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Pelvic Inflammatory Disease (PID): Diagnosis, Disposition, and Current Antimicrobial Guidelines

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Pelvic inflammatory disease (PID): Dangerous, deceptive, and debilitating. As practitioners know, the diagnosis of PID frequently is difficult to confirm and, typically, the patients are young and tend to be non-compliant with their treatment regimen. Moreover, the sequelae of inadequate treatment can have devastating consequences, and the number of antibiotic options, combinations, and treatment protocols is nothing less than daunting. Frequently managed in the ED setting, PID is a term that is most commonly used to describe infection of the uterus, fallopian tubes, and adjacent pelvic structures that is not associated with surgery or pregnancy. An estimated 1 million women per year are diagnosed with PID—a condition that is particularly common and problematic among lower socioeconomic groups in urban areas.[1,2]

In addition to the acute manifestations of the infection, long-term sequelae such as ectopic pregnancy and infertility occur in 25% of cases.[1-3] *In 1998, the direct and indirect costs of the disease and its complications were estimated to be greater than $5 billion. In view of the effect of this infection, a systematic approach to diagnosis and therapy is mandatory for all emergency and primary care practitioners who encounter patients with this condition and its related complications.*

In virtually all cases, PID results from ascending spread of organisms from the cervix and vagina to the upper genital tract. Sexual transmission of Neisseria gonorrhea and/or Chlamydia trachomatis accounts for more than half of all cases of PID, but H. hominis and other organisms have also been implicated.[1,2,6] *N. gonorrhea is the major cause of PID in urban areas, where gonococcal infection is prevalent, whereas C. trachomatis is responsible for a greater proportion of cases among college students, in whom gonococcal infection is less common.*

Organisms such as E. coli and other enteric pathogens, especially anaerobes, also may cause PID, especially when the normal vaginal flora (lactobacilli) are supplanted with other organisms. However, infection in the upper genital tract does not always result in clinically recognizable disease; indeed, many women with adverse sequelae associated with PID, such as infertility, have no known history of the disease.[4,5]

Accordingly, a high index of suspicion and a low threshold for initiating treatment in PID are essential for facilitating detection and optimizing patient outcomes. Clinical vigilance should be applied to all women of child-bearing age with pelvic pain. Lower abdominal tenderness, adnexal tenderness, and pain on manipulation of the cervix are present in physical examination in up to 90% of women.[1,6,7] *Other manifestations, such as elevated erythrocyte sedimentation rate or C-reactive protein and abnormal vaginal discharge vary widely in frequency. At present, there are no effective ways to detect clini-*

cally silent disease.

Although laparoscopic visualization of inflamed fallopian tubes and pelvic structures is possible and, according to some experts, represents a "gold standard" for the diagnosis, it is seldom practical in the acute setting. As a rule, therefore, the emergency physician must initiate empiric antibiotic therapy for PID based on clinical criteria, regional resistance patterns, patient history, and patient compliance patterns rather than on the basis of culture results.

Because new and highly effective treatment regimens have been introduced for PID, emergency physicians now have a number of therapeutic options available for managing problematic and, frequently, poorly compliant patients with this condition.[8-10] Many of the regimens are published in the Centers for Disease Control and Prevention (CDC) guidelines, and other drugs have not yet become part of the most current guidelines, but have indications for PID.

— The Editor

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Overview

Pelvic inflammatory disease (PID) represents a spectrum of infections and inflammatory disorders of the uterus, fallopian tubes, and adjacent pelvic structures. Variable in presentation and caused by myriad bacterial and atypical organisms, PID may include any combination of endometritis, salpingitis, tubo-ovarian abscess, oophoritis, and in its more extreme manifestation, pelvic peritonitis. Since the infection most often involves the fallopian tubes, salpingitis is commonly used as a synonym for PID, although this is not strictly correct.

Because reporting rates for PID probably do not reflect the estimated prevalence of the disease in the community, most experts agree that the true incidence of PID is not known and may never be confirmed with any degree of accuracy. Moreover, many episodes of PID are not recognized by the patient or the clinician. And although sexually transmissible diseases (STDs) are reportable entities, there is no mandatory reporting for PID, even though the etiologic organisms associated with PID are similar to those encountered with STDs. Finally, clinical diagnosis of this disease can be difficult, and definitive confirmation of pelvic inflammation and/or infection by laparoscopy and/or culture usually are lacking. As a result, estimating the prevalence of PID from chart reviews may not yield an accurate accounting of how many cases occur annually in the United States.

Despite the aforementioned difficulties with reporting, diagnosing, and confirming PID, the CDC estimates that one out of every 10 women will have at least one episode of PID during her reproductive years.[11] During each of the past five years, at least 1 million women have been diagnosed with PID annually and more than 200,000 women have been hospitalized annually as a result of this condition. At least one-quarter of women with PID will have major complications, including infertility, ectopic pregnancy, chronic pelvic pain, tubo-ovarian abscesses, and/or pelvic adhesions. Overall, the annual estimated cost of treating PID and its complications is estimated to be more than $5 billion annually in the United States alone.[12,13]

Etiology and Clinical Pathogenesis

PID is thought to arise from an ascending infection of the female genital tract. As a rule, the upper female genital tract is sterile. Presumably, PID results when pathogenic microorganisms spread from the cervix and vagina to the upper portions of the genital tract to such structures as the salpinx, ovaries, and adjacent structures. Predicting exactly which pathogens are responsible for individual cases of PID can be difficult, and consequently, expert panels recommend broad spectrum antibiotics (usually, but not always, two- or multiple-drug combinations) that are active against sexually transmissible agents such as *Neisseria gonorrhoeae* and *Chlamydia trachomatis,* as well as against anaerobes and gram-negative organisms.

Clearly, in some patients, pelvic infection is not transmitted sexually but is the consequence of a trans-cervical procedure such as dilation and curettage, suction abortion, or insertion of an intrauterine device (IUD). As a result, more often than not, decisions regarding initial antibiotic therapy, spectrum of coverage, and patient disposition in PID will have to be made on the basis of clinical judgment (empiric treatment is the rule) rather than culture-driven parameters.

Treatment recommendations for PID are constantly under review, updated, and published regularly STDs by the CDC

(usually, every two years). Empiric regimens recommended by this organization are designed to reflect etiologic patterns, changes in antimicrobial drug resistance, compliance issues, cost, and efficacy data generated by well-designed clinical trials. Because the CDC analyzes a broad range of clinical, epidemiological, and pharmacological data to generate its recommendations, CDC treatment pathways for PID commonly are incorporated into emergency department, hospital, and public health clinic protocols for disease management.

Not uncommonly, however, certain agents shown to be highly effective for management of PID or STDs will have been approved for these clinical indications by the Food and Drug Administration (FDA), but because of timing considerations related to review and publication of the CDC Guidelines, these antibiotics may not appear in the most current CDC recommendations. Many of these FDA-approved antibiotics eventually do go on to become part of the CDC guidelines, albeit after a "lag" period between gaining formal FDA indication and formal publication in the CDC Guidelines. Emergency physicians, as well as other clinicians, including OB-GYN specialists, should be aware of the possible discrepancies between antibiotics approved by the FDA for PID and those agents recommended in current CDC publications.

Finally, it should be stressed that there are wide regional and international variations in etiologic agents involved in PID.[13] Reports of quinolone resistance among gonococcal species in Asia is just one example requiring clinical consideration. Because of these geographical variations, a therapeutic regimen that is highly effective in one area may be suboptimal in another. In particular, antibiotics that can be used successfully in North America and Europe may be inappropriate for treating patients with PID or STDs in Asia and Africa.

Specific Etiologic Organisms. In North America, the etiology of PID, to a great degree, has been characterized by the use of cervical cultures and/or immunofluorescent tests for gonorrhea and chlamydia. Using these diagnostic techniques, chlamydia has been shown to be responsible for 25-50% of all cases of PID. In addition, 10-20% of female patients who are infected with gonorrhea will progress to PID.

Although PID caused by gonorrhea generally requires *parenteral* therapy, uncomplicated gonococcal urthethris can be treated with single-dose therapy. There are a variety of effective regimens based on quinolones, cephalosporins, and the macrolide azithromycin that vary considerably in cost. It should be stressed that because up to 30% of patients with gonorrhea may also have coexisting chlamydial infection, chlamydia must always be empirically treated along with gonorrhea. The importance of effective communication in enhancing compliance with medication regimens cannot be overemphasized.[5] Because significant noncompliance has been reported with seven-day doxycycline regimens for treatment of uncomplicated chlamydia cervicitis or urethritis, one-dose therapeutic modalities (these would include azithromycin 1 gm po once for uncomplicated chlamydial infection and a choice of several once-dose options for uncomplicated gonococcal infection) are generally preferred.

Infection with chlamydia is problematic because up to 70% of cases are asymptomatic, which predisposes to chronic, subclinical inflammation and tubal scarring. Recent data suggest that one-third of women 15-19 years of age and up to half of those younger than 15 years become reinfected with *Chlamydia* within six years of initial diagnosis.[14] A latent chlamydial infection with prolonged inflammatory response may further predispose to ascending infection or to direct effects of the chlamydial infection. Studies confirm that chlamydial infection causes more severe tubal scarring than gonorrhea and is more likely to be associated with chronic PID.[15]

Polymicrobial Infection. The natural history of PID is not fully elucidated, although one current hypothesis suggests that the infection begins with *Chlamydia* and/or gonorrhea.[16] The vaginal and cervical environment becomes altered as these organisms proliferate; changes in pH, availability of oxygen and nutrients, and the presence of microbiologic waste products encourage the overgrowth of endogenous and anaerobic flora, causing a co-existent bacterial vaginosis. If host defenses ebb or are compromised, organisms ascend along contiguous mucosal surfaces into the endometrium and then into the fallopian tubes.

Culture-based studies that evaluated culdocentesis specimens obtained from hospitalized patients with the clinical diagnosis of PID suggest that mixed infections are responsible for up to 70% of cases with PID.[17] These polymicrobial infections typically include both anaerobic and aerobic microorganisms. When samples are obtained by laparoscopy alone, a polymicrobial etiology is confirmed in only about 30-40% of cases.

From an etiologic perspective, anaerobes such as *Bacteroides, Peptostreptococcus,* and *Peptococcus* may have been reported, as have facultative bacteria, including *Gardnerella vaginalis, Streptococcus, E. coli,* and *Haemophilus influenzae.* Organisms associated with bacterial vaginosis have been confirmed by endometrial biopsy. These organisms include *Prevotella bivia, Peptostreptococcus, Ureaplasma urealyticum,* and *Mycoplasma hominis.*[18] The broad range of organisms known to cause PID generally requires empiric treatment with a combination of antimicrobial agents with activity against chlamydia and gonococcus, and in the majority of cases, against anaerobic organisms as well.

Risk Factors

A disease of younger women, PID occurs almost exclusively in sexually active women and is most common in adolescents. Risk factors include sexual activity, particularly with multiple sexual partners, young age, and certain types of mechanical contraception. There is considerable overlap between the risks of acquiring a STD and the risk for contracting PID.

Age. Women younger than 25 years of age comprise more than 75% of all cases of PID and have a 10-fold increase in incidence as compared to older women.[19] Sexually active teenagers are more than three times more likely to have PID than women with similar activity who are 25-29 years of age.[20] Physiologically, the risk of infection with PID is enhanced by the greater permeability of the cervical mucous plug in adolescents and by greater exposure of columnar epithelium in the cervix during adolescence. In addition, teenagers are more likely to have multiple sexual partners, whether in parallel or serially. Teenagers frequently are sexual "risk-takers" and indulge in unprotected sex and inconsistent use of barrier contraception.

Women with multiple sexual partners are at increased risk of acquiring diseases such as gonorrhea and chlamydia, which predispose PID. Other sexual behaviors that have been associated with increased risk of PID include multiple new partners within the past 30 days and an increased frequency of sexual intercourse.

Method of Contraception. A number of studies have implicated intrauterine devices as a predisposing factor for PID.[21] The

intrauterine device may increase susceptibility by altering the microbiologic milieu in the cervix and uterus, by impairing local host defenses with a "foreign body" effect, or by dragging vaginal flora into the uterus during insertion. Recent studies, including data from users of the current copper "T" device with progesterone show that most of the increased risk occurs within the first four months after the insertion of the device. Again, women without other significant risk factors for STDs have less risk of developing PID after insertion of an IUD.[22,23]

Barrier contraception appears to reduce the risk for PID, presumably because it may protect against some cervical infections. A number of studies demonstrate that there is *increased detection* rate of lower genital tract infection caused by chlamydia in patients who use oral contraceptives.[24] On the other hand, oral contraceptive users also seem to have a *lower* risk for developing PID. This paradox may be explained by the fact that there is a higher detection rate associated with oral contraceptive users—and therefore, earlier treatment—or it may be explained by the existence of some protective factor produced by oral contraceptives.

Other Factors. Menses may increase the risk of PID. Retrograde flow may spread infection from the uterus out to the fallopian tubes. This has been shown to occur in 25% of healthy women.[25] Classically, gonococcal PID occurs within a week of the onset of menses. In contrast, chlamydial PID does not appear to be temporally associated with menses. Recent studies have shown that vaginal douching may also predispose to the development of PID. Mechanical pressure causes upward spread of lower genital tract infection. Alteration of the pH creates a hospitable environment for infection. Abnormal bacterial flora of the vagina or "bacterial vaginosis" may also be a risk factor for PID.[18] In this disease, there is a predominance of anaerobic flora, an alkaline pH, and a significant reduction in lactobacilli. A purulent discharge is often present.

Complications and Adverse Sequelae

Long-term sequelae occur in about 25% of patients who have had PID. The most common, and dreaded, complications include infertility and ectopic pregnancy, both of which result from scarring of the fallopian tubes. Additional complications include recurrent infections, chronic pelvic pain, and dyspareunia.

Fitz-Hugh-Curtis Syndrome. Fitz-Hugh-Curtis syndrome is an extra-pelvic manifestation of PID. The presenting complaint is right upper quadrant abdominal pain which is secondary to to peri-hepatic inflammation.[26,27] This complication is seen in about 5-20% of all women with PID.[28] The syndrome includes pain (radiation to the right shoulder or back is common) and tenderness in the hepatic region and may be associated with abnormal liver function tests. String adhesions in the area of the liver may be seen on laparoscopy. The etiology may be due to spillage of purulent material from the fimbriated end of the fallopian tube.

Tubo-ovarian Abscess. Tubo-ovarian abscess (TOA) occurs as a complication in 7-16% of all cases of acute PID.[18] The process begins when salpingitis results in spillage of infected exudate onto the ovary. The ovary then adheres to the tube as the exudate covers its surface. The site of last ovulation may be particularly vulnerable and may become the focus for infection to spread within the body of the ovary.[18] As many as 15% of tubo-ovarian abscesses will rupture and soil the peritoneum, creating an acute surgical abdomen. Although chlamydia and gonorrhea may be isolated from the cervix of patients with TOA, only rarely are these organisms found within the abscess itself. Rather, the organisms most often cultured from the abscess are facultative anaerobes and strict anaerobes.[29] Ultrasound is the most useful technique for confirming the diagnosis of a tubo-ovarian abscess. Transvaginal ultrasound has a sensitivity of 85% and a specificity of almost 100% in the diagnosis of a tubo-ovarian abscess.[30]

Chronic Pelvic Pain. Extratubal scarring can produce pelvic adhesions that may result in chronic pain. The rate of hospital admission for conditions associated with abdominal pain is much higher in individuals with proven PID than in those without a history of this disease. Specifically, women with PID have 10 times as many subsequent admissions for nonspecific abdominal pain as controls.[31] Admission diagnoses include chronic pelvic pain, gynecological pain, and non-specific abdominal pain.

Ectopic Pregnancy and Infertility. Scarring and structural changes in the fallopian tubes are well-documented consequences of PID and increase the risk for tubal pregnancy. Specifically, the rate of ectopic pregnancy is increased four-fold in women who have had documented cases of PID.[32] The greater the number of recurrences of the original infection, the more scar tissue that is built up in the tubes. Gradual accretion of scar tissue from recurrent episodes of inflammation hampers ciliary function and may partially or completely occlude the fallopian tubes.

It also is well documented that tubal changes are responsible for the increased risk of infertility that is associated with PID infections.[33] In one large study of more than 1800 women, infertility was correlated with the severity of salpingitis and the number of episodes of PID, with each episode of PID almost doubling the rate of infertility.[33] In one prospective study, infertility due to tubal occlusion occurred in 8% of women after one episode of PID, in 19.5% after two episodes, and in 40% after three or more episodes.[34] Furthermore, as previously mentioned, many cases of PID are clinically silent, but as many as 70% of women who are infertile due to tubal obstruction have serum antibodies against chlamydia vs. only about 25% of women who are infertile for other reasons.[2,3,7]

Interestingly, more than one-half of patients with tubal factor infertility give no history of PID.[33] In most of these patients, however, antibodies to Chlamydia or gonorrhea are found, indicating prior infection. Nevertheless, both gross and microscopic examination of the fallopian tubes of women with tubal factor infertility fails to differentiate between patients with and without a history of PID.

Diagnosis and Evaluation

The definitive diagnosis of PID requires invasive testing. This can include an endometrial biopsy showing evidence of endometritis, laparoscopy with abnormalities consistent with PID, or transvaginal sonography showing thickened, fluid-filled tubes with or without free pelvic fluid or a tubo-ovarian abscess.[35]

Laparoscopy. Most experts agree that laparoscopy is still the "gold standard" for establishing the definitive diagnosis of PID. Despite the usefulness of this technique, the majority of patients managed in the emergency department receive a presumptive diagnosis on the basis of clinical criteria alone, in large part because laparoscopy simply requires more technical skill, surgical risk, and cost than clinical pathways and protocols have been willing to support. Moreover, it is unlikely that laparoscopy will ever become practical as a screening procedure.

Despite these limitations, laparoscopy is an important technique when the diagnosis of PID is in question or during situa-

tions in which the patient fails to improve. In a substantial number of patients, an alternate diagnosis such as appendicitis, ovarian tumor, ectopic pregnancy, or ovarian cyst may be identified.[36] Finally, although laparoscopy is considered the cornerstone of diagnosis in PID, there are limitations to this technique; since the laparoscope examines only the external surfaces of the tube and adjacent structures, early disease localized to the intra-tubal wall may be missed.[37]

Pelvic Ultrasound. Pelvic ultrasound has been well studied in PID and is useful for identifying tubal and ovarian pathology, with a reported sensitivity rate of up to 93%.[38] Although it is not necessary to obtain an ultrasound in every case of suspected PID, this modality is useful for making the diagnosis of tubo-ovarian abscess, for detecting other complications of PID, and for eliminating other entities in the differential diagnosis, such as ectopic pregnancy. As a general rule, ultrasound should be performed if a pelvic or a tubal mass is suspected. Moreover, an ultrasound is mandatory in a pregnant patient with abdominal pain. In addition, any patient who is treated with appropriate antibiotics and does not improve after 48 hours of therapy should have a pelvic ultrasound to exclude structural disease.[39] Transvaginal ultrasound is not only better for image quality and anatomic detail, but is more comfortable for most patients.

CT Scanning. Although CT scanning is not specifically mentioned in the CDC guidelines, this imaging technique can identify pelvi pathology consistent with PID and may be helpful for distinguishing among conditions with a similar presentation.

Major and Minor Determinants. Despite the advantages of these techniques, most women suspected of having PID in the ED are treated on the basis of a presumptive diagnosis generated by clinical signs and symptoms. Unfortunately, culture or other isolation of a sexually transmitted organism usually will not be available, rarely is an endometrial biopsy obtained, and direct visualization of the pelvic organs is the exception rather than the rule.

Typically, then, the presumptive diagnosis of PID is made in women who are sexually active who present with lower abdominal pain and are found to have cervical, uterine, or adnexal tenderness on pelvic examination. Not surprisingly, these criteria for clinical diagnosis have low sensitivity and specificity. PID, which is one of many conditions producing such symptoms, probably accounts for less than one-half of cases associated with this presentation.

Because clinical contingencies usually require that antibiotic treatment be initiated on the basis of noninvasive evaluation, the CDC has recommended minimum criteria required for empiric treatment of PID. These major determinants include lower abdominal tenderness, adnexal tenderness, and cervical motion tenderness.[39] Other authors have used these same major criteria but have also added the requirement that at least one minor determinant also be present. Unfortunately, these criteria have not been evaluated systematically in studies that correlate clinical examination with findings at laparoscopy.[40] Minor determinants (i.e., signs that may increase the suspicion of PID) include:

- Fever (oral temperature > 101°F; > 38.3°C);
- Vaginal discharge. One study notes that an increased WBC in the vaginal discharge was the laboratory test with the highest sensitivity in diagnosing PID.[41]
- Documented STD. Laboratory documentation of cervical infection with either gonorrhea or Chlamydia establishes presence of a milieu of PID. If a patient with a documented STD presents with abdominal pain, PID should be strongly suspected.
- Erythrocyte sedimentation rate (ESR). This test may be used to assist in the diagnosis of PID. It is nonspecific and can be elevated in a number of inflammatory conditions.
- C-reactive protein. C-reactive protein is an acute phase protein synthesized in the liver. The serum concentration increases a few hours after injury or inflammation and reaches a peak 24-48 hours later. Elevated C-reactive protein is seen in PID, and may be useful in early diagnosis of this disease.[42] Unfortunately, it is not specific and seen with a number of inflammatory conditions or injuries.
- Systemic signs. Nausea and vomiting may be found in patients with PID, but these symptoms are more common in other diseases such as appendicitis.
- Dyspareunia. Dyspareunia may be the first symptom that brings a patient to the emergency department. *(See Table 1.)*

Limitations of Diagnostic Criteria. One large study has demonstrated that no single historical, clinical, or laboratory finding, nor any combination of these, is both perfectly sensitive and specific for establishing the diagnosis of PID.[43] In large part, this is because the disease presents with a wide range of symptoms, depending on the severity of the disease. Moreover, the evolution of symptoms in PID is oftentimes gradual and the early complaints are mild, especially when *Chlamydia* is the offending organism.[44] PID due to *Chlamydia* tends to be associated with sexual activity at a very young age, and these patients are less likely to present for medical care during the early stages of disease. Minimum diagnostic criteria for PID include the presence of lower abdominal tenderness, adnexal tenderness, and cervical motion tenderness, although the entire triad may not be noted in early cases of PID. Instead, the patient may only complain of dyspareunia, spotting, fever, and/or abnormal vaginal or cervical discharge.

In summary, it should be stressed that the clinical diagnostic criteria are insensitive and nonspecific; false-positive and false-negative diagnoses are common. Unfortunately, the only alternative is to examine the pelvic anatomy directly with laparoscopy, but this invasive approach is not always feasible, as it requires general anesthesia, and is costly.[45] It is mandatory that other causes for the complex of symptoms should be identified. Specific diagnoses that should be considered include ectopic pregnancy, a ruptured ovarian cyst, endometriosis, and appendicitis.

Atypical Pelvic Inflammatory Disease. As noted earlier, there is a large reservoir of atypical PID. Attempts to find demographic, clinical, or behavioral predictors of atypical PID are disappointing, to say the least. In one study of 283 women with tubal occlusion or adhesion, 84% reported no history of PID.[46] The patient with atypical disease was more likely to be married, educated, and have a higher income than those with overt PID. They were less likely to report a history of gonococcal or herpes infections, and were more likely to report multiple partners.

Authors of one study felt that atypical PID was a sexually transmitted disease, but that it was caused by organisms other than *Chlamydia trachomatis, Neisseria gonorrhoeae*, trichomoniasis, or *Mycoplasma* species.[47] These clinical patterns suggest that identification of patients with atypical disease is difficult. Future efforts to identify women with atypical PID will have to rely on metabolic or immunological markers. Perhaps urine screening for chlamydia, gonorrhea, or some as yet unidentified pathogen will prove fruitful in the future.

Table 1. Laboratory Evaluation for Pelvic Inflammatory Disease

- Complete blood count with differential
- Pregnancy test of choice (unless patient is already known to be pregnant)
- Tests for Chlamydia and gonorrhea
- RPR or VDRL tests for syphilis
- Pelvic sonogram
- C-reactive protein or erythrocyte sedimentation rates may be helpful.

Management: Antibiotic Guidelines and Patient Disposition

As emphasized, a high index of suspicion and a low threshold for initiating treatment are important for facilitating detection and appropriate management of PID. This approach should be applied to all women of child-bearing age with pelvic pain. Although laparoscopic visualization of inflamed fallopian tubes and pelvic structures is possible and, according to some experts, serves as a "gold standard" for the diagnosis, it is seldom practical. As a rule, the emergency physician must initiate antibiotic therapy on clinical grounds, despite the limitations of this approach. From a clinical perspective, however, lower abdominal tenderness, adnexal tenderness, and pain on manipulation of the cervix are present in physical examination in up to 90% of women, and the presence of this triad will mandate treatment in nearly all cases.[1,6,7] Other manifestations, such as elevated erythrocyte sedimentation rate or C-reactive protein and abnormal vaginal discharge vary widely in frequency. At present, there are no effective ways to detect clinically silent disease.

Because new and highly effective treatment regimens have been introduced for PID, emergency physicians now have a number of therapeutic options available for managing problematic and, frequently, poorly compliant patients with PID.[8-10] In this regard, the CDC recommends a number of possible regimens, most of which mandate the use of a broad-spectrum cephalosporin administered parenterally (initially) along with an oral agent effective against chlamydia, such as doxycycline. Commonly used regimens for inpatient treatment of PID include the combination of cefoxitin, ceftriaxone, or cefotetan plus doxycycline; plus intravenous metronidazole followed by oral therapy with metronidazole plus doxycycline; gentamicin plus clindamycin; and intravenous ampicillin-sulbactam plus doxycycline. Although not included as part of the current CDC recommendation guidelines, intravenous azithromycin therapy followed by oral azithromycin (preferably in combination with an anti-anaerobic agent such asmetronidazole) for the treatment of PID has been shown to be safe and effective. Because azithromycin is FDA-approved for this indication, it will be included in treatment tables in conjunction with CDC-recommended regimens when applicable.

CDC Guidelines for Inpatient Therapy.[51] The CDC has established treatment guidelines for PID, identifying specific patient subgroups that have a higher risk for severe or fertility-compromising disease and, therefore, require hospitalization and inpatient therapy. Most of these recommendations are based on clinical common sense. For example, the ED physician should admit patients in whom the diagnosis is uncertain or who may have surgical diseases such as appendicitis or ectopic pregnancy. Likewise, if the patient with suspected PID fails to respond to outpatient therapy, the next appropriate step is to admit the patient and treat with intravenous antibiotics.

Nearly all patients with severely symptomatic PID should be hospitalized for an initial course of parenteral antibiotic therapy and pain management. In addition, those with potentially complicating disease should also be admitted. Hospitalization should also be considered when the patient is a substance abuser or a young adolescent, and in patients who are unreliable for clinical follow-up, are pregnant, have a possibility of surgical pathology, or are unable to tolerate outpatient therapy.

Antibiotic Therapy: Polymicrobial Vs. Monotherapeutic Approaches. The ideal drug for treatment of PID would be one that has a short course of therapy, is associated with few side effects, could be taken orally, and is inexpensive. It should also induce resistance only infrequently and should be effective against all important PID pathogens. Unfortunately, there is no single drug that satisfies all of these requirements in all patients.

Consequently, the majority of recommended or approved drug regimens for treatment of PID require two or more agents. *(See Table 2.)* Although azithromycin is FDA-approved as a single drug agent for PID, most clinicians add an additional agent to cover anaerobic pathogens. In general, treatment plans requiring more than one drug are associated with decreased compliance unless all drugs can be given simultaneously under the supervision of a clinician to confirm compliance. Increasing the number of drugs also increases the potential for side effects and interactions. Clearly, use of more than one drug increases cost.

Single-drug therapy may not be either appropriate or possible because of the possibility of infection with multiple organisms including anaerobes, facultative anaerobes, and aerobic organisms. Since specific microbiologic diagnoses are rarely made, treatment should be directed against a wide range of suspected organisms. The therapeutic agents should include agents that are active against both *N. gonorrhea* and *C. trachomatis*, as well as facultative gram-negative rods and anaerobes.

The CDC has recommended multiple drug therapy for treatment of PID since 1982.[49] These regimens are perhaps the oldest among all current CDC recommendations.[50] In a recent analysis of multiple drug regimens for the treatment of PID, the CDC recommendations were among the six best in clinical response.[18] They have pooled clinical cure rates ranging from 92% to 94%.[51,52] Changing patterns of drug resistance may provoke the next substantial change in recommendations.

Out-of-Hospital Antimicrobial Management for PID

Approaches to managing patients in the ED/outpatient environment requires additional discussion, since there are now other approved regimens in addition to those recommended by the CDC. Most of the CDC-endorsed regimens for outpatient management use a cephalosporin as an important component of the treatment plan. *(See Table 3.)* In this regard, the optimum choice of cephalosporin for outpatient regimens is still unclear, although ceftriaxone is widely used. Cefoxitin has better anaerobic coverage, but ceftriaxone is more effective against gonorrhea. Other cephalosporins have been proposed, including ceftizoxime and cefotaxime. These are less well studied.

Azithromycin. The evolving and increasingly important role

Table 2. Antibiotic Treatment Regimens of Choice for Inpatient/Hospitalized Management of PID

INPATIENT PARENTERAL REGIMEN OPTION ONE*

Azithromycin IV (500 mg qd for 1 or 2 days) followed by oral azithromycin 250 mg po once daily to complete a total of 7 days

Plus (as clinically indicated for suspicion for anaerobic infection)

Metronidazole 500 mg IV every 8 hours

*This is an FDA-approved regimen that does not currently appear in the CDC Guidelines for PID management.

INPATIENT PARENTERAL REGIMEN OPTION TWO

Cefotetan 2 g IV every 12 hours

Plus

Doxycycline 100 mg IV or po every 12 hours*

or

Cefoxitin 2g IV every 6 hours

Plus

Doxycycline 100 mg IV or PO every 12 hours*

*Parenteral therapy can be discontinued 24 hours after the patient improves. Oral therapy should be started with doxycycline 100 mg bid and continued for 14 days total therapy. If a tubo-ovarian abscess is present, many providers will use clindamycin or metronidazole to provide better coverage of anaerobic bacteria.

INPATIENT PARENTERAL REGIMEN OPTION THREE

Clindamycin 900 mg IV every 8 hours

Plus

Gentamicin 2mg/kg loading dose IV or IM (with 1.5 mg/kg maintenance dose every 8 hours)

Parenteral therapy can be discontinued 24 hours after the patient improves clinically. Oral therapy should then be started and continued for a total of 14 days of therapy. Oral therapy should consist of doxycycline 100 mg bid and clindamycin 450 mg qid. Clindamycin continues to have better coverage of *Bacteroides* species than the cephalosporins. This makes regimen option 2 particularly effective when there is a tubo-ovarian abscess or advanced disease where anaerobic organisms are more probable. A major disadvantage of the clindamycin plus aminoglycoside regimen is the ototoxicity of the aminoglycoside. This may be decreased with therapeutic serum level monitoring.

ALTERNATIVE PARENTERAL REGIMEN OPTIONS

Ofloxacin 400 mg IV every 12 hours

Plus

Metronidazole 500 mg IV every 8 hours

or

Ampicillin/sulbactam 3 g IV every 6 hours

Plus

Doxycycline 100 mg PO or IV every 12 hours

or

Ciprofloxacin 200 mg IV every 12 hours

Plus

Doxycycline 100 mg PO or IV every 12 hours

Plus

Metronidazole 500 mg IV every 8 hours

of azithromycin requires special attention, since it offers dosing advantages that make it attractive to emergency practice. One study evaluated results in a total of 221 women with PID treated with the following regimens: 1) azithromycin monotherapy (administered as 500 mg IV as the initial dose on day 1, followed by 250 mg daily for 6 additional days); 2) azithromycin in combination with metronidazole; and 3) metronidazole (either intravenous metronidazole 500 mg bid on day 1 followed by oral administration of 500 mg bid for 11 days or oral administration of 500 mg bid for 12 days), plus doxycycline (100 mg po bid 14 days), plus cefoxitin (2 gm IV or IM) with probenecid 1 g on the first day of treatment.[53,63]

In an intent-to-treat analysis conducted 15 days after therapy with these regimens, 93% of the patients receiving azithromycin alone, 94% of patients receiving azithromycin plus metronidazole, and 93% of those receiving the triad of cefoxitin, doxycycline, and metronidazole were either cured or improved. The bacteriologic eradication rates for all three regimens were in the 93-95% range. Azithromycin was well-tolerated in patients with PID. The most common side effects were diarrhea (8.5%) and nausea (6.6%). The addition of metronidazole to azithromycin increased slightly the incidence of gastrointestinal side effects, with 10.3% reporting nausea, 3.7% abdominal pain, and 2.8% vomiting.[53]

Based on this data, azithromycin IV (500 mg qd for 1 or 2 days) followed by oral azithromycin 250 mg po qd to complete a total of seven days of therapy should be considered a primary treatment modality for managing patients who require initial intravenous therapy for PID caused by *C. trachomatis, N. gonorrhoeae,* or *M. hominis*. The timing of the switch from intravenous to oral therapy should be made by the physician, who should make this decision based on clinical parameters. Moreover, it should be stressed that when anaerobic infection is strongly suspected to play an etiologic role in any individual patient with PID, the ED physician should combine an antimicrobial agent such as metronidazole that provides anaerobic coverage along with azithromycin.

Although many patients with PID, especially those who appear to be systemically toxic, have abdominal rebound tenderness, have WBC counts greater than 15,000, have a unilateral mass suggestive of tubo-ovarian abscess, have a history or profile indicating risk for poor medication compliance, are in the adolescent age group, and those in whom preservation of fertility is a high priority will require hospitalization, a significant percentage can be treated with initial IV or IM therapy in the ED, followed by oral therapy out of the hospital to complete the antimicrobial course.

As outlined, current options for out-of-hospital management of mild PID include the well-established regimen of ceftriaxone 500 mg IM, followed by doxycycline 100 mg po bid for 14 days with or without metronidazole 500 mg po tid for 10-14 days. These CDC-endorsed regimens have an excellent track record for efficacy and safety. With approval of the azithromycin IV/oral sequenced combination regimen outlined above, it is now possible to streamline therapy for PID into a seven-day course, and substantially reduce the number of oral doses required to complete the treatment course.

The practical implications for the ED physician are as follows: If, on the basis of the clinical findings, the ED physician deems that a patient with mild PID can be managed out of the

Table 3. Antibiotic Treatment Regimens of Choice for ED/Outpatient Management of PID

OUTPATIENT/ED TREATMENT REGIMEN OPTION ONE

Azithromycin 500 mg as a single dose *intravenously* given in the emergency department *followed by* oral azithromycin 250 mg once daily orally to complete a total of seven days of therapy.*

Plus/Minus

Metronidazole 500 mg orally twice daily for 14 days (as clinically indicated for suspicion for anaerobic infection—usually recommended)

*The FDA-approved regimen for azithromycin treatment of PID specifies 1 to 2 days of intravenous azithromycin therapy (500 mg) followed by oral azithromycin (250 mg) to complete a seven-day course of therapy. Because it is possible to give a single intravenous dose in the emergency department (this dose would constitute day 1 of IV therapy), this would satisfy the minimal FDA criteria of 1 to 2 days of intravenous therapy. Patients, who on the basis of clinical signs and symptoms, require in-hospital management may be more suitable for 2 days of intravenous therapy in the inpatient setting.

ED/OUTPATIENT ORAL TREATMENT REGIMEN OPTION TWO

Ceftriaxone 250 mg IM once

Plus

Doxycycline 100 mg orally twice daily for 14 days

Plus/Minus

Metronidazole 500 mg orally twice daily for 14 days (as clinically indicated for suspicion for anaerobic infection—usually recommended)

ED/OUTPATIENT ORAL TREATMENT REGIMEN OPTION THREE

Cefoxitin 2 g IM plus probenecid 1 gram orally concurrently

Plus

Doxycycline 100 mg orally twice daily for 14 days

Plus/Minus

Metronidazole 500 mg orally twice daily for 14 days (as clinically indicated for suspicion for anaerobic infection—usually recommended)

ED/OUTPATIENT ORAL TREATMENT REGIMEN OPTION FOUR

Ofloxacin 400 mg orally twice daily for 14 days

Plus

Metronidazole 500 mg orally twice daily for 14 days

hospital, and that a single intravenous dose of azithromycin in the ED is sufficient prior to oral therapy, then azithromycin should be administered as an infusion at a rate of 2 mg/mL over 1 hour, or 1 mg/mL over three hours. Azithromycin IV should always be infused over a period of not less than one hour, and should never be administered by bolus or intramuscular injection. If patients with PID have signs and symptoms that suggest the need for more than one intravenous dose, hospitalization will usually be necessary.

The one-hour minimum infusion time required for this antibiotic is not as convenient as the IM route of administration required for the ceftriaxone (plus oral doxycycline) regimen. However, the post-parenteral therapy phase of the azithromycin treatment regimen (which requires only an additional 6 days of oral therapy following the IV dose) is considerably more convenient and compliance-enhancing (both with respect to daily dose frequency and duration of therapy) than the ceftriaxone regimen, which requires consolidation with 28 oral doses of doxycycline over a 14-day period. In a patient population at high risk for noncompliance, the azithromycin regimen offers a potential window of opportunity that should be considered in this difficult patient population.

Other Antibiotics. It should be stated that there is a diversity of opinion regarding newer antibiotics for the treatment of PID, and to some extent, there is a paucity of good data. Multiple authors recommend diverse antibiotic regimens with both new single drugs and various combinations of antibiotics.[54] Clinical judgment, experience, and local resistance patterns should help direct the clinician toward the optimal regimen in any given patient. Multiple, small studies exist to support these diverse antibiotic regimens, but statistically significant studies are not common.

A number of practical aspects of antimicrobial treatment for this disease should be pointed out, so that clinical outcomes can be optimized. For example, many clinicians add metronidazole to outpatient regimens to ensure adequate anaerobic coverage. This view is endorsed in both the 1993 and the 1998 CDC recommendations. Metronidazole lacks activity against both gram-positive and gram-negative aerobic organisms. As mentioned, azithromycin has no significant activity against many anaerobic organisms encountered in PID, so it should usually be used with an additional agent such as metronidazole.

The quinolone story also is changing rapidly and requires special scrutiny. The lack of reliable activity of the older quinolones such as ciprofloxacin against *Chlamydia* means that these agents should not be used to treat PID. Moreover, growing quinolone resistance among *N. gonorrhoeae* infections may make a significant impact on the utility of these agents in the near future.[55] Ofloxacin has established efficacy against *Chlamydia* when given for at least seven days.[56,57] It has shown good results in well-controlled, published studies, hence its inclusion in the CDC outpatient protocols and alternative inpatient protocols. Of concern, however, is the growing resistance rates to the quinolones in general (especially in Asia) and ofloxacin in particular. Disturbingly, increasing resistance among *E. coli* species also has been reported.[58]

While several new combination regimens have been proposed for treatment of PID, none of these have been adequately evaluated for clinical efficacy in the treatment of PID. In small studies, there is a statistically higher cure rate using "newer" antibiotics. In one small study of 100, patients treated with clindamycin and aztreonam had a clinical response rate of 98%.[59] Other small studies with piperacillin had response rates of 95%, but only 60 patients were involved. Imipenem is a broad spectrum antimicrobial with good anaerobic coverage. When combined with cilastatin to decrease renal excretion, imipenem may be a potential antibiotic for the treatment of PID. In three studies with this drug, there was a 94.7% clinical response rate in PID patients.[60] However, imipenem does not adequately cover Chlamydia, so another agent would be required.

Disposition, Adjunctive Therapy, and Follow-up

All women seen in the ED with suspected or confirmed PID require a pregnancy test to determine appropriate management.

If present, intrauterine devices should be removed once antibiotic therapy is initiated. Close follow-up of outpatients within 24-48 hours after treatment is started is important. Failure to improve indicates the need for reassessment of the diagnosis (using laparoscopy, ultrasonography, or hospitalization) rather than a change in antibiotic therapy.

Male sexual partners of patients with PID need to be evaluated; this should include examination for sexually transmitted infections other than chlamydial and gonococcal disease, although, as a minimum, they must be treated for these two infections. Women who have had PID should be advised against the use of intrauterine devices and to protect themselves as much as possible against subsequent sexually transmitted infection to reduce their likelihood of infertility and other long-term sequelae. In women with concomitant HIV infection, hospitalization and intravenous therapy are indicated.

In addition to antibiotics, there are adjunctive therapies that may mitigate damage to the reproductive system. Non-steroidal anti-inflammatory agents may mitigate the damage caused in the tubes.[61] There are no significant human data available and animal studies show inconclusive results.[62] Certainly, ibuprofen and similar agents are inexpensive and well tolerated. They may give substantial relief when pain is a significant symptom. Bed rest is advocated in other countries for treatment of PID and more patients are hospitalized in these countries. There is no data to support or refute a benefit from this practice.

If the patient is HIV positive, inpatient therapy and IV antibiotics using one of the two recommended regimens is the most prudent course. Recommendations do not otherwise differ for the HIV-positive or immunocompromised patient.

Finally, the ED physician should ensure that the sexual partner(s) are treated. This may not only decrease the likelihood of recurrent disease, but may decrease the chance of spreading the disease to others. No woman should be considered adequately treated until her partner(s) are also treated. Screen target groups regularly for STDs. This would include sexually active teenagers, inmates of jails, illicit drug users, and those with multiple sexual partners. Women who report a new sexual partner should always be offered screening for sexually transmitted diseases.

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Physician CME Questions

17. Long-term sequelae such as ectopic pregnancy and infertility occur in about what percentage of cases of PID?
    A. 5%
    B. 15%
    C. 25%
    D. 35%
    E. 45%

18. The triad of lower abdominal tenderness, adnexal tenderness, and pain on manipulation of the cervix are reported in up to:
    A. 30% of cases of PID
    B. 60% of cases of PID
    C. 90% of cases of PID
    D. none of the above

19. PID is thought to result from:
    A. descending infection from tuobo-ovarian structures to cervix
    B. ascending infection from anal structures to cervix
    C. descending infection from renal structures to salpinx
    D. ascending infection from cervix and vagina to upper portion of the genital tract
    E. none of the above

20. Generally speaking, antibiotic treatment of PID requires multiple drug regimens active against:
    A. gram positive cocci, Neisseria gonorrhoeae, and anaerobes
    B. Chlamydia pneumoniae, Neisseria gonorrhoeae, and anaerobes
    C. Chlamydia trachomatis, gram positive cocci, and Neisseria gonorrhoeae
    D. Chlamydia trachomatic, Neisseria gonorrhoeae, anaerobes and gram negative organisms
    E. none of the above

21. All FDA-approved antimicrobial regimens for treatment of PID are included in the current CDC Guidelines for treatment of PID.
    A. True
    B. False

22. Pelvic ultrasound is:
    A. not the "gold standard" for diagnosis of PID.
    B. has a sensitivity rate of up to 93% for identifying tubal and ovarian pathology.
    C. useful for making the diagnosis of tubo-ovarian abscess.
    D. should be performed if a pelvic mass is suspected.
    E. all of the above.

23. The following is an FDA-approved treatment course for PID:
    A. Azithromycin IV (500 mg qD for 1-2 days) followed by oral azithromycin 250 mg orally one daily to complete a course of therapy of 7 days plus metronidazole 500 mg orally twice daily for 14 days (when required for anaerobic infection).
    B. Azithromycin 500 mg PO for 1-2 days, followed by azithromycin 250 mg orally once daily to complete a course of therapy of 7 days plus metronidazole 500 mg orally twice daily for 14 days (when required for anaerobic infection).
    C. Azithromycin 500 mg PO once daily to complete a course of therapy of 7 days plus metronidazole 500 mg orally twice daily for 14 days (when required for anaerobic infection).
    D. None of the above.
    E. All of the above.

24. Cure rates based on pooled data using CDC-endorsed recommendations for PID range from:
    A. 80% to 82%.
    B. 82% to 85%.
    C. 85% to 87%.
    D. 87% to 90%.
    E. 90% to 92%.

In Future Issues: Sexually Transmissible Diseases