

# Antibiotic Therapy for Acute Pelvic Inflammatory Disease: The 2006 Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines

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**Pelvic inflammatory disease (PID) is a substantial cause of reproductive morbidity in young women. A systematic review of the literature related to PID management was performed in preparation for the 2006 Centers for Disease Control and Prevention sexually transmitted diseases treatment guidelines. This search was conducted using PubMed and was limited to articles written in English and published between 1 January 2002 and 31 January 2005 that were related to PID treatment. Studies were evaluated for new data on PID with regard to site, route, and timing of antimicrobial administration; regimen adherence; experience in adolescents and women >35 years of age; coinfection with human immunodeficiency virus; and management of sex partners. Strong evidence suggests that neither site nor route of treatment administration affects the short- or long-term major outcome of women with mild or moderate clinical presentations. Data on these outcomes in women with more severe clinical presentations are inadequate to provide guidance as to the preferred agents or route of administration. Important contributions to the literature that impact the 2006 guidelines are described in this article.**

Nearly 1 million women in the United States have acute pelvic inflammatory disease (PID) diagnosed each year, according to a new analysis based on a national survey of hospital discharges and visits to emergency departments and outpatient health care settings [1]. This figure is a conservative estimate, given the flaws inherent in the data sources, and reflects a decrease in the reported incidence of PID during the period 1985–1999 in both inpatient and outpatient settings, although the decrease appears to have been most marked among inpatients, whose numbers decreased 69% during this interval. Even with only 11% of women with PID being

treated in hospital settings, acute PID remains a leading gynecologic reason for hospitalization in the United States [2]. Furthermore, the medical costs associated with the treatment of acute PID are substantial, with recent estimates indicating that direct costs of the treatment of acute PID and its sequelae in 1998 were nearly \$2 billion [3].

Although incidence rates may have declined, PID remains a major source of short- and long-term morbidity in women. There is no evidence to suggest that there has been any reduction in the serious reproductive complications traditionally associated with PID, which include infertility, ectopic pregnancy, and chronic pelvic pain. Despite its clinical importance, a range of subtle clinical presentations and the lack of reliable diagnostics have hampered the study of PID. The availability of a number of different antimicrobial agents (either singly or in combination) with potential efficacy against PID pathogens, as well as the ongoing issue of antimicrobial resistance, require ongoing evaluation of the various

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antibiotic regimens to treat the acute PID episode and to reduce the adverse sequelae of this infection by preserving future fertility. The present article reviews the pertinent contributions to the treatment of acute PID from the past 5 years.

## METHODS

In the spring of 2005, the Centers for Disease Control and Prevention (CDC) convened a meeting of experts in the field of sexually transmitted diseases (STDs) to update the CDC STD treatment guidelines last written in 2002 [4]. A systematic search of the literature on the treatment of women with acute PID was conducted using PubMed (National Library of Medicine) on 31 January 2005. Medical Subject Headings terms included “pelvic inflammatory disease,” “PID,” and “salpingitis,” and the search was limited to articles written in English and published from 1 January 2002 to 31 January 2005.

The cost and antimicrobial activity of commonly used PID treatment regimens was constructed as follows. We structured all treatment regimens to last for 14 days. We calculated parenteral dosing for a 65-kg woman and presumed it would be administered for a total of 48 h before transitioning to its oral component. The calculated cost was based on average wholesale drug prices drawn from the 2005 Cardinal Distribution [5]. Pharmacy costs were set at \$8 per parenteral dose and per oral course of therapy. Some “oral” regimens include a single parenteral dose at treatment initiation.

## RESULTS

### Target Spectrum of Activity: The Importance of Anaerobic Coverage for PID Treatment Regimens

PID is a polymicrobial infection. Excellent data support the role of *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and facultative gram-negative and anaerobic bacteria in causing the symptoms and signs of the infection itself as well as the damage that often ensues [6–12]. Investigators have suspected for a long time that other specific agents might function prominently in the pathogenic process, although consistent reproducible evidence to support this contention has been lacking.

More contentious is the extent to which anaerobes participate in upper genital tract pathogenesis and whether regimens should necessarily target them. Many experts advocate the routine use of antibiotic regimens with activity against anaerobic organisms for the treatment of acute PID. Anaerobic and facultative bacteria are frequently recovered from the endometrium and fallopian tubes of women with acute PID [8, 9, 11–13]. The finding that more than one-half of women with acute PID also have bacterial vaginosis provides further argument for inclusion of anaerobic coverage in PID treatment regimens [11]. However, studies showing the superiority of regimens that include anaerobic coverage are lacking. A recent multicenter study of women with mild to moderate PID offers data collected using extensive microbiolog-

ical techniques [14]. In this study of 278 women drawn from the PID Evaluation and Clinical Health (PEACH) study, women with acute endometritis and mild to moderate clinical signs and symptoms of PID had a high likelihood of being culture positive for *Gardnerella vaginalis* (30.9%); for anaerobic gram-negative rods, which include many *Prevotella* and *Bacteroides* species (21.9%); and for anaerobic gram-positive cocci (16%). In addition, half of the women had bacterial vaginosis. The authors conclude that recovery of bacterial vaginosis-associated organisms is common among women with mild to moderately severe PID, and they recommend that treatment regimens for all women with PID include agents effective against anaerobes. However, in the subset of women who had endometrial cultures analyzed, reproductive outcomes in women testing positive for endometrial anaerobic bacteria did not differ from those observed in women who did not test positive for endometrial anaerobic bacteria [15].

Further clouding the issue of anaerobic coverage in PID regimens are the treatment data from the PEACH trial [16]. This study compared inpatient versus outpatient treatment regimens for PID. Participants randomized to receive inpatient treatment received intravenous cefoxitin and doxycycline for a minimum of 48 h (followed by oral doxycycline for a total of 14 days), whereas those in the outpatient treatment arm received a single dose of cefoxitin and a 2-week course of doxycycline. Arguably, the single dose of cefoxitin received by participants in the outpatient arm had little impact on the killing of anaerobic bacteria that were likely involved in the pathogenesis of acute PID, whereas participants in the inpatient arm received anaerobic therapy for at least 48 h. Despite the difference in anaerobic coverage between the 2 treatment arms, no superiority was demonstrated with either antibiotic regimen. The results of the PEACH trial call into question the importance of anaerobic therapy for women with acute PID. There is still concern about the importance of anaerobes in the pathogenesis and treatment of acute PID and that omitting anaerobic coverage in PID regimens is premature because of limited data on the effectiveness of this strategy. Clearly, additional studies are necessary to explore the importance of anaerobic coverage in PID treatment regimens. Until data are available demonstrating that anaerobic coverage does not enhance short-term cure rates and preserve long-term fertility outcomes, clinicians should consider including anaerobic coverage when treating women with acute PID.

Clindamycin has long been used in combination therapy for PID and other pelvic infections because of its activity against anaerobic organisms. New data from a multicenter survey of changing in vitro antimicrobial susceptibilities of 556 clinical isolates of anaerobes of the type commonly identified in women with PID revealed lower rates of susceptibility to clindamycin, particularly in the *Bacteroides fragilis* group [17]. Resistance to clindamycin has also recently been observed among isolates

recovered from the lower genital tract. Among nonpregnant women with bacterial vaginosis, 17% of isolates demonstrated clindamycin resistance at baseline, a rate that increased to 53% after clindamycin therapy [18]. Clindamycin continues to be part of a recommended regimen for the treatment of acute PID, on the basis of earlier studies and extensive successful experience with regimens that are comprised of this agent in the treatment of pelvic infections. There are no data indicating that these observations are associated with PID treatment failures with clindamycin-based regimens. However, there is concern that resistance to clindamycin may be on the rise; whether clinicians will observe a higher rate of treatment failure remains to be seen. In light of these recent developments, new studies of PID treatment are critically needed.

Clinicians must be cognizant of bacterial resistance when selecting antimicrobial therapy. In this light, renewed interest has lately been focused on ampicillin-sulbactam which, in contrast to clindamycin, does not appear to have the same problems with selective pressure for microbial resistance. Several studies have documented the efficacy of ampicillin-sulbactam for the treatment of acute PID and other serious intra-abdominal infections [19–22]. Similar clinical and microbiological cure rates have been observed with ampicillin-sulbactam and cefoxitin in comparative trials [19, 21, 22]. The addition of the  $\beta$ -lactamase inhibitor to ampicillin increases the activity of this agent against a number of organisms, with the result of excellent activity against anaerobic organisms. Moreover, ampicillin-sulbactam has not been associated with the emergence of resistant organisms, which has often been demonstrated with other antimicrobial agents [23]. The addition of doxycycline for antichlamydial coverage is warranted.

### Anti-Infective Treatment Regimens

Logically, the management of PID is directed at the containment of this infection. Although this may seem to be a simple concept, it has broadened considerably over the past few decades to include not only the resolution of clinical symptoms and signs but also the eradication of pathogens from the upper genital tract and pelvis and the prevention of subsequent complications, including infertility, ectopic pregnancy and chronic pelvic pain. Only a few prospective studies have examined long-term outcomes in women treated for PID.

An extensive body of literature has investigated the efficacy of modern antimicrobial regimens used to treat PID and serves as the basis for recent PID treatment guidelines. A previously published meta-analysis served as the basis for past recommendations for PID treatment regimens [4, 24]. This work was updated by surveying all the English-language treatment trials published from 2002 through January 2005.

**Parenteral antimicrobial regimens for acute PID.** A number of parenteral antimicrobial regimens appear to have very

good short-term clinical and microbiological efficacy. The combinations with the broadest support in the literature are (1) cefoxitin or cefotetan plus doxycycline and (2) gentamicin plus clindamycin; these 2 regimens constitute the current recommended treatment regimens established by the CDC. Cefotetan is currently not available in the United States, which restricts clinicians' choices of antibiotic regimens. Fewer studies have also established high efficacy rates for (1) ofloxacin with or without metronidazole and (2) ampicillin-sulbactam plus doxycycline; these 2 regimens remain as alternative parenteral regimens in the 2006 CDC STD treatment guidelines (table 1).

A multicenter US single-arm trial used ofloxacin to treat 70 hospitalized women with laparoscopically proven PID [25]. Its clinical efficacy of 98% and microbiological efficacy of 100% were similar to previous data gleaned from comparative trials. The primary contribution of this study was that cases were more accurately diagnosed (i.e., by laparoscopy) than is common in routine PID clinical trials. Ofloxacin is already a recommended parenteral regimen for PID; however, whereas parenteral ofloxacin is not available currently in the United States, similar quinolone agents are available. There are, at this time, no published trials of parenteral levofloxacin in women with acute PID. However, this drug is the optical isomer of ofloxacin,

**Table 1. Recommended parenteral antibacterial therapy for acute pelvic inflammatory disease: 2006 Centers for Disease Control and Prevention sexually transmitted diseases treatment guidelines.**

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Recommended parenteral regimen A

Cefotetan, 2 g iv every 12 h

**or**

Cefoxitin, 2 g iv every 6 h

**plus**

Doxycycline, 100 mg po or iv every 12 h

Recommended parenteral regimen B

Clindamycin, 900 mg iv every 8 h

**plus**

Gentamicin loading dose, iv or im (2 mg/kg of body weight), followed by a maintenance dose (1.5 mg/kg) every 8 h; single daily dosing may be substituted

Alternative parenteral regimens

1. Levofloxacin, 500 mg iv once daily<sup>a</sup>

**or**

Ofloxacin, 400 mg iv every 12 h<sup>a</sup>

**with or without**

Metronidazole, 500 mg iv every 8 h

2. Ampicillin-sulbactam, 3 g iv every 6 h

**plus**

Doxycycline, 100 mg po or iv every 12 h

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**NOTE.** im, intramuscularly; iv, intravenously; po, orally.

<sup>a</sup> Quinolones should not be used to treat those with a history of recent foreign travel or partner travel or those with infections acquired in California or Hawaii or in other areas with increased prevalence of quinolone-resistant *Neisseria gonorrhoeae* infection.

and its once-daily dosing makes it a convenient choice that may facilitate adherence to therapy. Levofloxacin has broad-spectrum activity against gram-positive and -negative microorganisms, including *N. gonorrhoeae* and *C. trachomatis*, and has greater activity against anaerobic organisms than does ofloxacin. However, there is growing concern that the fluoroquinolones are demonstrating weaker in vitro activity against anaerobic organisms, particularly species in the *Bacteroides* group [26]. The addition of metronidazole to levofloxacin will broaden the anaerobic spectrum, should levofloxacin be selected to treat acute PID. Clinicians must also be aware that quinolone-resistant strains of *N. gonorrhoeae* are becoming common in many communities worldwide. In the United States in 2004, 7.6% of *N. gonorrhoeae* isolates in the Gonococcal Isolate Surveillance Project were either resistant to or intermediately resistant to ciprofloxacin [27]. Although the majority of these isolates were recovered from men who have sex with men, quinolone-resistant *N. gonorrhoeae* is encountered increasingly frequently among heterosexual individuals [28, 29]. If a quinolone-resistant *N. gonorrhoeae* strain is suspected in a woman with a diagnosis of acute PID, a regimen that does not contain a quinolone should be employed. The presence of such strains might be suspected if (1) the patient's infection was acquired in California or Hawaii or in other areas with increased prevalence of quinolone-resistant *N. gonorrhoeae*, (2) the patient or their sex partner engaged in recent foreign travel, or (3) the patient has had sex with bisexual men. Should infections with quinolone-resistant strains of *N. gonorrhoeae* become more common in women, the role of quinolones in the treatment of acute PID will need to be reconsidered. Currently, quinolone therapy with either ofloxacin or levofloxacin, with or without the addition of metronidazole, is listed as an alternative regimen for the treatment of acute PID in the 2006 STD treatment guidelines.

Given its widespread use in the treatment of chlamydial infections, azithromycin has been used by some clinicians to treat acute PID. Research on its immunomodulatory properties has implied that azithromycin may enhance host defense mechanisms and restrict local inflammation [30]. A recent European multicenter, open-label trial compared azithromycin, alone or with metronidazole, and 2 broad-spectrum antibiotic combinations: cefoxitin-metronidazole-doxycycline and amoxicillin-clavulanate-doxycycline [31]. Azithromycin was administered intravenously on day 1 and/or 2 of the study, followed by oral therapy to complete a 7-day course, whereas subjects receiving metronidazole received 12 days of therapy. The analysis consisted of combined data from 2 separate studies. Most of the 300 study participants underwent laparoscopy, and the diagnosis was confirmed in three-quarters of participants. Women with palpable tubo-ovarian abscesses (TOAs) were excluded. The authors reported clinical and microbiological cure rates in

excess of 95% for azithromycin, as monotherapy or in combination with metronidazole. Although a strength of this investigation is that the diagnosis of PID was confirmed by laparoscopy, only one-third of the participants completed the study per protocol. Furthermore, anaerobic organisms were recovered from only 27 participants, a rate that is remarkably low in contrast with the much higher rates of recovery of anaerobes in other studies of acute PID [11, 32–34]. There are no data on long-term reproductive outcomes with regimens containing azithromycin. Furthermore, there is concern about the emergence of antimicrobial resistance in women infected with *N. gonorrhoeae*. At this point, additional clinical data are needed before azithromycin can be recommended for the treatment of acute PID, and, therefore, this agent is not currently recommended for the treatment of acute PID.

The current list of parenteral treatment options with excellent data to support their efficacy that were included in the 2006 CDC STD treatment guidelines is given in table 1. Given the absence of data available in the literature on newer regimens for the treatment of acute PID since the previous guidelines were published in 2002, there are no significant changes to the recommended regimens from 2002 [4]. The choice of therapy can be guided by cost, hospital formulary, allergy history, and adverse-effect profile.

**Oral antimicrobial therapy for acute PID.** Over the previous decade, oral therapy for acute PID has been used far more frequently than parenteral therapy in the treatment of acute PID. Only with recently published data have clinicians had confidence in the outpatient regimens for the treatment of mildly and moderately severe acute PID. A large randomized clinical trial comparing inpatient therapy with outpatient therapy for the treatment of acute PID was performed at 13 clinical sites in the United States [16]. The inpatient regimen consisted of intravenous cefoxitin and either oral or parenteral doxycycline during a minimum 48-h hospital stay, followed by doxycycline to complete a 14-day course. Women randomized to the outpatient arm of the study received a single intramuscular dose of cefoxitin (with probenecid), with doxycycline administered orally for 14 days. Evaluable long-term outcomes were available for 808 patients, 398 of whom were treated with the inpatient regimen and 410 of whom were in the outpatient arm. Approximately 40% of subjects tested positive for *N. gonorrhoeae* or *C. trachomatis*, and 59% had bacterial vaginosis. Short-term rates of clinical cure at the visit 30 days after enrollment were similar in the 2 treatment groups, with ~3% of women in each group requiring a change in treatment. Microbiological eradication of *N. gonorrhoeae* and *C. trachomatis* was also similar in each treatment group. A strength of this study is the availability of data on long-term outcomes. With a mean follow-up period of nearly 3 years, the pregnancy rates among women treated with the outpatient regimen and among those

treated with the inpatient regimens were virtually identical (42.0% and 41.7%, respectively). Similarly, other long-term outcomes—specifically, recurrent PID, infertility, ectopic pregnancy, and chronic pelvic pain—were similar in each treatment group. Endometritis detected by analysis of endometrial biopsy specimens, which were obtained at enrollment from the majority of participants, was present in just less than one-half of patients with diagnoses of PID, which calls into question whether a large proportion of participants in this trial did not have acute PID. However, a subsequent analysis restricting assessment to those women with histologic evidence on endometrial biopsy confirmed the similarity of outcomes in each treatment group, providing reassurance that the women with confirmed acute PID responded equally well to outpatient and inpatient therapy [15]. It is essential to note that 90% of women enrolled in this study had clinically mild or moderate disease, and, therefore, the findings cannot be extrapolated to women with clinically severe presentations of acute PID. The PEACH data do provide the clinician with evidence of the effectiveness of outpatient therapy for the treatment of acute PID. Outpatient therapy is appropriate for the treatment of mild to moderate PID, particularly in the compliant patient (table 2).

A noncomparative study of oral levofloxacin in 41 women with PID was conducted in Japan [35]. Diagnostic criteria and outcome measures are carefully described. Clinical efficacy was assessed using a 4-category rating system and was judged by both doctors in charge and by committee, and it ranged from 85.4% to 87.8%; bacteriologic efficacy was 88.9%. Levofloxacin is the only drug with broad enough coverage against the most bacteria within the spectra believed to be involved in PID to be considered appropriate as a single agent for the duration of therapy, and its once-daily dosing makes it attractive from an adherence perspective. Clinicians may elect to add metronidazole for enhanced activity against anaerobic organisms, as is described above.

One of the only other acute PID treatment trials published since the 2002 CDC guidelines were published was performed in India by Malhotra et al. [36]. In this randomized but unblinded trial, 165 women with acute PID were randomized to receive 1 of 3 antibiotic regimens: (1) ciprofloxacin and tinidazole twice daily for 7 days; (2) single doses of azithromycin, secnidazole, and fluconazole; and (3) a 7-day course of doxycycline administered twice daily and metronidazole administered 3 times daily. Cure rates by 4 weeks after therapy were in excess of 90% in each treatment group, with the highest cure rates observed in the ciprofloxacin-tinidazole group. None of these women had laboratory confirmation of acute PID (e.g., by laparoscopy or endometrial biopsy), and microbiological test results were not reported, which limits the interpretation of the data and precludes the recommendation of these regimens.

Hong et al. [37] described their experience with ambulatory

**Table 2. Recommended oral antibacterial therapy for acute pelvic inflammatory disease: 2006 Centers for Disease Control and Prevention sexually transmitted diseases treatment guidelines.**

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Recommended oral regimen A
Levofloxacin, 500 mg orally once daily for 14 days <sup>a</sup>
<b>or</b>
Ofloxacin, 400 mg orally once daily for 14 days <sup>a</sup>
<b>with or without</b>
Metronidazole, 500 mg orally twice a day for 14 days
Recommended oral regimen B
Ceftriaxone, 250 mg im in a single dose
<b>or</b>
Cefoxitin, 2 g im in a single dose; and probenecid, 1 g orally administered concurrently in a single dose
<b>or</b>
Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime)
<b>plus</b>
Doxycycline, 100 mg orally twice a day for 14 days
<b>with or without</b>
Metronidazole, 500 mg orally twice a day for 14 days

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**NOTE.** im, intramuscularly.

<sup>a</sup> Quinolones should not be used to treat those with a history of recent foreign travel or partner travel or those with infections acquired in California or Hawaii or in other areas with increased prevalence of quinolone-resistant *Neisseria gonorrhoeae* infection.

treatment of women with acute PID in an observational report of women from the People's Republic of China. Two hundred consecutively seen women who were attending outpatient clinics and who had diagnoses of acute PID were administered a single 500-mg intramuscular dose of ceftriaxone, followed by a 2-week course of metronidazole and doxycycline. Two-thirds (68.5%) of the women returned for follow-up, and cure or improvement was noted in 97%. Endometrial biopsies to confirm acute PID were not performed as part of the trial. Furthermore, only 3% of women were febrile, indicating that the cohort consisted of women with acute PID of mild or moderate severity. These data are similar to those from the PEACH trial and add confidence when selecting the outpatient regimen of ceftriaxone, metronidazole, and doxycycline for the treatment of women with mild or moderate acute PID [16].

The optimal duration of therapy for acute PID is unknown, and most trials evaluate therapy regimens that last longer than 1 week. A study conducted in India sheds some light on the concerns regarding short-course antibiotic therapy for acute PID [36]. In this randomized study of women with clinical diagnoses of acute PID, 3 antibiotic treatment regimens were studied in a nonblinded manner. The shortest course of therapy consisted of single doses of azithromycin (1 g) and secnidazole (2 g); secnidazole is structurally related to and possesses anaerobic coverage similar to that of the more commonly used 5-nitroimidazoles metronidazole and tinidazole. This regimen



was inferior to a 1-week course of ciprofloxacin and tinidazole in the resolution of inflammatory masses. In the European trial of azithromycin for the treatment of acute PID, a high rate of clinical cure or improvement was observed among those women treated with a 1-week course of azithromycin [31]. The first 1 or 2 daily doses were administered intravenously, and, therefore, this study did not evaluate a purely oral regimen. Furthermore, nearly two-thirds of women enrolled in the study were not compliant with the study protocol. There are few data available to support shorter courses of antimicrobial therapy. Therefore, the 2006 STD recommendations maintain the recommendation of a 14-day course.

There are no published data on the use of azithromycin, either alone or with metronidazole, as a strictly oral regimen for the treatment of PID. One article describes the use of azithromycin for the treatment of acute PID, but the initial doses of antimicrobial therapy were administered in the inpatient setting [31]. Further data are needed on the efficacy of a purely oral course of azithromycin for the treatment of acute PID.

#### **Adherence to PID Treatment Regimens**

Many studies have shown that treatment trials performed under controlled circumstances with optimal patient selection may not reflect common practices and probably overestimate success rates in the general population. A disturbing study was published recently on data drawn from the PEACH study [38]. It showed that, irrespective of whether the study subject had been hospitalized at the time of treatment initiation, women took an average of 70% of prescribed oral medication doses, took them for less than half of the number of outpatient days recommended, took an unscheduled drug holiday for nearly 25% of their outpatient days, and took only 17% of their doses within the optimal timing interval. It remains unknown whether noncompliance with oral regimens is associated with lower treatment success. Although the outpatient regimen in the PEACH cohort was as effective as the inpatient regimen, one cannot extrapolate from these findings and assume that suboptimal compliance has no impact on treatment outcomes. These data underscore the need to enhance patient education and motivation and to identify effective regimens involving simpler, shorter courses and longer dosing intervals.

#### **Site and Route of Treatment Administration**

Before 1998, the CDC categorized their recommendations for hospitalization on the basis of the assumption that parenteral regimens would be administered to inpatients and oral regimens would be provided to outpatients. However, it is no longer necessary to hospitalize women to treat parenterally. The past 2 decades and the revolution in the US health care economy have seen an amazing trend away from inpatient care [39, 40]. This has fostered the development of a broad infrastructure

designed to enhance delivery of many sophisticated health care services, including the administration of most parenteral antibiotics, outside of the acute-care setting. This has broadened treatment options, allowing for outpatient parenteral therapy for selected women with PID.

For this reason, antibiotic regimens for PID are categorized by the route of administration during the first days of treatment. Thus, antibiotics that require more than a single parenteral dose in the initial stages of treatment are considered “parenteral,” despite the fact that nearly all of these women are weaned within a few days to oral antibiotics to complete their treatment courses, once the acute phase of illness has passed. Parenteral regimens may be administered in an acute-care facility or at home, depending on the conclusiveness of the diagnosis, the severity of the clinical presentation, and associated clinical factors. Alternatively, regimens that are primarily oral, with or without an initial sole parenteral dose, are designated as “oral” and are most commonly administered to outpatients. To further guide clinicians in the selection of a regimen, the cost and antimicrobial activity of PID treatment regimens are presented in table 3.

Hospitalization with intravenous administration of antibiotics has long been considered the reference standard for treatment of women with acute PID, in light of the capacity to monitor patients closely and to maximize bed rest, as well as the theoretical ability to achieve higher tissue levels of parenteral drugs. In the absence of compelling data, the criteria proposed in the past for hospitalization of women with PID for parenteral therapy were based largely on anecdotal information and the consensus opinion of clinical experts. These historical criteria included uncertain diagnosis in which surgical emergencies have not been excluded, pregnancy, failure of outpatient management, inability to tolerate or follow an oral regimen, severe illness, presence of a TOA, inability to follow up after a 72-h trial of an outpatient regimen, being an adolescent, and co-existent HIV infection.

The CDC hospitalization criteria were reevaluated and revised for the 1998 and 2002 guidelines process, in an effort to make them more evidence based. High rates of fetal wastage and preterm delivery have been reported among pregnant women with PID and make hospitalization appropriate [43, 44]. In addition, there are ample data available suggesting that women with TOAs should be hospitalized to maximize antimicrobial dosing and to allow for early recognition of serious complications, such as leaking or rupture [45–47]. For the other criteria, specific data were not available, and decisions regarding the site of treatment administration were less obvious. Diagnostic uncertainty, particularly when the differential diagnosis includes an illness that might require surgical intervention, makes sense even in the absence of explicit evidence. Similarly,

women who are severely ill typically require intravenous hydration and a high level of supportive care.

For women with mild signs and symptoms who require parenteral therapy, individual circumstances should guide the treatment setting. Those for whom oral treatment has failed require parenteral therapy and may benefit from hospitalization to achieve careful observation in a monitored environment. Women who cannot follow an oral regimen or who may not physically tolerate one require parenteral therapy, although the need for hospitalization may not be immediately obvious. Finally, it has long been held that women who are candidates for oral therapy but who cannot return for a follow-up visit within 72 h after treatment initiation should be hospitalized, because assessment of treatment response would be compromised and the transition to appropriate parenteral intervention delayed. It would seem that creative outpatient support solutions might prevail once a patient understood the gravity of this requirement and its implications for her own long-term health and well-being.

Perhaps the most important contribution to this discussion in decades was published recently by Ness et al. [16] and is described above. In this multicenter, randomized, controlled trial, no significant differences in the short-term clinical and microbiological response rates were observed between inpatient and outpatient regimens. Furthermore, long-term outcomes, including pregnancy, time to pregnancy, recurrence of pelvic inflammatory disease, chronic pelvic pain, and ectopic pregnancy, were similar as well. Pregnancy rates calculated after a mean follow-up of 35 months were 42.0% among women treated as outpatients and 41.7% among hospitalized women. These data suggest that neither the site nor the route of treatment administration affect the short- and long-term major outcomes of women with mild or moderate clinical presentation. The only benefit for hospitalized patients receiving parenteral antibiotics was lower rates of posttreatment histologic endometritis. The clinical significance of this finding is currently unknown. Ongoing subclinical PID (as defined by histologic endometritis) is not infrequently observed among women with untreated lower genital tract infection [48]. The potential for smoldering infection with subsequent tubal damage and increased rates of infertility among women with inadequately treated acute PID has been observed in previous studies [49]. There are no data demonstrating that women receiving outpatient therapy for acute PID are at higher risk for ongoing infection and its sequelae than are those receiving inpatient therapy.

### Adolescents

There are no data to support the practice of hospitalization of adolescent girls with PID, and, therefore, adolescence is not listed among the criteria for hospitalization. Despite this guid-

ance, some experts have advocated that all adolescents and nulligravid young women be hospitalized for treatment and education on the basis of theoretical concerns, arguing that adolescence should be considered to be a proxy for poor adherence, high-risk sexual behavior, delayed presentation for medical care, and high antimicrobial failure rates [50]. Furthermore, some opine that the fertility of adolescents should be protected to a degree greater than that of more mature women. Thus, many providers of health care to adolescents continue to hospitalize their patients, despite the lack of data to suggest that their patients benefit from inpatient PID treatment. If there were data to suggest that hospitalization either improved the outcome of the immediate infection or resulted in fewer long-term complications, then hospitalization would be recommended for all women, irrespective of age or parity. Such is not the case, however. The data described above from Ness et al. [16] provide strong evidence that there is no compelling benefit to hospitalization and parenteral therapy in women with mild or moderate PID. Further subanalysis of outcome data stratified by age of the PEACH participants indicates that fertility outcomes of adolescents were similar in the inpatient and outpatient treatment arms (R. B. Ness, personal communication). Even if superiority was demonstrated with inpatient therapy, it is difficult to justify altering recommendations merely on the basis of age or fecundity, because the fertility of all women should be equally valued and protected, regardless of age or pregnancy history. There is no reason to expect that adolescent women would respond differently than adults, and, therefore, treatment decisions should not be influenced by age. Clinicians should be aware that the safety of quinolone agents has not been established for children <18 years of age.

### Acute PID in Women >35 Years of Age

An interesting recent finding is that women  $\geq 35$  years of age who are hospitalized with PID appear to be at increased risk for complications, including surgical intervention, readmission for PID, or a hospital stay  $\geq 14$  days (OR, 3.9; 95% CI, 1.3–11.6) [51]. Although this question is different from that of whether women in this age group require hospitalization in the first place, these findings suggest that older women might have a more complicated course of PID. There are no data suggesting that inpatient therapy is superior for older women with acute PID. As is noted above for adolescents, age should not be a factor in deciding PID treatment regimens.

In another study that raised concerns for older women with PID, women with sonographically diagnosed TOAs whose conditions did not respond to broad-spectrum antibiotic regimens were older than those who were cured (mean age  $\pm$  SD, 45.3  $\pm$  6.6 vs. 39.6  $\pm$  8.3 years;  $P = .02$ ) [52]. Postmenopausal women with TOAs are more likely to harbor a genital tract

malignancy (47%) than are premenopausal control subjects (1.3%), according to a recent retrospective case-control study of 93 women [53]. In both cases, the women with TOAs would likely be admitted for treatment on the basis of the finding of a TOA.

### Acute PID in Women with HIV Infection

It has long been suspected that, when HIV-1–infected women develop acute PID, they have a more serious clinical presentation. An early retrospective case-control study found that HIV-infected women exhibited a diminished immune response and poorer response to antimicrobial therapy, which resulted in an increased incidence of surgical intervention (OR, 5.5; 95% CI, 1.0–29.3) [54]. New data suggest that HIV infection increases the risk of TOA. A US study of women with clinically diagnosed acute PID compared 44 HIV-positive women with 163 HIV-negative women [55]. Symptoms before medical evaluation were similar between the 2 groups, although more women in the HIV-positive group had received antibiotics already. HIV-infected women were more likely to have a TOA, although this difference did not achieve statistical significance (45.8% vs 27.1%;  $P = .08$ ). In a group of Kenyan women with laparoscopically proven PID, the risk of TOA was increased among those coinfecting with HIV-1 (OR, 2.8; 95% CI, 1.2–6.5) but was not significantly associated with immunosuppression (OR, 3.1; 95% CI, 0.6–15.3) [56]. Immunosuppressed women (i.e., those with a CD4 cell percentage <14%) had prolongation of their hospital stay.

There are no data to suggest that immunosuppressed women benefit from hospitalization or parenteral therapy for PID. In the US study described above, clinical response to antibiotic regimens recommended by the CDC STD treatment guidelines did not differ by serostatus. In addition, rates of infection with sexually transmitted and other bacteria do not differ appreciably by serostatus, although mycoplasmas and streptococci were isolated more frequently from HIV-seropositive women [55]. Similarly, in the Kenyan cohort, HIV-infected women responded as well as HIV-uninfected women to standard parenteral antibiotic regimens and had hospital stays that were similar in duration to those of their HIV-uninfected counterparts. In a subsequent study, 162 Kenyan women with pelvic pain of new onset underwent endometrial biopsy to screen for PID [57]. Endometritis was more frequent among HIV-1–infected women (OR, 3.0; 95% CI, 1.5–5.9). Clinical improvement or cure after outpatient oral therapy was documented in 81% of those with HIV infection and in 86% of HIV-seronegative women, which was not a statistically significant difference. Therefore, HIV-positive women with diagnoses of acute PID can be treated similarly to HIV-negative women. HIV screening should be encouraged for all women with diagnoses of acute PID.

### Anti-Infective Timing Issues

Early recognition and initiation of treatment appear to be critical to the prevention of long-term sequelae of acute PID in both animal models and human treatment trials. Mouse chlamydial PID models have shown that antibiotic treatment initiated within 6 days of onset of clinically apparent infection results in good fertility outcome [58]. Hillis et al. [59] reported that women treated within 3 days of symptom onset had fertility rates significantly higher than those among women whose antibiotic treatment began later (92.7% vs. 81.3%). The best data have used follow-up laparoscopy or hysterosalpingography to assess tubal patency after treatment. Viberg [60] reported 0% involuntary infertility and 100% tubal patency on hysterosalpingography when treatment was initiated within 2 days of clinical onset, compared with only 70% tubal patency among women whose treatment did not commence until day 7 or later after symptom onset. Thus, early recognition and treatment of acute PID is a key component in the optimization of fertility.

It has become evident that many women with PID do not have the classic constellation of symptoms and signs traditionally seen in women with acute PID. Rather, PID may present with more subtle clinical findings [61]. Leukocytosis may not be present, and only a minority of women with PID have an elevated temperature [16]. Many women with fallopian tube damage do not recall a history of acute PID, despite serologic evidence of past infection with *C. trachomatis* or *N. gonorrhoeae* [62]. Furthermore, evidence is mounting that women with lower genital tract infections in the absence of the classic symptoms and signs of acute PID have ongoing upper genital tract inflammation [48, 63]. Taken together, these data suggest that many women with acute PID have subtle indicators of pelvic infection. Given the importance of early detection and treatment of acute PID for subsequent fertility, the diagnostic criteria have been made less strict; acute PID should be suspected in women at risk for STDs who have pelvic or lower abdominal pain and the physical findings of cervical, uterine, or adnexal tenderness. It is recognized that these diagnostic criteria are nonspecific, but, given the damage associated with untreated PID, clinicians must maintain a low threshold for the diagnosis of PID.

Most parenteral regimens involve continuation of parenteral therapy for 48 h before transitioning to oral therapy. The rationale for this appears to be arbitrary, and this transition may be modified at the discretion of the provider, on the basis of clinical response. Both doxycycline and the quinolones have nearly 100% bioavailability after oral administration, a feature that supports early transition to oral therapy in women receiving parenteral therapy for acute PID. The extremely high bioavailability of these agents also provides reassurance to clinicians when deciding whether to treat women with acute PID with an oral or parenteral regimen. Recommendations for a

treatment duration of 14 days have been maintained because of concern about the long half-life of *C. trachomatis* and the potential delay in antimicrobial access to the upper genital tract. Although evidence evaluating shorter treatment durations is scant, there has been interest in shortening treatment duration to 7 or 10 days on theoretical grounds, to enhance adherence. There are inadequate data to guide the clinician as to the ideal duration of therapy, and, therefore, 14 days of therapy remains the recommended treatment duration. Clinical experience should guide all decisions regarding the overall length of the treatment course and the timing of the transition from parenteral to oral therapy.

Traditional recommendations rely on maintenance of adequate dosing for 72 h before considering nonresponse to therapy to be a failure. At that time, consensus suggests reconsideration of the antimicrobial regimen and consideration of imaging studies (e.g., ultrasound or CT) and, possibly, surgical exploration.

### Management of Sex Partners

Although specific data on reinfection rates among women with gonococcal or chlamydial PID are scant, Eschenbach and Holmes [64] reported nearly 30 years ago that 25% of women with gonococcal PID were readmitted to the hospital with recurrent PID within 10 weeks, despite adequate treatment and negative posttreatment test-of-cure results. The current guidelines for partner notification are that men who have had sexual contact with women who later received diagnoses of PID, when the sexual contact occurred within 60 days of the onset of her symptoms, should be evaluated for sexually transmitted infections. The CDC recommends that those partners be treated empirically with regimens effective against *C. trachomatis* and *N. gonorrhoeae*.

### PID in Users of Intrauterine Contraceptive Devices (IUDs)

The IUD is becoming a more popular contraceptive choice for women. This is particularly true in the United States since the introduction of the IUD containing progestin. The risk of acute PID due to IUD use is mainly confined to the first 3 weeks after insertion and is uncommon thereafter [65]. As IUD use becomes more common, practitioners may encounter PID in a woman using an IUD. There are no data indicating that antibiotic selection should be influenced by the presence of an IUD. However, some have theorized that the IUD, as a foreign body, should be removed to optimize treatment. Few studies have evaluated whether the IUD should be removed at the time of diagnosis of PID. Soderberg and Lindgren [66] described a small randomized trial, conducted in Sweden, of 46 women with IUDs who had received diagnoses of acute PID. There were no differences in treatment response, regardless of whether the IUDs were removed at the time of treatment initiation or

left in place, as measured by decreases in erythrocyte sedimentation rates and clinical failure rates. A slightly larger randomized trial from Turkey examined the effect of IUD removal on treatment for mild and moderately severe acute PID [67]. Clinical improvement, as measured by absence of pelvic pain, vaginal discharge, dysuria, and pelvic tenderness, was more common in the group randomized to undergo IUD removal. Similarly, the leukocyte count and erythrocyte sedimentation rate were significantly reduced with IUD removal. For many women worldwide, the IUD is the best (and sometimes the only) contraceptive method available, and, certainly, a woman's contraceptive needs must be considered. At present, there are conflicting data on the need to remove an IUD at the time of PID diagnosis. Furthermore, there are no data on the optimal way to manage an IUD with regard to long-term fertility outcomes in women with acute PID. On the basis of the published evidence to date, caution should be exercised if the IUD remains in place, and close clinical follow-up is mandatory.

### CONCLUSION

The treatment of women with acute PID hinges on the recognition of the polymicrobial etiology of the infectious process. Microorganisms recovered from women with acute PID include *N. gonorrhoeae*, *C. trachomatis*, aerobic and anaerobic vaginal microflora, and genital mycoplasma. A proportion of cases of acute PID are nongonococcal and nonchlamydial in origin, which focuses attention on treating organisms that are components of the vaginal microflora that ascend to the upper genital tract. Several antibiotic treatment regimens are available for the treatment of women with acute PID. For those with disease of mild or moderate severity, outpatient therapy has short- and long-term outcomes similar to those of inpatient therapy. Anaerobic organisms are frequently isolated from the upper genital tracts of women with acute PID and are likely involved in the pathogenesis of a substantial proportion of cases of acute PID. Further research is needed on the importance of anaerobic coverage for the treatment of acute PID. The emergence of resistant organisms, particularly *N. gonorrhoeae* and anaerobes, necessitates continued analysis of the effectiveness of treatment of women with diagnoses of acute PID.

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