gonorrhoeae and Chlamydia trachomatis infection of 100%, although microbiological cure data for other pathogens were not presented. One azithromycin trial reported a 98% eradication of C. trachomatis, N. gonorrhoeae, Mycoplasma hominis, and anaerobes. Moxifloxacin exhibited high eradication rates for N. gonorrhoeae, C. trachomatis, M. hominis, Mycobacterium genitalium, and gram-negative anaerobes. Clinical cure rates from 2 doxycycline-metronidazole trials were low (35% and 55%). Although a handful of studies have shown that monotherapies for PID achieve high rates of clinical cure, the efficacy of these regimens in treating anaerobic PID and in preventing adverse reproductive sequelae is not fully elucidated.

Pelvic inflammatory disease (PID), the infection and inflammation of a woman’s upper genital tract, is a frequent cause of infertility, ectopic pregnancy, and chronic pelvic pain among women of childbearing age [1]. Surveillance data are sparse but suggest that PID is diagnosed in general practice in 1.7% of women aged 16–46 years in the United Kingdom annually and in ~8% of US women and 15% of Swedish women in their lifetime, with >1 million US women treated annually [2–6]. PID is thought to occur when microorganisms, frequently Chlamydia trachomatis or Neisseria gonorrhoeae, ascend from the lower genital tract and infect the uterus, fallopian tubes, and ovaries [7]. However, PID has a multimicrobial etiology, and up to 70% of cases are nongonococcal and nonchlamydial. Anaerobic gram-negative rods, Mycoplasma genitalium, and bacterial vaginosis are also associated with PID [8–12].

Because of its polymicrobial nature, PID is treated with antibiotics covering a broad spectrum of pathogens. Guidelines of the Centers for Disease Control and Prevention recommend outpatient treatment of PID with ofloxacin, levofloxacin, ceftriaxone plus doxycycline, or cefoxitin and probenecid plus doxycycline, all with optional metronidazole for full coverage against anaerobes and bacterial vaginosis (table 1) [13]. In a meta-analysis of 34 treatment trials published primarily between 1985 and 1992, 4 inpatient regimens and 1 outpatient regimen were found to have pooled clinical cure rates ranging from 92% to 95% and microbiological cure rates ranging from 91% to 100% [14]. These inpatient regimens included the following drugs: clindamycin and aminoglycoside (clinical cure rate, 92%; microbiological cure rate, 97%); cefoxitin and...
Table 1. 2006 US Centers for Disease Control and Prevention–recommended outpatient regimens for the treatment of pelvic inflammatory disease.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>Ofloxacin</td>
<td>400 mg po twice per day for 14 days</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500 mg po once daily for 14 days</td>
</tr>
<tr>
<td>Ceftriaxone plus doxycycline</td>
<td>250 mg im in a single dose and 100 mg po twice per day for 14 days</td>
</tr>
<tr>
<td>Cefoxitin plus probenecid plus doxycycline</td>
<td>2 g im in a single dose, 1 g po administered concurrently in a single dose, and 100 mg po twice per day for 14 days</td>
</tr>
<tr>
<td>Other parenteral third-generation cephalosporin (e.g., cefotizoxime or cefotaxime) plus doxycycline</td>
<td>100 mg po twice per day for 14 days</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Added to any of the above regimens; 500 mg po twice per day for 14 days</td>
</tr>
</tbody>
</table>

**NOTE.** Adapted from [13].

doxycycline (clinical cure rate, 93%; microbiological cure rate, 98%); cefotetan and doxycycline (clinical cure rate, 94%; microbiological cure rate, 100%); and ciprofloxacin (clinical cure rate, 94%; microbiological cure rate, 96%) [15]. A fifth inpatient regimen, which included metronidazole and doxycycline, was found to have much lower rates of clinical and microbiological cure (75% and 71%, respectively) [14]. These low efficacy rates are likely attributable to the poor coverage of this latter combination against *N. gonorrhoeae* [15]. One outpatient regimen (cefoxitin, probenecid, and doxycycline) was included in this meta-analysis and was found to have a pooled clinical cure rate of 95% and a microbiological cure rate of 91% [14]. Since the publication of this meta-analysis, additional studies of PID treatment have been conducted, including several new monotherapies. Here, we summarize and evaluate these recent randomized clinical trials.

**FLUOROQUINOLONE TRIALS**

Table 2 provides a summary of the randomized clinical trials of treatment for PID published between 1992 and 2006. In general, these recent treatment trials have focused on monotherapies, which are believed to increase compliance. One randomized trial comparing ofloxacin with cefoxitin plus doxycycline among 249 women with clinically suspected PID reported high rates of clinical cure or improvement (95% vs. 93%) and eradication of *N. gonorrhoeae* (100% in both groups) [16]. Ofloxacin was associated with greater eradication of *C. trachomatis* (100% vs. 88%) and a lower prevalence of adverse effects (7% vs. 15%) [16]. Although anaerobes, aerobes, and mycoplasmal species were obtained from culture for some women, data about eradication of pathogens were not presented [16]. Thus, it is impossible to determine from this study the microbiological efficacy of ofloxacin in treating PID due to anaerobic species.

Two nonrandomized studies of laparoscopically confirmed salpingitis similarly support the efficacy of ofloxacin for the treatment of gonococcal and chlamydial PID by demonstrating that ofloxacin, administered every 12 h intravenously followed by a 10- to 14-day oral regimen, was associated with a gonococcal cure rate of 100% [23, 24], a chlamydial cure rate of almost 100% [23, 24], and a clinical cure rate of 98% [24]. However, although all patients with anaerobic bacteria cultured at study admission were considered to be clinically cured at follow-up in one of these studies [24], follow-up anaerobic cultures were not reported, and therefore, microbiological cure of anaerobes cannot be determined.

Because the lack of anaerobic coverage with ofloxacin is a concern, emphasized by the high rate of treatment failure among patients with nongonococcal, nonchlamydial PID [16], the Centers for Disease Control and Prevention suggests the optional addition of metronidazole [13]. Alternatively, a randomized clinical trial of 131 women with laparoscopically confirmed PID investigated the regimen of another fluoroquinolone, ciprofloxacin, plus clindamycin [17]. In this study, clindamycin-ciprofloxacin was found to be as effective as ceftriaxone plus doxycycline for the clinical cure of PID (97% vs. 95%) and *C. trachomatis* eradication (100% in both groups) [17]. *N. gonorrhoeae* was less prevalent; it was found in only 2 women who were treated with clindamycin plus ciprofloxacin, and 1 of these women achieved microbiological cure (a cure rate of 50%). Although aerobic and anaerobic isolates were frequently identified before treatment, no comparisons of microbiological cure for these pathogens were presented.

In the most recent fluoroquinolone randomized clinical trial by Ross et al. [18], moxifloxacin was found to have high rates of clinical resolution (90%) and microbiological cure. The microbiological cure rate was 100% for *N. gonorrhoeae*, *Mycoplasma hominis*, *M. genitalium*, *Escherichia coli*, and other gram-negative anaerobes. Although the eradication rate of *C. trachomatis* was lower (89%), it was slightly higher than that
of the comparator regimen (86%) [18]. Further, the eradication rate for *N. gonorrhoeae* was much higher (100%, compared with 82%) and the rate of drug-related adverse events was lower (23%, compared with 31%) among women treated with moxifloxacin.

**AZITHROMYCIN TRIALS**

Also of interest because of its association with enhanced compliance, single-dose or short-duration azithromycin in the treatment of PID has been examined in a handful of studies. Not surprisingly, compliance with single-dose azithromycin therapy has been reported to be 100% [25]. In a randomized clinical trial from India of 165 women with clinically suspected PID, a kit containing 1 tablet of fluconazole (150 mg), 1 tablet of azithromycin (1 g), and 2 tablets of secnidazole (2 g) was associated with a PID clinical cure rate of 93%, which is similar to that found among a group treated with ciprofloxacin plus tinidazole for 7 days (clinical cure rate, 96%) and better than that found among women treated with doxycycline plus metronidazole for 1 week (clinical cure rate, 91%) [19]. However, although this trial showed high rates of clinical cure, data on microbiological cure were not presented. In a randomized clinical trial in the United Kingdom that compared azithromycin monotherapy, azithromycin plus metronidazole, and standard 21-day regimens of metronidazole-doxycycline-cefoxitin-probenecid or doxycycline-amoxicillin-clavulanate among 300 patients with PID, azithromycin was found to have a high rate of clinical success, similar to that of other regimens (97% for azithromycin monotherapy, compared with 96% for azithromycin-metronidazole and 95% for a comparator regimen) [20]. Moreover, azithromycin provided excellent rates of eradication of *C. trachomatis*, *N. gonorrhoeae*, *M. hominis*, and anaerobes [20]. Complicating the interpretation of this study, however, was the combining of 2 different trials in the analyses. In 1 trial, 500 mg of azithromycin was administered intravenously on day 1, followed by 250 mg of oral azithromycin for 6 days. In the other trial, the intravenous protocol was conducted for 2 days, followed by oral azithromycin therapy for 5 days. The comparator regimens in each trial differed as well. Therefore, the optimal azithromycin regimen cannot be determined. Furthermore, the dropout rate at the final follow-up visit was extremely high (78%), and this reduces the validity and generalizability of the microbiological cure evaluation.

**DOXYCYCLINE AND METRONIDAZOLE TRIALS**

A few studies have further examined the outpatient combination regimen of doxycycline and metronidazole. In a randomized clinical trial of 40 patients with laparoscopically confirmed salpingitis, combined doxycycline-metronidazole treatment exhibited a low clinical cure rate of 35%, with a 50% clinical improvement rate [21]. The low efficacy of this regimen was replicated in an observational study in the United Kingdom involving 135 women with PID, in which only 55% experienced a clinical cure 2 or 4 weeks after treatment [26]. The addition of ceftriaxone to this regimen resulted in a higher but still suboptimal cure rate of 72% [26]. Because combined doxycycline-metronidazole provides poor coverage against *N. gonorrhoeae* and was also associated with the lowest pooled clinical and microbiological cure rates in the meta-analysis conducted by Walker et al. [14], this is not considered to be an optimal regimen for treatment of PID.

**INPATIENT MEROPENEM TRIAL**

Most randomized clinical trials of monotherapy for PID have been conducted among women with mild to moderate PID who were treated as outpatients. In a study of 84 women hospitalized because of PID, meropenem, which has demonstrated in vitro activity against a broad spectrum of gram-negative and gram-positive aerobic and anaerobic bacteria, was found to be associated with high rates of clinical response and microbiological cure that were relatively similar to those found with treatment with clindamycin plus gentamicin (clinical response rate, 88% vs. 90%; microbiological cure rate, 88% vs. 86%) [22]. However, only 37% of patients had cultures performed after treatment and were included in comparisons of microbiological cure. Further studies are needed to confirm the use of this well-tolerated [22] broad-spectrum inpatient monotherapy regimen for the treatment of PID.

**DISCUSSION**

Among the recent trials of treatment for PID, regimens including ofloxacin, moxifloxacin, azithromycin, and clindamycin-ciprofloxacin all yielded high rates of clinical cure and eradication of *N. gonorrhoeae* and *C. trachomatis*, although microbiological cure data among women with PID due to anaerobes are limited. This is attributable, in part, to the complexity of studying PID due to anaerobes, because the organisms may be present as commensal bacteria in the lower genital tract, and transcervical sampling of the endometrium may result in contamination of endometrial biopsy specimens by vaginal or cervical microorganisms. However, we have previously demonstrated that contamination likely does not account for the relationships between bacterial vaginosis–associated microorganisms and acute endometritis. In the PID Evaluation and Clinical Health (PEACH) study, we have shown that anaerobic gram-negative bacteria are associated with acute endometritis independent of bacterial vaginosis [9]. Furthermore, anaerobic gram-negative rods and anaerobic gram-positive cocci—but not other organisms frequent among women with bacterial vaginosis (e.g., *Gardnerella vaginalis* and *M. hominis*)—are associated with acute endometritis [9]. Another barrier to the study of microbiological cure of PID is the lack of 100% cor-
Table 2. Randomized clinical trials since 1992 for the treatment of pelvic inflammatory disease.

<table>
<thead>
<tr>
<th>Drug study</th>
<th>Year</th>
<th>Regimen</th>
<th>Clinical cure, proportion of patients (%)</th>
<th>Microbiological cure rate(s)</th>
<th>AEs and compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ofloxacin</td>
<td>1993</td>
<td>Ofloxacin (400 mg twice daily po for 10 days)</td>
<td>122/128 (95)</td>
<td>100% Neisseria gonorrhoeae and Chlamydia trachomatis eradication</td>
<td>7% rate of AEs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cefoxitin (2 g im) followed by Dox (100 mg twice daily po for 10 days)</td>
<td>112/121 (93)</td>
<td>100% N. gonorrhoeae and 88% C. trachomatis eradication</td>
<td>15% rate of AEs; overall, 12 patients did not comply with study drug regimen; no difference in compliance between treatment regimens</td>
</tr>
<tr>
<td>Clin and Cpfx</td>
<td>1996</td>
<td>Clin (300 mg, 2 capsules 3 times daily) and Cpfx (250 mg, 1 tablet twice daily) for 14 days</td>
<td>65/67 (97)</td>
<td>100% C. trachomatis eradication; 2 women with results positive for N. gonorrhoeae, 1 of whom was microbiologically cured; of women with both C. trachomatis and N. gonorrhoeae infection, all had negative results after treatment</td>
<td>1 patient withdrew because of AEs</td>
</tr>
<tr>
<td>Comparator: ceftriaxone (250 mg im, single dose) and Dox (100 mg, 1 capsule twice daily) and placebo (2 capsules 3 times daily for equivalent diseases of Clin) for 14 days</td>
<td>61/64 (95)</td>
<td></td>
<td>100% C. trachomatis and N. gonorrhoeae eradication</td>
<td>1 patient withdrew because of AEs</td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>2006</td>
<td>Moxifloxacin (400 mg once daily for 14 days)</td>
<td>248/275 (90)</td>
<td>88% overall bacteriological success rate; 100% eradication of N. gonorrhoeae, 99% eradication of C. trachomatis, and 75%–100% eradication of Mycobacterium hominis, Mycobacterium genitalium, Escherichia coli, Streptococcus, and other gram-negative anaerobes; 0% eradication of other gram-positive anaerobes</td>
<td>AEs led to discontinuation in 14% of patients</td>
</tr>
<tr>
<td>Comparator: ofloxacin (400 mg twice daily) plus Mtz (500 mg twice daily)</td>
<td>262/289 (91)</td>
<td></td>
<td>82% overall bacteriological success rate; 82% eradication of N. gonorrhoeae, 86% eradication of C. trachomatis, and 100% eradication of M. hominis, M. genitalium, E. coli, and other gram-positive anaerobes; 50% eradication of other gram-negative anaerobes</td>
<td>AEs led to discontinuation in 20% of patients</td>
<td></td>
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</tbody>
</table>
### Azithromycin

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Year</th>
<th>Treatment</th>
<th>Comparator</th>
<th>Eradication Rate at End of Treatment</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malhotra et al. [19]</td>
<td>2003</td>
<td>Kit containing 1 tablet of fluconazole (150 mg), 1 tablet of azithromycin (1 g), and 2 tablets of secnidazole (2 g)</td>
<td>Comparator: Cpfx (500 mg) and tinidazole (600 mg) twice daily for 7 days</td>
<td>43/46 (93)</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Comparator: Dox (100 mg) twice daily and Mtz (200 mg) 3 times daily for 7 days</td>
<td>47/49 (96)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Bevan et al. [20]</td>
<td>2003</td>
<td>Azithromycin (500 mg iv for 1–2 days followed by 250 mg po for 5–6 days)</td>
<td>Comparator: Cpfx (500 mg) and tinidazole (600 mg) twice daily for 7 days</td>
<td>99/102 (97)</td>
<td>Eradication rate at end of treatment was 24/24 (100%) for <em>C. trachomatis</em>, 6/6 (100%) for <em>N. gonorrhoeae</em>, 10/12 (83%) for <em>M. hominis</em>, and 99/100% for anaerobes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Comparator: Dox (100 mg) twice daily and Mtz (200 mg) 3 times daily for 7 days</td>
<td>101/105 (96)</td>
<td>Eradication rate at end of treatment was 24/25 (96%) for <em>C. trachomatis</em>, 5/5 (100%) for <em>N. gonorrhoeae</em>, 15/18 (83%) for <em>M. hominis</em>, and 11/11 (100%) for anaerobes</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Comparators: Mtz (500 mg iv 3 times daily for 1 day) plus Dox (100 mg po twice daily for 14 days) plus cefoxitin (2 g im 4 times daily) plus probenecid (1 g po single dose) or Dox (100 mg po twice daily for 21 days) plus amoxicillin-clavulanate (1 g iv 3 times daily for 5 days) plus amoxicillin-clavulanate (500 mg po 3 times daily)</td>
<td>88/93 (95)</td>
<td>Eradication rate at end of treatment was 30/30 (100%) for <em>C. trachomatis</em>, 5/5 (100%) for <em>N. gonorrhoeae</em>, 9/11 (82%) for <em>M. hominis</em>, and 7/7 (100%) for anaerobes</td>
</tr>
</tbody>
</table>

### Dox-Mtz

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Year</th>
<th>Treatment</th>
<th>Comparator</th>
<th>Eradication Rate at End of Treatment</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Witte et al. [21]</td>
<td>1993</td>
<td>Dox (200 mg first day followed by 100 mg daily) and Mtz (500 mg every 8 h for 10–14 days)</td>
<td>Comparator: Pefloxacin (800 mg daily) plus Mtz (500 mg every 8 h for 10–14 days)</td>
<td>7/20 (35)</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Comparator: Pefloxacin (800 mg daily) plus Mtz (500 mg every 8 h for 10–14 days)</td>
<td>9/20 (45)</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

### Meropenem

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Year</th>
<th>Treatment</th>
<th>Comparator</th>
<th>Eradication Rate at End of Treatment</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemsell et al. [22]</td>
<td>1997</td>
<td>Meropenem (500 mg iv every 8 h for 2–10 days)</td>
<td>Comparator: Clin (900 mg iv) plus gentamicin (1.5 mg/kg, following a loading dose of 2.0 mg/kg, iv every 8 h for 2–10 days)</td>
<td>185/211 (88)</td>
<td>88% eradication of <em>N. gonorrhoeae</em>, anaerobes, and aerobes</td>
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<td></td>
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<td></td>
<td></td>
<td>166/184 (90)</td>
<td>86% eradication of <em>N. gonorrhoeae</em>, anaerobes, and aerobes</td>
</tr>
</tbody>
</table>

**NOTE.** AE, adverse event; Clin, clindamycin; Cpfx, ciprofloxacin; Dox, doxycycline; Mtz, metronidazole.
relation between the microbiological makeup of the endometrium and fallopian tube and the unlikelihood of determining the microbiological flora of the fallopian tube after treatment. Despite the challenges facing the study of PID due to anaerobic organisms as a result of the fact that only one-third to one-half of PID cases are attributed to \textit{N. gonorrhoeae} and/or \textit{C. trachomatis} and the fact that bacterial vaginosis, anaerobic gram-negative rods, and mycoplasma bacteria have been identified among women with PID [9, 10, 12, 27, 28], the microbiological efficacy of treatment regimens for both chlamydial and/or gonococcal and nonchlamydial and/or nongonococcal PID should be determined. Unfortunately, previous trials of metronidazole showed it to have limited efficacy, perhaps because poor tolerability limits adherence. Indeed, the highest rates of adverse effects and study discontinuation in the randomized clinical trials reviewed herein occurred in women who were assigned to comparator regimens containing metronidazole [18–20]. This fact underscores the need for research on agents for the treatment of PID that are bactericidal for anaerobes. Regimens with shorter duration and monotherapy regimens are promising and may increase compliance and decrease sequelae. However, there is currently limited evidence for the recommendation of alternative therapies for the treatment of anaerobic PID. Although azithromycin provides coverage against a range of anaerobic and aerobic pathogens (including black-pigmented gram-negative rods) [20, 29], fluoroquinolones, including ofloxacin, have generally been found to have limited activity against anaerobes [30, 31]. In a recent trial of moxifloxacin versus ofloxacin plus metronidazole, moxifloxacin was found to be as clinically efficacious as ofloxacin plus metronidazole and to exhibit similar cure rates for \textit{C. trachomatis} and \textit{Mycoplasma} and better cure rates for \textit{N. gonorrhoeae} and gram-negative anaerobes [18]. However, women treated with moxifloxacin experienced a worse cure rate for gram-positive anaerobes [18]. Alternatively, a study has shown azithromycin to be effective for the treatment of anaerobic PID [20]. Clinical cure rates and eradication of anaerobes are similar among women whose PID is treated with azithromycin alone and women treated with combination azithromycin-metronidazole (clinical cure rate, 97% vs. 96%; anaerobe eradication rate, 100% vs. 100%) [20]. This initial study is promising, and further work may support the use of azithromycin monotherapy for the treatment of anaerobic PID. However, neither azithromycin nor quinolones are optimal for the treatment of gonococcal PID, because increasing drug resistance is being reported [32–36].

Treatment efficacy in the studies reviewed was restricted to short-term clinical and microbiological cure. There are limited data on the efficacy of any PID treatment regimen in the prevention of adverse reproductive sequelae. From the PEACH study, we have previously reported that, among women with clinically suspected mild to moderate PID treated with the standard antibiotic regimen of doxycycline and cefoxitin, endometritis and upper genital tract gonococcal and chlamydial infection were not associated with reproductive morbidity [37]. One interpretation is that these antibiotics that are used to treat modern-day mild to moderate chlamydial and gonococcal PID limited to the uterus are so effective that reproductive morbidity is not elevated among women with treated endometritis. However, despite the high rates of clinical cure and eradication of \textit{N. gonorrhoeae} and \textit{C. trachomatis} observed in the PEACH study at 30 days after treatment [38], rates of infertility (17%) [38], recurrent PID (14%) [38], and chronic pelvic pain (37%) [39] were distressingly elevated over the course of follow-up. This suggests a need to discover and provide coverage against all possible damaging PID pathogens and also to focus on long-term morbidity in treatment efficacy evaluations.

It is possible that women with nongonococcal PID may be more likely to experience adverse sequelae. In the PEACH study, we reported that women with nongonococcal bacteria identified in the endometrium were generally more likely to experience reproductive morbidity than were women with gonococcal infection. Infertility rates were 13% for women with \textit{N. gonorrhoeae} identified, 19% for women with \textit{C. trachomatis} identified, 22% for women with anaerobic bacteria identified, 27% for women with \textit{U. urealyticum} identified, and 17% for women with \textit{M. hominis} identified; chronic pelvic pain rates were 27% for women with \textit{N. gonorrhoeae} identified, 21% for women with \textit{C. trachomatis} identified, 33% for women with anaerobic bacteria identified, 41% for women with \textit{U. urealyticum} identified, and 54% for women with \textit{M. hominis} identified. Similarly, in a study by Brunham et al. [40] of 50 women with laparoscopically confirmed salpingitis, 54% of women with nongonococcal infections had future adverse reproductive outcomes, compared with none of the women with gonococcal infections. Collectively, the PEACH study [37] and the study by Brunham et al. [40] suggest that, although these regimens may have high short-term clinical and microbiological cure rates, the standard antibiotic regimens of doxycycline-cefoxitin [37], doxycycline-clindamycin [40], and doxycycline-metronidazole [40] may not be optimal for the prevention of adverse sequelae among women with nongonococcal PID.

Animal models may provide insight into better regimens for the treatment of nongonococcal PID. Rapid single-dose oral azithromycin therapy has been found to prevent infertility in a mouse model of chlamydial salpingitis [41]. Similarly, azithromycin was found to be more effective than doxycycline in the microbiological cure of \textit{C. trachomatis} infection and the prevention of immunopathological upper reproductive tract damage in a macaque model of PID [42]. Studies of reproductive sequelae following various PID treatment regimens in humans are needed.
In summary, a focus on reproductive and gynecologic morbidity, rather than on short-term clinical and microbiological cure, is greatly needed. Whether currently prescribed PID antibiotic regimens are effective in the prevention of subsequent reproductive morbidity is largely unknown. Arguably, long-term PID sequelae represent the most important treatment outcomes. Ultimately, microbe-specific and optimized treatment needs to preserve fertility following PID and also prevent recurrent and persistent infection, ectopic pregnancy, and chronic pain, improving the long-term prognosis for women who have PID.

Acknowledgments

References


