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SEXUALLY TRANSMITTED DISEASES (L BACHMANN, SECTION EDITOR)

Pelvic Inflammatory Disease: Current Concepts of Diagnosis and Management

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Abstract Pelvic inflammatory disease (PID), one of the most common infections in non-pregnant women of reproductive age, remains an important public health problem. It is associated with major long-term sequelae, including tubal factor infertility, ectopic pregnancy, and chronic pelvic pain. In addition, treatment of acute PID and its complications incurs substantial health care costs. Prevention of these long-term sequelae is dependent upon clinicians having a high index of suspicion in order to make an early diagnosis and development of treatment strategies based on knowledge of the microbiologic etiology of acute PID. It is well accepted that acute PID is a polymicrobic infection. The sexually transmitted organisms, *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, are present in many cases and microorganisms comprising the endogenous vaginal and cervical flora are frequently associated with PID. This includes anaerobic and facultative bacteria, similar to those associated with bacterial vaginosis. Genital tract mycoplasmas, most importantly *Mycoplasma genitalium*, have recently also been implicated as a cause of acute PID. As a consequence, treatment regimens for acute PID should provide broad spectrum coverage that is effective against these microorganisms.

Keywords Salpingitis · Pelvic inflammatory disease · Diagnosis · Treatment

Introduction

Pelvic inflammatory disease (PID) manifests with a spectrum of upper genital tract infections that includes endometritis, salpingitis, tubo-ovarian abscess and/or pelvic peritonitis [1••] and is associated with evidence of lower genital tract inflammation (eg cervicitis, bacterial vaginosis, or leukorrhea). Typically, acute PID is caused by ascending spread of microorganisms from the vagina and/or endocervix to the endometrium, fallopian tubes, and/or adjacent structures [1••, 2, 3].

Among women, PID is the most significant complication of sexually transmitted diseases with nearly 800,000 cases of PID annually in the United States [4•]. PID remains a major public health issue [4•, 5–8] and is associated with significant long-term sequelae and reproductive morbidity including tubal factor infertility, ectopic pregnancy and chronic pelvic pain [9, 10••, 11–13]. In addition, the estimated annual health care cost for PID and its complications in the United States is over $2 billion [7].

Recently subclinical PID has been recognized as an important entity which is common among women with lower genital tract infections, especially *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and bacterial vaginosis (BV) [14••, 15]. Subclinical PID is as common as clinically recognized acute PID and is responsible for a greater proportion of PID related sequelae than clinically recognized disease [15].

Prevention or amelioration of the significant adverse reproductive sequelae of acute PID requires early diagnosis and institution of appropriate antimicrobial therapy. In turn this requires an understanding of the clinical presentation, and the microbiologic etiology of acute PID.

Over the past 25 years important advances have occurred in understanding the etiology, diagnosis and treatment of acute PID. As a result, major paradigm shifts have occurred in our approach to both the diagnosis and treatment of acute PID.

Our approach to diagnosis has shifted from reliance on a rigid set of criteria requiring abdominal pain, cervical motion tenderness, adnexal tenderness, fever and leukocytosis. Currently, the diagnosis is suspected in young sexually

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active women with lower abdominal/pelvic pain in whom pelvic tenderness (CMT, uterine tenderness or adnexal tenderness) and evidence of lower genital tract inflammation (leukorrhea or endocervicitis) are present. In the past PID was believed to be a monoetiologic infection, primarily caused by *Neisseria gonorrhoeae*. Today the polymicrobic etiology of PID is well established and has led to utilization of broad spectrum antimicrobial regimens for treatment of acute PID [1••, 2, 16–18].

Diagnosis

Acute PID presents with a wide spectrum of manifestations ranging from overt clinical infection to unrecognized (subclinical) infection [19••]. Overt PID ranges from mild to severe presentations, with the majority of laparoscopically confirmed cases of acute PID presenting as mild-to-moderate infection. Multiple studies have demonstrated that approximately two-thirds (range 30% to 70%) of women with post infection-associated tubal factor infertility (TFI) have no history of being diagnosed with or treated for acute PID [19••]. This finding led Wolner-Hansen and colleagues to propose the concept of unrecognized or subclinical PID [15].

Subclinical PID

While recent literature suggests that subclinical PID may be the largest contributor to development of post infection TFI, diagnosis of subclinical PID in clinical practice is difficult. The "gold standard" for the diagnosis of subclinical PID is an endometrial biopsy demonstrating acute endometritis (≥5 neutrophils per 400X field of superficial endometrium and ≥1 plasma cell per 100X field of endometrial stroma) [14••, 20]. Studies have attempted to identify clinical predictors and the presence of subtle symptoms and signs in women with subclinical PID [19••, 21]. Unfortunately none of the socio demographic predictors are clinically useful in identifying women with subclinical PID. Thus we must rely on endometrial biopsy to identify women with subclinical PID which precludes widespread clinical application.

Overt Acute PID

Jacobson and Westrom in their classic study utilizing laparoscopy to confirm the diagnosis of acute salpingitis challenged the traditional rigid diagnostic criteria [22••]. Only 20% of patients with visually confirmed salpingitis had the entire constellation of the traditional symptoms and signs of acute PID. Moreover, there were no significant differences in the incidence of lower abdominal pain, increased discharge, irregular bleeding, urinary symptoms, or gastrointestinal symptoms. The only significant difference was a history of fever and chills among patients with confirmed salpingitis (41% vs. 19.6% in controls). While evaluation of clinical signs and laboratory data (adnexal tenderness, elevated erythrocyte sedimentation rate, abnormal vaginal discharge and fever) revealed significantly higher rates among women with laparoscopically confirmed salpingitis compared to those with normal pelvis in those findings, the overlap was so large it precluded reliance on these factors to differentiate between those with adnexal tenderness and women with normal pelvis. Even documented fever was present in only 33% of women with visually confirmed salpingitis. As a result of this study it became evident that no single symptom or sign can reliably identify those women with acute PID.

Logistical problems and economic cost make laparoscopy impractical for all patients suspected of having acute PID. Moreover, laparoscopy cannot diagnose endometritis or cervicitis and may not detect early or subtle inflammation of the fallopian tube.

In an attempt to standardize the diagnosis of acute PID, the Infectious Diseases Society for Obstetrics and Gynecology initially proposed criteria for diagnosis of salpingitis based on clinical grounds [23]. These criteria required the presence of lower abdominal pain and tenderness, CMT and adnexal tenderness. Because these are all subjective findings, at least one of the following six findings suggesting the presence of acute inflammation was necessary: 1) fever of ≥38°C; 2) leukocytosis; 3) culdocentesis revealing peritoneal fluid with leukocytes and bacteria; 4) presence of an inflammatory mass on pelvic exam or imaging study; 5) elevated ESR or CRP; or 6) evidence for the presence of *N. gonorrhoeae* and/or *C. trachomatis* in the endocervix.

Unfortunately, evaluation of the accuracy of these criteria for the diagnosis of acute PID has revealed that they are far from optimal [24]. The criteria were noted to be more predictive of acute PID in high-risk populations (eg, adolescents, STD-clinic patients). However, no single symptom, physical finding or laboratory result is both sensitive and specific to be able to detect all patients with and exclude those without acute PID.

Laboratory Tests

When elevated white blood cell (WBC) counts are helpful in confirming a suspected case of acute PID. However, only 60% of acute PID patients present with leukocytosis [25].

Elevated levels of inflammatory markers such as ESR or CRP have been assessed for use in the diagnosis of acute PID. Elevated ESR (>15 mm/h) levels are present in approximately 75% of laparoscopy confirmed PID cases [22••]. However, ESR is a non-specific marker of inflammation and is not specific for the diagnosis of acute PID. Similarly, CRP is a non-specific marker of inflammation with good (not great) sensitivity (93%) and specificity (83%) [26].

Several investigations have demonstrated a association between elevated levels of the tumor marker serum CA125 and laparoscopy confirmed acute PID [27–30]. Moreover, these studies reported a relationship between the degree of elevation of CA 125 and the extent of inflammation seen at laparoscopy.

Microscopy of vaginal secretions to assess for the presence of leucorrhea (>1 leukocyte per epithelial cell) has been demonstrated to be a very useful sign associated with acute PID [19••, 22••]. Similarly, mucopurulent cervicitis, often due to chlamydial and/or gonococcal infection is an indicator of upper genital tract infection [19••, 31, 32]. The absence of mucopurulent cervicitis and/or inflammatory cells on the wet mount of vaginal secretions carries an excellent negative predictive value for excluding acute PID [19••, 22••]. In the Swedish cohort of laparoscopy confirmed acute PID none of these women had normal microscopy of their vaginal secretions and clear cervical secretions [22••].

Endometrial Biopsy

Endometrial biopsy has been advanced as a less invasive alternative to laparoscopy for confirmation of acute PID. Demonstration of endometrial inflammation (presence of neutrophils and plasma cells) on biopsy has both good sensitivity (70% to 80%) and specificity (67% to 89%) [19••]. Using a combination of both >1 plasma cell per 120X field n endometrial stroma and >5 PMN leukocytes per 400X field of superficial endometrium provides excellent prediction for laparoscopy confirmed acute PID-sensitivity 92% and specificity 87% [20].

Imaging Studies

Imaging studies have also been suggested as an aid in diagnosing acute PID. Ultrasonography is recommended as the first line approach with Magnetic Resonance Imaging (MRI) as an alternative. Computed tomography (CT) should be reserved to assess the extent of this infection within the abdominal cavity and for interventional therapy to drain pelvic abscesses [33]. Ultrasonography has the advantage of being widely available and relatively noninvasive. In particular, transvaginal ultrasonography should be used with the finding of thickened fluid-filled fallopian tube(s) with or without free pelvic fluid being highly suggestive of acute PID [34]. More recently the use of Doppler technology increases the sensitivity for diagnosing acute PID [33]. While MRI is more sensitive (95% vs. 81% per ultrasound) it is substantially more expensive [35].

Criteria for Diagnosis of Acute PID

Utilizing a public health approach to minimize the potential for adverse effects on the reproductive health of young women resulting from missed cases of acute PID, the CDC recommends a low threshold for the diagnosis of acute PID (Table 1) [1••]. They recommend empiric treatment for acute PID in sexually active young women (≤25 years of age) and other women at risk for STIs (multiple sexual partners or history of STI) if they are experiencing pelvic or lower abdominal pain, if no other cause can be identified and if one or more of three minimum criteria (CMT, uterine tenderness or adnexal tenderness) are present on pelvic examination [1••].

As noted by Jaiyeoha and Soper, this approach is limited because it does not discriminate among the spectrum of diseases associated with acute pelvic pain in reproductive-aged women [33]. In order to increase the specificity for the diagnosis of acute PID, the CDC suggests that additional diagnostic criteria (Table 1) can be utilized [1••]. In particular those additional criteria assess for evidence of systemic inflammation (Temperature ≥38.3°C, elevated ESR, elevated CRP) or for the presence of lower genital tract inflammation (abnormal cervical/vaginal mucopurulent discharge, leukorrhea on microscopy of vaginal secretions, laboratory documentation of cervical infection with *N. gonorrhoeae* or *C. trachomatis*). If there is no evidence of endocervicitis and no leukocytes are present on direct microscopy of the vaginal secretions, a diagnosis of acute PID is highly unlikely and alternative diagnosis should be sought.

Table 1 Criteria for the clinical diagnosis of pelvic inflammatory disease

Minimal criteria (1 required)
• Cervical motion tenderness
OR
• Uterine tenderness
OR
• Adnexal tenderness
Additional criteria
• Oral temperature ≥38.3°C (101°F)
• Abnormal cervical or vaginal mucopurulent discharge
• Presence of abundant WBCs on saline microscopy of vaginal secretions
• Elevated erythrocyte sedimentation rate (ESR)
• Elevated c-reactive protein (CRP)
• Laboratory documentation of cervical infection with *N. gonorrhoeae* or *C. trachomatis*
Most specific criteria
• Endometrial biopsy with histologic evidence of endometritis
• Transvaginal sonography or MRI showing thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex or Doppler studies suggesting pelvic infection (eg, tubal hyperemia)
• Laparoscopy demonstrating acute PID

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The most specific criteria and most invasive and/or costly include: 1) evidence of histologic endometritis with an endometrial biopsy; 2) transvaginal sonography or MRI revealing thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex, or Doppler studies suggesting pelvic infection (eg, tubal hyperemia); and 3) laparoscopic abnormalities consistent with PID [1••, 19••]. Although these more specific criteria are invasive and costly they may be indicated in some circumstances where the diagnosis is uncertain [19••].

Treatment of Acute PID

Prevention of the significant long-term sequelae associated with PID requires development of effective treatment strategies. Such treatment regimens should be based upon an understanding of the microbiologic etiology of acute PID.

PID results from the intracannicular ascending spread of microorganisms from the cervix and/or vagina into the upper genital tract. Prior to the mid-1970s PID was believed to be a monoetiologic infection due primarily to *N. gonorrhoeae*. Subsequent studies utilizing culdocentesis of peritoneal fluid and laparoscopy and/or endometrial aspirations to obtain specimens from the upper genital tract led to the recognition that the etiology of acute PID is polymicrobic with a wide variety of microorganisms involved [1••, 2, 19••, 36–50, 51•]. Included among these are *N. gonorrhoeae*, *C. trachomatis*, genital tract mycoplasmas (particularly *M. genitalium*), anaerobic and aerobic bacteria which comprise the endogenous vaginal flora (eg, *Prevotella* species, black-pigmented Gram-negative anaerobic rods, *Peptostreptococci* sp., *Gardnerella vaginalis*, *Escherichia coli*, *Haemophilus influenzae*, and aerobic streptococci).

Investigations by our group conducted in the 1980s that utilized laparoscopy and/or endometrial aspirations to obtain upper genital tract specimens demonstrated that approximately two-thirds of acute PID cases are associated with *N. gonorrhoeae* and/or *C. trachomatis*. In nearly one-third only anaerobic and aerobic bacteria are recovered. In addition, half of the women with *N. gonorrhoeae* and/or *C. trachomatis* have concomitant anaerobic and/or aerobic bacteria recovered. More recently, in the PEACH study, the largest treatment trial of mild to moderate acute PID in the U.S. *N. gonorrhoeae* and *C. trachomatis* were recovered in less than one-third of patients [52].

Many of the nongonococcal, nonchlamydial microorganisms recovered from the upper genital tract in acute PID are similar to those associated with bacterial vaginosis (BV), a complex perturbation of the vaginal flora leading to loss of hydrogen peroxide producing lactobacillus and overgrowth of *G. vaginalis*, *Prevotella* sp. (especially *P. bivius*, *P. disiens*, and *P. capillosus*), *Mobiluncus* sp., black-pigmented anaerobic Gram negative rods, alpha-hemolytic streptococci and mycoplasmas [53]. Multiple investigations have demonstrated an association between BV and acute PID [42, 44–46, 53–57]. In addition, use of a broad-range 16SrDNA polymerase chain reaction to identify uncultivable bacteria has identified bacterial 16S sequences of anaerobic bacteria associated with BV in the fallopian tube of women with laparoscopically-confirmed acute PID [58].

Although *M. genitalium* was identified in the early 1980s as a cause of non-gonococcal urethritis in men, its role in genital tract infections in women remained unclear, due in large part to difficulty in culturing this organism. With the advent of polymerase chain reaction (PCR) technology, *M. genitalium* has been demonstrated to be an etiologic agent in nongonococcal nonchlamydial PID [47–50].

The therapeutic goals for treatment of acute PID include both short-term outcomes such as clinical cure and microbiologic cure and prevention of long-term sequelae such as infertility, ectopic pregnancy, recurrent infection, and chronic pelvic pain. While some antibiotic regimens have been successful in producing initial clinical and microbiologic cure with short-term follow-up, only a few studies have determined the efficacy of these treatment regimens for eliminating endometrial or fallopian tube infection. In addition, few studies have attempted to assess the incidence of long-term sequelae (eg, tubal factor infertility, ectopic pregnancy and chronic pelvic pain) following treatment with these antibiotic regimens [1••, 10••, 11, 52].

The putative role of nongonococcal nonchlamydial bacteria, especially anaerobes and more recently *M. genitalium*, in the pathogenesis of acute PID and whether antimicrobial regimens for treatment of PID should provide coverage against these microorganisms is more controversial. Some propose that anaerobic coverage is only required in patients with severe PID [2], especially those with tubo-ovarian abscesses. Others suggest that anaerobic coverage should be provided to all women with acute PID [1••]. Clearly anaerobic bacteria have been demonstrated in the upper genital tract of women with acute PID. Anaerobes have been recovered from the upper genital tract in 13% to 78% of women with PID [40–46]. In addition, anaerobes (eg, *Bacteroides fragilis*) have caused tubal damage in-vitro studies [1••].

Bacterial vaginosis (BV) has been noted to be frequently present in women presenting with acute PID [1••, 45, 53, 57]. Moreover, in the PEACH study women with acute endometritis on endometrial biopsy were commonly infected with BV-associated microorganisms in their upper genital tract [45]. Multiple previous studies [42, 44, 45, 53–55] support the findings of the PEACH study conclusion that BV is associated with acute PID.

The PEACH Study authors concluded that BV-associated organisms are very commonly present in women with mild-

to-moderately severe PID and suggested that treatment regimens for all women with PID include antimicrobial agents effective against anaerobes associated with BV. In a similar vein, the CDC notes that until treatment regimens that do not adequately cover these BV associated anaerobes have been demonstrated in clinical trial to prevent the long-term sequelae of PID as efficaciously as regimens which provide effective coverage for these microbes, use of regimens with anti-anaerobic activity should be considered [1••].

Duration of symptoms is the major determinant of subsequent infertility. Early diagnosis and treatment are crucial for preserving fertility and the effectiveness of antibiotic therapy is dependent upon the interval from the onset of symptoms to the initiation of treatment. In an updated analysis of the Lund, Sweden cohort of women with laparoscopically confirmed PID, Hillis and colleagues [68] demonstrated that women treated with ≥3 days of symptoms had a significantly greater infertility rate compared to those <3 days from symptom onset (19.7% vs. 8.3%).

Thus it is crucial that clinicians have a high index of suspicion for PID in young sexually active women presenting with abdominal pain, pelvic tenderness, and evidence of inflammation in the lower genital tract.

Antimicrobial Treatment Regimens

In 2010 the Center for Disease Control and Prevention updated their Guidelines for treatment of acute PID (Table 2). According to their guidelines, PID treatment regimens must provide empiric, broad spectrum coverage of likely pathogens [1••]. These guidelines recommend that all treatment regimens should be effective against *N. gonorrhoeae* and *C. trachomatis* even in the presence of negative endocervical screening for these organisms. Although the CDC notes that the need to eradicate anaerobes from women with PID has not been definitively determined, they point out that anaerobic bacteria have been isolated from the upper genital tract of women with PID, that in vitro studies have demonstrated that anaerobes (eg, *Bacteroides fragilis*) can cause tubal and epithelial destruction, and that BV is present in many women with PID. Consequently, they suggest that until regimens without adequate coverage for anaerobes have been shown to prevent long-term sequelae as successfully as those that include anaerobic coverage, regimens which provide coverage of anaerobes should be considered for the treatment of acute PID.

As noted by the CDC [1••] multiple randomized clinical treatment trials have demonstrated efficacy of both parenteral and oral regimens. It is important that empiric treatment be initiated as soon as a presumptive diagnosis of acute PID is made because prevention of long-term sequelae is determined by early administration (<72 h) of appropriate antimicrobial therapy [1••, 59]. In addition, selection of a treatment regimen should consider availability, cost, patient acceptance, and antimicrobial susceptibility [1••, 60].

Because parenteral antibiotics do not necessarily require hospitalization, antibiotic regimens for the treatment of acute PID are categorized as follows:

1) regimens requiring more than a single parenteral dose as initial therapy are "parenteral" and
2) regimens that are primarily oral with or without an initial single parenteral dose are considered "oral."

Table 2 Centers for disease control and prevention recommendations for the treatment of acute pelvic inflammatory disease[a]

Parenteral treatment
Recommended regimen A
Cefotetan 2 g IV every 12 h
OR
Cefoxitin 2 g IV every 6 h
PLUS
Doxycycline 100 mg orally or IV every 12 h
Recommended regimen B
Clindamycin 900 mg IV every 8 h
PLUS
Gentamicin loading dose IV or IM (2 mg/Kg body weight) followed by a maintenance dose (1.5 mg/Kg body weight) every 8 h. A single daily dosing (3–5 mg/Kg) can be substituted
Alternative parenteral regimen
Ampicillin/Sulbactam 3 g IV every 6 h
PLUS
Doxycycline 100 mg orally or IV every 12 h
Oral treatment
Recommended regimens
1. Ceftriaxone 250 mg IM in a single dose
PLUS
Doxycycline 100 mg orally twice a day for 14 days
WITH OR WITHOUT
Metronidazole 500 mg orally twice a day for 14 days
2. Cefoxitin 2 g IM in a single dose and Probenecid 1 g orally administered concomitantly as a single dose
PLUS
Doxycycline 100 mg orally twice a day for 14 days
WITH OR WITHOUT
Metronidazole 500 mg orally twice a day for 14 days
3. Other parenteral third generation cephalosporins (eg, ceftizoxime or cefotaxime) in a single dose
PLUS
Doxycycline 100 mg orally twice a day for 14 days
WITH OR WITHOUT
Metronidazole 500 mg orally twice a day for 14 days

[a] CDC sexually transmitted diseases treatment guidelines 2010 MMWR 2010:59(No.-RR12):63–67

Parenteral Treatment

Most of the literature supports the combination of 1) cefoxitin or cefotetan plus doxycycline and 2) clindamycin plus gentamicin. These two regimens remain the parenteral regimens recommended by the CDC for the treatment of PID (Table 2). However, cefotetan is not currently marketed in the United States.

According to the CDC, there are limited data available supporting a role of other second or third generation parenteral cephalosporins (eg, ceftizoxime, cefotaxime, or ceftriaxone) as effective therapy for acute PID and/or replacements for cefotetan or cefoxitin [1••]. Moreover, these antimicrobial agents are less active against anaerobic bacteria than cefoxitin or cefotetan.

Intravenous doxycycline frequently causes pain and, thus, doxycycline should be administered orally whenever possible. Fortunately, oral and intravenous administration of doxycycline provide similar bioavailability [1••].

With regimen A, parenteral therapy can be discontinued 24 h after clinical improvement occurs [1••]. However, oral doxycycline (100 mg twice a day) should be continued to complete a 14 day course of therapy. In cases of tubo-ovarian abscess, either clindamycin (450 mg orally four times a day) or metronidazole (500 mg orally every 6 h) should be used for continued therapy in order to provide more effective coverage against anaerobic bacteria.

While single dose gentamicin has not been specifically evaluated for the treatment of acute PID, it has been efficacious in the treatment of other pelvic and abdominal infections and is an option in parenteral regimen B. With this regimen, parenteral therapy may be discontinued 24 h after clinical improvement. While the CDC suggests that either doxycycline 100 mg orally twice a day or clindmycin 450 mg orally four times a day to complete a total of 14 days of therapy may be used [1••], it is the author's opinion that clindamycin is preferred because of its better anaerobic coverage. In the presence of severe PID, especially tubo-ovarian abscess, clindamycin continued therapy is recommended by the CDC [1••].

There has been renewed interest in alternative agents, particularly ampicillin-sulbactam plus doxycycline [17]. Following clinical improvement, oral therapy with doxycycline 100 mg twice a day to complete 14 days of therapy should be continued. With severe disease, especially Tubo-ovarian abscess, metronidazole 500 mg orally four times daily should be commenced as well.

While not included in the CDC 2010 recommended or alternative regimens for the treatment of PID, azithromycin has been studied for the treatment of acute PID [17, 18, 61, 62]. A randomized clinical trial in the United Kingdom among 300 women with laparoscopically confirmed PID demonstrated excellent short-term clinical care rates and microbiologic cure rates with azithromycin monotherapy for 1 week (500 mg IV daily for one or two days followed by 250 mg for 5–6 days) or in combination with a 12 day course of metronidazole [63].

Oral Treatment

Over the past 20 years there has been a dramatic shift from hospital-based parenteral antibiotic regimens to oral ambulatory based regimens [6, 7]. This shift was initially driven by the emergence of managed care and other economic factors without the benefit of clinical studies demonstrating that oral therapy was as effective as parenteral regimens, especially for prevention of long term sequelae.

The PEACH study provided evidence that supported the use of oral regimens on an ambulatory basis for the treatment of mild and moderately severe acute PID [52, 64]. This study compared inpatient parenteral therapy (intravenous cefoxitin and oral or intravenous doxycycline during ≥48 h hospitalization followed by oral doxycycline to complete a 14 day course) with outpatient oral therapy (a single intramuscular dose of cefoxitin with doxycycline administration orally for 14 days). In the PEACH study both short-term and long-term outcomes for over 800 patients (398 inpatient and 410 outpatient) with mild-to-moderately severe PID were determined. The short-term clinical cure rates at 30 days were excellent in both groups (3% of women in each group requiring additional treatment). At a mean follow-up of 35 months, the pregnancy rates were 42.0% and 41.7% in the outpatient and inpatient regimens respectively. Long-term outcomes including infertility, ectopic pregnancy, recurrent PID, and chronic pelvic pain were also similar in both groups. However, despite excellent rates of clinical cure and eradication of *N. gonorrhoeae* and *C. trachomatis*, the rates of infertility (17%), recurrent PID (14%), and chronic pelvic pain (37%) were disappointingly high [18].

As noted by the CDC [1••] outpatient oral therapy can be considered for treatment of women with mild-to-moderately severe acute PID. The oral regimens listed in Table 2 provide coverage against the major etiologic agents of acute PID. Which of the cephalosporins is the optimum selection is unclear [1••]. On the one hand cefoxitin has better anaerobic coverage, while ceftriaxone has better coverage against *N. gonorrhoeae*. The dose of ceftriaxone was increased to 250 mg IM in the 2010 CDC guidelines [1••]. The extent of efficacy against anaerobic bacteria with a single dose of cefoxitin is questionable. However, in the PEACH study single dose cefoxitin was effective in obtaining clinical response [52, 64]. The CDC [1••] and Walker and Wiesenfeld [17] suggest that theoretical limitations in coverage of anaerobes by recommended cephalosporins may require addition of metronidazole to the oral treatment recommendations. This approach is the author's recommendation. In

addition, metronidazole will effectively treat bacterial vaginosis, which as noted above is frequently associated with PID. There is no published data on the use of oral cephalosporins for treatment of acute PID [1••].

Information regarding alternative oral (outpatient) regimens is quite limited. Several alternative regimens have been assessed in at least one clinical trial and contain broad spectrum coverage [1••]. These include: 1) amoxicillin/clavulanic acid and doxycycline [65] and 2) Azithromycin monotherapy [63] or a combination of ceftriaxone 250 mg IM single dose with azithromycin 1 g orally once a week for 2 weeks [66]. If one of these alternative regimens is selected, the CDC suggests the addition of metronidazole should be considered to cover anaerobic bacteria [1••]. With the emergence of quinolone-resistant *N. gonorrhoeae*, regimens that include a quinolone agent are no longer recommended by the CDC for treatment of acute PID [1••].

The CDC recommends that patients treated with an oral regimen should evidence substantial clinical improvement within 3 days of commencing treatment [1••]. Clinical improvement is determined by defervescence, reduction in direct or rebound abdominal tenderness, and/or reduction in uterine, adenexal and cervical motion tenderness. When patients fail to improve within this window, hospitalization is usually required for additional diagnostic tests (eg, rule out TOA), parenteral antibiotic therapy and/or surgical intervention [1••].

Hospitalization for Treatment of Acute PID

In the past many clinicians recommended that all patients with PID be hospitalized for parenteral antibiotics and bed rest. As previously discussed, the PEACH study provided evidence that women with mild-to-moderately severe PID, had similar short-term and long-term clinical outcomes with outpatient oral therapy as did those with inpatient therapy [52]. As a result the CDC suggests that a decision regarding the need for hospitalization should be based on the judgment of the health-care provider and whether the patient meets any of the CDC suggested criteria for hospitalizations which include: 1) surgical emergencies (eg, appendicitis) cannot be ruled out; 2) patient is pregnant; 3) patient does not respond clinically to oral antimicrobial therapy; 4) patient is unable to follow or tolerate outpatient therapy; 5) patient has severe illness, nausea, vomiting or high fever; or 6) patient has a TOA [1••].

Pregnant women with PID have high rates of fetal wastage and preterm delivery, supporting the appropriateness of hospitalization [67, 68]. Similarly, the literature supports hospitalization of women with TOAs in order to maximize antimicrobial dosing and close monitoring for early recognition of severe sepsis or of leaking/rupture of the abscess [1••, 19••].

The absence of data to support benefit from hospitalization for adolescent girls with PID led the CDC to remove this criteria for hospitalization [1••]. Rather they suggest that a decision to hospitalize adolescents with PID should be based on the same criteria used for older women [1••]. Subanalysis of the outcome data of the PEACH study stratified by age demonstrated that fertility outcomes of the adolescents were similar in the inpatient and outpatient treatment arms [64]. However, some clinicians continue to advocate that all adolescents and never pregnant young women should be hospitalized for treatment [69]. They argue that adolescence is a proxy for poor compliance, high-risk sexual activity, delayed care, and high antimicrobial failure rates.

Whereas the presence of HIV infection or immunosuppression has previously been an indicator for hospitalization and parenteral therapy, currently it is recommended that HIV-positive women with acute PID be treated similarly to HIV-negative women. Although HIV-infected women who develop PID may have more severe clinical presentations and are more likely to have TOAs [70–72], there is no evidence to suggest that immunocompromised women benefit from hospitalization or parenteral therapy for uncomplicated PID [17, 73, 74].

Management of PID Associated with Intrauterine Contraceptive Device IUD

With the renewed popularity for the IUD as a contraceptive choice for young women, clinicians will be confronted with cases of PID in women using IUDs. As noted by Walker and Wiesenfeld, there does not exist any data to indicate that selection of treatment regimens should be influenced by the presence of an IUD [17]. In the past, clinicians generally removed IUDs to optimize the treatment of PID. This was primarily based on concerns that as a foreign body, removal of the IUD enhanced clinical response. Only a few studies addressed this issue and the results are conflicting [75, 76].

Management of Sex Partners

Male sex partners of women diagnosed with acute PID should be examined and treated if they had sexual contact with the patient during the preceding 60 days [1••]. If the last episode of sexual intercourse was >60 days prior to onset of symptoms, the last sexual partner should be treated [1••]. The CDC suggests that women diagnosed with acute PID should refrain from sexual intercourse until treatment is completed and they and their partner(s) are asymptomatic. Sex partners of women with PID should be treated empirically with regimens that provide coverage against *N. gonorrhoeae* and *C. trachomatis* [1••]. In those settings where only women

are treated, arrangements should be undertaken to either provide care or appropriate referral for male sex partners [1••]. Expedited partner treatment or enhanced patient referral are acceptable alternative approaches for the treatment of male partners of women who have PID with chlamydial or gonococcal infection [1••].

Conclusions

Prevention or minimization of the adverse reproductive sequelae associated with acute PID requires early diagnosis and appropriate antimicrobial therapy. To accomplish these goals, clinicians must understand the wide spectrum of clinical manifestations in acute PID, have a high index of suspicion for the diagnosis, and an understanding of the polymicrobic etiology of acute PID.

The diagnosis of acute PID should be suspected and empiric antibiotic therapy initiated in sexually active young women with pelvic or lower abdominal pain, especially those at risk for STIs, if no other cause is apparent and a pelvic examination discloses the presence of both pelvic organ tenderness (CMT, uterine tenderness, or adnexal tenderness) and lower genital tract inflammation (cervicitis and/or leukorrhea).

Treatment strategies for women with acute PID should be based on the polymicrobial nature of this infection. The microorganisms recovered from the upper genital tract of women with acute PID include *N. gonorrhoeae*, *C. trachomatis*, anaerobic and aerobic bacteria common to the endogenous vaginal flora and genital mycoplasmas, especially *M. genitalium*. However, the putative role of *M. genitalium* remains an open question and the CDC does not recommend coverage for this microorganism [1••]. Several antibiotic regimens are available which meet these requirements (Table 2).

Oral therapy for acute PID is currently the most commonly used approach, in response to both economic issues and the evidence from the PEACH study demonstrating that both short-term and long-term outcomes were similar for the oral and parenteral regimens. Due to the increased quinolone resistance of *N. gonorrhoeae*, choices of oral regimens are more limited. Ceftriaxone or cefoxitin demonstrated excellent short-term clinical and microbiological results. The addition of oral metronidazole to this regimen is suggested by some experts including this author to provide improved anaerobic coverage and at least to treat BV which is present in up to 70% of women with acute PID.

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