



## Pelvic inflammatory disease: new diagnostic criteria and treatment

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Pelvic inflammatory disease (PID) is a disease that affects young, sexually active, reproductive-age women. Most cases are considered to be the sequelae of the sexually transmitted pathogens *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, although non–sexually transmitted disease (STD)-related PID is an established and recognized entity. Exact estimates of the incidence and prevalence of PID in the United States are unclear largely because PID is not a reportable disease. The incidence of PID increased in the 1970s and 1980s partly because of the growing epidemic of STDs, with estimates of 1 million annual cases of PID during that era [1]. Since that peak in the early 1980s, diagnosis and hospitalization rates for PID have declined. Most recent estimates of incidence provided by the Centers for Disease Control and Prevention (CDC), using discharge and outpatient database investigation, stated that approximately 780,000 cases of acute PID are diagnosed annually [2]. It is unclear if this is a true decrease in incidence or if other factors, such as shifts to more outpatient care, variation in STD incidence, or a reporting bias, produce this apparent decrease in incidence. Researchers estimate that a large proportion of PID cases are unrecognized or subclinical, which makes precise estimates impossible [3,4]. This factor combines to make PID estimates likely inaccurate and underestimates the true burden of disease.

Several demographic, behavioral, and contraceptive factors are identified as risk factors for PID (Table 1). Lower age incurs an increased risk of PID because of biologic and behavioral risk factors [5]. Adolescents tend to have cervical ectopy, which provides large zones of columnar epithelium for the targeted attachment of *C trachomatis* and *N gonorrhoeae*. [1,6]. There are also concerns about increased rates of high-risk sexual behavior among adolescents, including participation in high-risk social networks [7]. Women with multiple sexual partners, especially in the preceding 30 days, have a fourfold elevated risk of acquisition of PID [8,9]. A

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Table 1  
Risk factors for pelvic inflammatory disease

Characteristic	Risk factors
Accepted	Young age
	Multiple sexual partners
	Prior history of PID
	Sexually transmitted infection (gonorrhea, chlamydia)
	Non-use of barrier contraceptives
Proposed and unresolved	Low socioeconomic status
	Race
	Unmarried
	Urban living
	High frequency of sexual intercourse
	Coitus during menstruation
	Use of intrauterine device
	Douching
	Cigarette smoking
Substance abuse	

prior history of PID is a recognized risk factor for PID [8,10,11]. Studies have shown at least a twofold increase in the risk of PID with a history of prior tubal infection [8,11]. A proposed theory for this increased risk is the presence of damaged and dysfunctional tubal epithelium from previous infection, which produces depressed local defenses and an altered immune response that results in increased susceptibility to infection [8].

Contraceptives play an important role in predisposing women to acquisition of PID. Non-use of contraception is a risk factor for PID, whereas barrier methods can decrease the risk of STD acquisition and subsequent development of PID [9,12–15]. Most studies that evaluate the role of oral contraceptive pills in PID development have demonstrated a protective role [12,16–18]. Speculation as to the mechanism of protection yields many as yet unproven theories: thickening of the cervical mucus from the progestin component of oral contraceptive pills, lessening of the amount and duration of menstrual flow, and a decreased “receptivity” of the endometrium to infection under progestin influence [1]. A correlation between regular oral contraceptive use and less “risky” sexual behavior is also a possible mechanism for protection. Although use of an intrauterine device traditionally has been believed by most clinicians to confer an elevated risk of PID, the risk seems to be primarily restricted to the first 3 months after insertion, likely because of bacterial contamination at the time of insertion [1,3,16,19–23].

The last factor to consider as a risk factor for PID is vaginal douching. In a recent study that evaluated the relationship between douching and PID, nearly twice as many women with PID had recently douched compared with women without PID, and there seemed to be a dose-response relationship [24]. The vaginal flora-altering affects of douching and a theoretical mechanical “flushing” of organisms into the upper genital tract have been postulated to explain the relationship. It is still unclear what exactly confers this elevated risk.

## Microbial etiology

PID is a polymicrobial inflammatory condition that results from ascension of microorganisms from the cervix and vagina to the upper genital tract (uterus, fallopian tubes) and peritoneal cavity. The sexually transmitted pathogens commonly isolated and implicated include *C trachomatis* and *N gonorrhoeae*, with possible but unproven contributions from genital tract mycoplasmas and some of the sexually transmitted viruses (ie, herpes simplex and cytomegalovirus). The endogenous micro-organisms found at high levels in women with bacterial vaginosis also have been implicated in the pathogenesis of PID, such as gram-positive and -negative anaerobic organisms and aerobic/facultative gram-positive and -negative rods and cocci [1]. Estimates approximate that of all proven cases of PID, roughly two thirds involve either *C trachomatis* or *N gonorrhoeae*. In most cases of PID, bacterial vaginosis-associated microflora are identified in the upper genital tract [25–28]. This has important diagnostic implications because failure to isolate a sexually transmitted agent from the cervix does not rule out PID as the cause of the given symptomatology. Women who are seropositive for HIV and have PID seem to have a similar microbiologic etiology as HIV-negative patients [29].

## Sequelae of pelvic inflammatory disease

The significant burden of disease attributed to PID comes predominantly from the long-term reproductive sequelae of tubal infection: tubal factor infertility, ectopic pregnancy, and pelvic adhesions, which lead to chronic pelvic pain. Treatment goals encompass not only the amelioration of the acute inflammatory condition but also the prevention or lessening of the risk for long-term reproductive sequelae.

### *Acute complications*

Tubo-ovarian abscess (TOA) is a serious acute complication of PID that is characterized by an inflammatory mass that involves the fallopian tube, ovary, and often adjacent structures (eg, bowel, pelvic peritoneum). It is estimated to occur in up to one third of women hospitalized with acute PID [30,31].

The finding of an inflammatory mass in the pelvis in women with PID necessitates initial hospital admission for intravenous antibiotic therapy and close monitoring for signs of rupture or unfavorable response to antibiotics. TOAs also may have atypical presentations and may not be associated with PID, including subacute presentations of abdominal pain with gastrointestinal symptoms, low-grade fevers, and weight loss.

The microbiology of TOAs is similar to PID infections; they are polymicrobial with a predominance of anaerobic organisms [32]. It is unusual to recover the *N gonorrhoeae* and *C trachomatis* from the abscess itself, but researchers believe that they play a major role in inciting the original ascent of various micro-

organisms (including anaerobes) into the upper genital tract [32]. Common isolates include the anaerobic organisms *Peptostreptococcus spp*, *Bacteriodes spp*, and *Prevotella spp* and facultative gram-negative rods (*Escherichia coli*) and aerobic streptococci [31,32]. Treatment includes broad-spectrum antibiotics with or without a drainage procedure, with surgery often reserved for patients with suspected rupture or patients who fail to respond to antibiotics.

Fitz-Hugh-Curtis syndrome (perihepatitis), which affects anywhere from 1% to 30% of women with PID, is characterized by inflammation and adhesion formation that involves the liver capsule and the anterior abdominal wall [1,33]. This condition is associated with gonococcal and chlamydial PID [1]. Clinically, patients present with right upper quadrant pain that can be mistaken for liver or gallbladder disease, and patients may or may not demonstrate associated signs and symptoms of PID [1,3,33]. Mild elevations in liver function tests also may be present [1,3]. Diagnosis is confirmed by laparoscopic visualization of the characteristic “string-like” adhesions between the liver capsule and the anterior abdominal wall. The long-term consequences of this condition are not clear.

### *Long-term complications*

Tubal factor infertility, ectopic pregnancy, and chronic pelvic pain are responsible for the large portion of the public health and economic impact of PID. Tubal factor infertility, with its associated psychosocial and financial costs, is the single-most important sequela of PID. Westrom et al [34] demonstrated that women with a prior history of PID had a near tenfold increased risk of infertility compared with controls. The risk of infertility seemed to double with each successive episode of salpingitis, ranging from 8% infertility after one episode to as high as 40% after three episodes. Data from a cohort of American women with acute PID suggest an even higher risk of tubal factor infertility [35]. The severity of disease also may be a predictor of infertility risk, with higher infertility rates observed in women with more severe presentations [34,36].

Ectopic pregnancy is also significantly more common in women with a prior history of PID, with a seven- to tenfold increased rate of ectopic pregnancy in women with a history of PID [5]. Like tubal factor infertility, rates also double with successive episodes of PID, from a 6% risk for one episode to 22% risk with three or more episodes of salpingitis [34]. Worse severity of infection also seems to predict a higher likelihood of ectopic pregnancy [34,37].

The least studied of the long-term sequelae attributed to PID is chronic pelvic pain. Approximately 20% of women suffer from chronic pelvic pain at some point after developing PID [36]. Compared with hospitalized controls, PID patients were four to ten times more likely to be admitted at a later time for abdominal or pelvic pain [38]. Similar to tubal infertility and ectopic pregnancy, the rate of chronic pain also was proportional to the number and severity of PID episodes [39].

Taken together, the short- and long-term sequelae of PID necessitate prompt accurate diagnosis and appropriate therapy in an attempt to lessen the overall public health and economic consequences of PID. The impact of this condition on

women's health warrants continued investigation into new diagnostic methods, more effective therapies, and reduction of the underlying predispositions to PID.

## Diagnosis

The clinical diagnosis of PID is often a challenge even in the most experienced hands. The CDC highlighted this fact in their latest guidelines, which state that the clinical diagnosis of PID has anywhere from a 65% to 90% positive predictive value [27]. The converse of this statistic means that clinicians are wrong up to 35% of the time—or in one of three patients—when making this diagnosis. The reason for the low accuracy of clinical diagnosis is the fact that many adjacent organ systems (ie, urinary, gastrointestinal, and musculoskeletal) can produce symptoms that mimic PID. Numerous other gynecologic disorders (including ovarian cysts, adnexal torsion, ectopic pregnancy, endometriosis) also can produce symptoms and physical examination findings that overlap with PID. No single symptom, physical finding, imaging study, or serologic marker is specific and sensitive for the diagnosis of PID; thus the reason for several qualifying criteria set forth by the CDC and the low positive predictive value mentioned. A large percentage of women with tubal factor infertility give no previous history of PID, so it seems that subclinical nondiagnosed infection is common. Sweet estimated that approximately 60% of the total burden of PID is subclinical, 36% being mild to moderate, and the remaining 4% being severe [1].

PID can manifest with various clinical presentations that range from mild to severe with TOA formation and peritonitis. In the past, the CDC recommended diagnosis and treatment in women who manifested a combination of all three major criteria—lower abdominal tenderness, cervical motion tenderness, and bilateral adnexal tenderness—and had one of the minor supporting criteria—oral temperature higher than 38.3°C, mucopurulent cervicitis, elevated erythrocyte sedimentation rate or C-reactive protein, documentation of cervical infection with *C trachomatis* or *N gonorrhoeae*, or presence of inflammatory mass on pelvic sonography [40]. Much concern has arisen that the previous PID diagnostic criteria are too stringent and fail to identify the large proportion of women with mild disease. Wiesenfeld et al [4] have shown that upper genital tract inflammation is seen in women who do not meet the 1998 CDC diagnostic criteria for acute PID. Thirteen percent of women with biopsy-proven upper genital tract infection who did not meet the 1998 CDC clinical criteria of acute PID demonstrated subtle signs and symptoms of PID. Recognizing that many women with PID have mild symptoms and signs and that these women previously would fail to be diagnosed and treated appropriately, the 2002 CDC guidelines are less stringent and currently state that “empiric treatment of PID should be initiated in sexually active young women and other women at risk for STDs if the following minimum criteria are present and no other cause for the illness can be identified: uterine/adnexal tenderness or cervical motion tenderness” [27]. Additional criteria increase the specificity of the diagnosis of PID. The implications of arriving at a diagnosis of

PID in unaffected women, namely the cost and risks of antibiotics and the psychosocial impact of the incorrect diagnosis, remain to be determined.

The first step in making the diagnosis of PID is a thorough history. Historic factors that are suggestive of “classic” PID include dull abdominal pain, fevers, vaginal discharge, onset of symptoms after menstruation, and abnormal vaginal bleeding. The intensity and character of the pain varies greatly, tends to be bilateral, and is typically present for less than 3 weeks [1,8,41–43]. One of the diagnoses often confused with PID is appendicitis. Investigation has revealed that right lower quadrant pain of shorter duration (approximately 21 hours) tends to be more specific for appendicitis, whereas women with PID tend to have diffuse pain of at least 48 hours’ duration [43]. Women with appendicitis also complain more commonly of gastrointestinal symptoms, including nausea and vomiting. In more than 50% of women with PID, however, these gastrointestinal symptoms are also present [43].

Whereas many physical examination findings also suggest PID, no single finding is sensitive and specific for the diagnosis. This fact is the reason that combinations of physical examination findings have been used to help make the diagnosis of PID. Kahn et al [44] performed a systematic review of diagnostic criteria of PID. Some objective features are shown in Table 2. Certain physical examination findings (eg, adnexal tenderness, cervical motion tenderness, and vaginal discharge) did have a slightly higher sensitivity with similar specificity compared with some of the historic factors (eg, abdominal pain, irregular menses, vaginal discharge). Elevated temperature and the presence of a palpable mass provide inconsistent evidence in terms of predicting PID. Only one third of women with acute PID have an elevated temperature ( $>38^{\circ}\text{C}$ ) [42].

Similar to historic differences between PID and appendicitis, subtle objective differences also exist between the two conditions. Investigators have demonstrated that women with PID have cervical motion tenderness and adnexal tenderness more often than women with appendicitis, although women with appendicitis often demonstrate these physical findings [43]. The adnexal tenderness in women with

Table 2

Sensitivity and specificity for the diagnosis of pelvic inflammatory disease of selected objective findings

Finding	Sensitivity (% range)	Specificity (% range)
Physical examination		
Vaginal discharge	26–81	42–83
Temperature ( $>38^{\circ}\text{C}$ )	24–40	79–91
Palpable mass present	24–49	74–79
Laboratory		
Elevated C-reactive protein	74–92	50–90
Elevated erythrocyte sedimentation rate (ESR $>15$ )	75–81	25–57

Data from Kahn JG, Walker CK, Washington AE, Landers DV, Sweet RL. Diagnosing pelvic inflammatory disease: a comprehensive analysis and considerations for developing a new model. *JAMA* 1991;266:2594–2604.

PID is more likely to be bilateral compared with predominantly right-sided tenderness in women with appendicitis. Any intra-abdominal pathologic condition that produces peritonitis may confuse the clinical picture.

Numerous laboratory studies also have been investigated for their role in the prediction of PID. Peripheral white blood cell count is a nonspecific marker of PID and is elevated in less than half (44%) of women with PID [8]. Elevated levels of the erythrocyte sedimentation rate and C-reactive protein have been studied, and both seem to perform well in terms of sensitivity (range 74%–93%) and specificity (range 25%–90%), with C-reactive protein performing slightly better than erythrocyte sedimentation rate in the prediction of PID [41,44–46]. Despite their reassuring performance, clinical usefulness of these tests is limited because of inconsistent availability and a lack of timeliness returning the results to the clinician. Recent investigators have highlighted the high sensitivity and high negative predictive value of polymorphonuclear leukocytes on a vaginal wet smear [47,48]. The finding of three or more white blood cells per high power field on a vaginal wet smear has a sensitivity rate of 87% to 91% [47,48]. The absence of white blood cells on a vaginal wet smear has a high negative predictive value (94.5%) [48]. This simple and clinically useful test may be used to rule out disease in women with an unclear diagnosis.

Other methods used to help in the evaluation of women with characteristic symptoms and signs of PID include ultrasound, endometrial biopsy, and diagnostic laparoscopy. Ultrasound features consistent with PID include large, dilated fallopian tubes or the presence of a TOA. In a small series of 51 women with clinically suspected PID, Cacciatore et al [49] demonstrated that among 13 women with histopathologically confirmed plasma cell endometritis, 11 (85%) had large, dilated fallopian tubes on transvaginal ultrasound. Importantly, none of the women with normal sonograms had plasma cell endometritis (85% sensitivity and 100% specificity). A more recent study of transvaginal ultrasound for the diagnosis of upper genital tract infection demonstrated high specificity rate (97%) but low sensitivity rate (32%) [50]. The value of ultrasound in the diagnosis of upper genital tract infection remains to be fully delineated.

Endometrial biopsy is helpful for making a diagnosis of PID, and it demonstrates good sensitivity and specificity. Using the criteria of having leukocytes and plasma cells on histologic section yields a sensitivity rate that ranges from 70% to 90% and a specificity rate of 67% to 90% for the diagnosis of PID [51]. The most rigorously tested and validated criteria for the diagnosis of endometritis using histopathology were published by Kiviat et al [52]. These investigators demonstrated that the presence of five or more neutrophils per 400 × field in the endometrial surface epithelium together with one or more plasma cells per 120 × field in the endometrial stroma yielded a sensitivity rate of 92% and specificity rate of 87% for the prediction of women with upper genital tract microbial infection and laparoscopically confirmed salpingitis. Although endometrial biopsy offers this high sensitivity and specificity, it has limited clinical use in the immediate management because of the minimum of a 2-day delay in reading and reporting results. Endometrial biopsy is a useful tool, because confirmation of the diagnosis of PID

provides invaluable prognostic information to the patient. A negative endometrial biopsy result mandates additional investigation to determine the cause of the patient's clinical presentation.

Laparoscopy is considered the gold standard for the diagnosis of PID. Findings consistent with PID on laparoscopy include edema and erythema of fallopian tubes, purulent fallopian tube exudate, and the presence of peritubal adhesions [41]. These laparoscopic findings that indicate PID have been used to generate much of the sensitivity and specificity data for the various clinical predictors of PID. Some investigators have questioned the accuracy of laparoscopy for the diagnosis of PID [53,54]. Sellors et al [53] used fimbrial biopsy to demonstrate that visualization alone had only 50% sensitivity rate and 85% specificity rate for PID [53]. Eckert et al [55] recently demonstrated that the absence of visual evidence of salpingitis does not exclude the presence of upper genital tract inflammation. Out of 152 women with clinically suspected PID, 26 had histologic endometritis in the absence of laparoscopic evidence of salpingitis. Intraobserver and interobserver reliability in the laparoscopic diagnosis of PID recently was shown to be inconsistent [56]. Notwithstanding, laparoscopy is still considered the gold standard and must be considered in appropriate patients. Costs, limited access, and surgical risks preclude the universal use of laparoscopy for the diagnosis of PID. A low threshold for diagnostic laparoscopy is appropriate in patients who appear ill with an unclear diagnosis. Patients found to have inflammatory masses at the time of laparoscopy can undergo culture and drainage procedures and the diagnostic confirmation. Drainage may optimize treatment in the case of larger TOAs. Research has demonstrated that the size of a TOA is inversely proportional to the need for surgical intervention, with 15% of women requiring surgery for drainage with masses 4 to 6 cm in size and nearly 70% requiring surgical drainage when the mass was 10 cm or larger [57].

### **Subclinical pelvic inflammatory disease**

There is a growing body of evidence that most cases of PID are subclinical and recognized by neither the patient nor her physician. Most experts believe that subclinical PID is an often overlooked cause of infertility and is responsible for more cases of postinfectious tubal infertility than acute PID. It has long been realized that many women with tubal factor infertility have serologic evidence of prior chlamydial or gonococcal infection yet do not have a history of acute PID [58,59]. The World Health Organization Task Force on the Prevention and Management of Infertility demonstrated that nearly two thirds of women with bilateral tubal occlusion and serologic evidence of previous gonococcal or chlamydial infections denied any history of PID symptoms [60]. These retrospective data suggest that many women with PID are asymptomatic or have such mild clinical presentations that the disease remains undetected. Studying endometrial biopsies on a large cohort of women without acute PID, Wiesenfeld et al [4] demonstrated that one in four women infected with *N gonorrhoeae* or

*C trachomatis* and 15% of women with bacterial vaginosis have ongoing evidence of upper genital tract inflammation (endometritis). Women with subclinical PID have similar demographic features and microbiologic features as women with acute PID, which suggests that acute and subclinical PID represent similar pathogenic conditions. These data indicate that a large proportion of women with common lower genital tract infections (chlamydia, gonorrhea, and bacterial vaginosis) have concurrent upper tract inflammation and are at risk for post-PID sequelae. More aggressive surveillance and treatment may be warranted to reduce the reproductive morbidity of subclinical PID.

## Treatment

Treatment regimens for PID reflect the polymicrobial etiology and require coverage for *N gonorrhoeae* and *C trachomatis* and bacterial vaginosis-associated organisms (ie, facultative gram-negative rods, anaerobes). There are two goals of treatment for PID: relief of the acute symptoms and inflammation and prevention of the long-term sequelae associated with PID. Studies that compared the pre-antibiotic era to the post-antibiotic era showed superior outcomes with antibiotic use, most notably, improved fertility [39]. Mean pregnancy rates after PID in the pre-antibiotic era (28%) were much lower than rates observed after widespread use of antibiotics (73%) [39]. Fertility is enhanced when patients are treated earlier in the disease process (within 48 hours of symptom onset), which emphasizes the importance of early diagnosis and timely treatment [61–63].

Once the diagnosis of acute PID is made, a clinician is faced with the decision to hospitalize a patient for intravenous antibiotic therapy or initiate outpatient therapy. Important factors to consider in this management decision include severity of the illness, comparative efficacy of inpatient and outpatient regimens, and prevention of long-term sequelae. The CDC recommends inpatient parenteral-based therapy for women who have any of the following characteristics:

### 2002 CDC CRITERIA FOR HOSPITALIZATION AMONG WOMEN WITH PELVIC INFLAMMATORY DISEASE [27]

- ◆ Pregnancy
- ◆ Inability to exclude surgical emergency (ie. appendicitis)
- ◆ Failure to respond to outpatient oral therapy
- ◆ Inability to tolerate oral therapy (eg. severe nausea/vomiting)
- ◆ Severe illness (eg. high fever, peritonitis)
- ◆ Presence of a tubo-ovarian abscess

Concerns for antibiotic noncompliance in the adolescent population and concern for preservation of fertility have prompted some clinicians in the past to recommend admission for all adolescents diagnosed with acute PID. Currently,

there are insufficient data to show that adolescents benefit from hospitalization, and age should not influence treatment selection.

Reflecting the efforts to reduce health care costs in the United States witnessed over the past two decades, most women diagnosed with acute PID received outpatient therapy [2]. Although outpatient therapy has lower initial costs than inpatient management, much concern existed regarding the impact of outpatient treatment on long-term morbidity, particularly infertility. Recently, researchers have directly compared outpatient PID treatment to inpatient treatment in a randomized, controlled clinical trial of 831 women with signs and symptoms of mild to moderate PID [64]. Participants randomized to the inpatient arm received intravenous cefoxitin plus doxycycline for a minimum of 48 hours, followed by oral doxycycline for a total of 14 days. The outpatient regimen consisted of a single intramuscular dose of cefoxitin plus probenecid plus 14 days of oral doxycycline. There were no significant differences in many short-term outcomes, including clinical cure, development of a TOA, adverse drug reaction, or necessity of changing treatment. There were no differences in many of the important long-term outcomes between inpatient and outpatient regimens, including pregnancy rates (41.7% versus 42%), infertility (17.9% versus 18.4%), frequency of PID recurrence (16.6% versus 12.4%), chronic pelvic pain (29.8% versus 33.7%), and ectopic pregnancy (0.3% versus 1%) [64]. There was a trend, however, toward improved eradication of endometritis at 30 days in the inpatient group (37.6% versus 45.9%;  $P = 0.09$ ) [64]. Whereas less than half of the participants had objective confirmation of PID (histologic endometritis), a subanalysis of women with endometritis revealed similar outcomes between the treatment groups [65]. The results of this study support the widespread practice that women with mild or moderate PID can be treated with outpatient antibiotic regimens.

The current CDC-recommended treatment regimens include inpatient parenteral-based therapy and outpatient oral regimens (Box 1). The overall pooled clinical and microbiologic cure rates for the recommended regimens are 75% to 94% and 71% to 100%, respectively [66]. The pooled clinical cure rates with numbers of patients for some of the different regimens are displayed in Table 3. The first CDC-recommended outpatient oral regimen uses ofloxacin or levofloxacin as agents against *C trachomatis* and *N gonorrhoeae* [67,68]. Because of their lack of anaerobic coverage, however, metronidazole is often added for the total 14 days. Levofloxacin has the advantage of once-daily dosing. The second oral regimen includes a single intramuscular dose of ceftriaxone (250 mg) plus doxycycline (100 mg orally twice a day). Some authors have emphasized the need for continued anaerobic coverage and recommend the addition of metronidazole [69]. Single-agent studies have been conducted using drugs with limited anaerobic coverage (ciprofloxacin/ofloxacin), and the results have demonstrated equivalent short-term clinical efficacy to regimens with anti-anaerobic coverage [70–72]. One study did demonstrate diminished microbiologic efficacy against bacterial vaginosis-associated organisms compared with regimens with adequate anaerobic coverage [70]. There is no hard evidence that inadequate anaerobic coverage leads to suboptimal outcomes. Because anaerobic microorganisms are believed to be important in the

**Box 1. 2002 Centers for Disease Control and Prevention recommended treatment regimens for pelvic inflammatory disease****PARENTERAL:****Recommended:**

- A. Cefotetan 2 gm IV q12h **OR** Cefoxitin 2 gm IV q6h + Doxycycline 100 mg po/IV q12h<sup>a</sup>
- B. Clindamycin 900 mg IV q8h + Gentamicin IV/IM (2mg/kg load, then 1.5mg/kg q8h) \*<sup>a</sup>

**Alternative:**

- C. Ofloxacin 400 mg IV q12h **OR** Levofloxacin 500 mg IV qd with or without Metronidazole 500 mg IV q8h. <sup>b</sup>
- D. Ampicillin/Sulbactam 3 g IV q6h + Doxycycline 100 mg po/IV q12h<sup>a</sup>

**ORAL:**

- A. Ofloxacin 400 mg po bid × 14 days **OR** Levofloxacin 500 mg po qd × 14 days with or without Metronidazole 500 mg po bid × 14 days
- B. Ceftriaxone 250 mg IM × 1 dose **OR** Cefoxitin 2 gm IM × 1 dose and Probenicid 1 g po × 1 dose **OR** Other 3<sup>rd</sup> generation cephalosporin IM + Doxycycline 100 mg po bid × 14 days with or without Metronidazole 500 mg po bid × 14 days

<sup>a</sup> After clinical improvement, therapy is continued with oral doxycycline 100 mg bid (regimen A & D) or either oral doxycycline or oral clindamycin 450 mg qid (regimen B) to complete a 14 day treatment course.

<sup>b</sup> After clinical improvement, continue with oral formulations of these antimicrobials to complete a 14 day treatment course.

\* Single daily dosing can be substituted.

*Data from* Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2002. *MMWR Morb Mortal Wkly Rep* 2002;51:1–77.

pathogenesis of PID, however, many experts recommend adequate coverage of anaerobic bacteria to minimize ongoing tissue damage from endogenous anaerobic bacteria [1,27,69].

Limited data exist on other oral agents in the treatment of acute PID. Amoxicillin/clavulanic acid plus doxycycline seems to have acceptable efficacy,

Table 3  
Pooled pelvic inflammatory disease clinical cure rates

Regimen	No. patients	Clinical cure rates (%)
Inpatient:		
cefoxitin + doxycycline	338	93
cefotetan + doxycycline	86	94
Ciprofloxacin	90	94
Ampicillin/sulbactam + doxycycline	37	95
Outpatient:		
Cefoxitin-doxycycline	59	95
Clindamycin-ciprofloxacin	67	97
Ofloxacin	37	95
Amoxicillin-clavulanic acid	35	100

Data from Refs. [1,66–68,70–73,79,80,86].

although it may be limited by a high rate of digestive system side effects [73]. There also has been interest in azithromycin as an acceptable oral agent. The author found one abstract of a small three-arm clinical trial that used either single-agent azithromycin ( $n = 11$ ), azithromycin plus metronidazole ( $n = 10$ ), or cefoxitin/doxycycline ( $n = 8$ ) for laparoscopically confirmed PID. The author demonstrated equal clinical cure in all treatment groups (27/29, or 93% overall) and complete microbiologic cure for all 29 women at 40 days follow-up. The author concluded that azithromycin alone or in combination with metronidazole is effective therapy for PID [74]. Currently, inadequate data are available to recommend azithromycin for the treatment of PID [27].

If an outpatient oral regimen is chosen, it is imperative that follow-up occur within 48 to 72 hours to ensure clinical improvement. If clinical improvement has not occurred in that time period, hospitalization for parenteral therapy and consideration of alternative diagnoses is in order [1,3,27]. The positive predictive value of a clinical diagnosis of PID can be as low as 65%, which highlights the need to entertain alternative diagnoses in patients who fail to respond to one of the approved regimens [27].

The CDC-recommended parenteral regimens are also listed in Box 1. A minimum of 24 to 48 hours of hospitalization is necessary to assess response to therapy and rule out other diagnoses. The first regimen, which consists of a second-generation cephalosporin plus doxycycline, provides excellent coverage of gonorrhea and chlamydia and anaerobic and aerobic/facultative gram-negative and most gram-positive organisms. Of note, doxycycline has a high rate of peripheral phlebitis and pain at the infusion site and can be given orally if tolerated, given its near equal oral bioavailability [27]. After clinical improvement, patients may be discharged with a prescription for a total of 14 days of oral doxycycline. The second regimen consists of clindamycin and gentamicin. This regimen provides excellent coverage against gram-positive organisms (clindamycin), gram-negative organisms (gentamicin), and anaerobes (clindamycin), although neither is the drug of choice for *N gonorrhoeae* or *C trachomatis* [27]. In vitro studies have demonstrated that nearly 90% of chlamydia strains are eradicated by clindamycin and that

it has achieved 100% eradication rates in chlamydial tubal infection [75,76]. Both drugs are effective against strains of gonorrhea that do not produce  $\beta$ -lactamase [77]. Numerous studies have shown 90% or more clinical and microbiologic cure rates for this combination [66]. Once-daily dosing of gentamicin is appropriate given its proven efficacy in similar infections, ease of administration, theoretical improved eradication with concentration-dependent killing, and less toxicity than multiple-daily dosing [27,78]. The other parenteral-based regimens listed in have limited but reassuring data and may be considered in patients with relevant allergy histories and other clinical situations that preclude use of the two other regimens [79,80].

The treatment regimens recommended for HIV-seropositive women are the same as those for women who are seronegative (Box 1). The literature suggests that women with HIV and PID may have a longer clinical course and a predilection to the formation of TOAs requiring surgical intervention [81,82]. This finding is not uniformly seen in all studies, however [83,84]. The CDC recently removed HIV seropositivity as a condition requiring hospitalization because of a lack of data showing benefit of inpatient therapy [27]. Choice of one of the recommended regimens for PID and clinical judgment regarding hospitalization is appropriate when managing HIV-positive women with PID.

Finally, given the high frequency of isolation of STDs in women with PID, empiric treatment of women's male sexual partners is imperative to prevent reinfection and improve the long-term health of these women [1,27]. Women tend to return to the same social circle they were in before diagnosis, and many of their sexual partners continue to harbor asymptomatic STDs [1]. Estimates of a 25% readmission rate within 3 months of original treatment for gonococcal PID highlights the necessity of partner treatment [85]. Treatment of the sexual partner should consist of regimens effective against *N gonorrhoeae* and *C trachomatis* [27]. This empiric treatment is recommended regardless of test positivity in the female index case because inability to isolate these sexually transmitted pathogens from the cervix does not preclude their presence in the upper genital tract and their central role in pathogenesis of upper genital tract infection.

In addition to partner treatment, the diagnosis of PID gives the provider an opportunity to perform extensive counseling regarding safer sex practices and risk reduction and should be part of every conversation with patients. Given the high rate of STD positivity, it is also imperative to counsel, offer, and conduct HIV testing on all patients with PID and offer hepatitis B vaccination.

## Summary

PID is a common infection in reproductive-age women that presents an enormous public health and economic burden. It is responsible for much short- and long-term morbidity that may necessitate interventions subsequent to the original infection. Mild PID seems to be much more common than severe or "classic" PID, and the importance of early recognition and treatment cannot be

understated. Current treatment regimens seem to be effective in terms of immediate clinical efficacy. As we learn more about the frequency and importance of subclinical PID, the true burden of upper genital tract infection upon reproductive age women continues to be elucidated.

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