Clinical Guideline

Pelvic inflammatory disease.

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GUIDELINE TITLE

Pelvic inflammatory disease.

BIBLIOGRAPHIC SOURCE(S)

- Pelvic inflammatory disease. Philadelphia (PA): Intracorp; 2005. Various p. [18 references]

GUIDELINE STATUS

This is the current release of the guideline.

All Intracorp guidelines are reviewed annually and updated as necessary, but no less frequently than every 2 years. This guideline is effective from July 1, 2005 to July 1, 2007.

MAJOR RECOMMENDATIONS

Diagnostic Confirmation

Subjective Findings

- Lower abdominal pain, diffuse and bilateral - often poorly localized
- Pelvic pain or pressure
- Fevers
- Vaginal discharge; often foul smelling
- Abnormal uterine bleeding
- General ill feeling
- Pain with intercourse (dyspareunia)
- Urinary tract symptoms:
    - Dysuria or suprapubic pain occurring only during micturition, without frequency or urgency. NOTE: This should prompt suspicion of pelvic inflammatory disease (PID), as urine will show no signs of infection.

- Nausea and vomiting

Objective Findings

- Physical and pelvic examinations:
    - Bilateral adnexal tenderness
    - Cervical motion tenderness - sensitive but not specific for PID
    - Cervicitis and vaginal discharge (seen in more than 50% of patients with sexually transmitted organisms)
    - Firm, possibly tender uterus
    - Peritoneal signs or perihepatic irritation with right upper quadrant tenderness if infection becomes severe

Diagnostic Tests

- Pregnancy test; for all women, except those who have had a hysterectomy)
- Urinalysis to rule out urinary tract infection (UTI)
- Complete blood count (CBC); this is of limited usefulness; leukocytosis may or may not be present
- Laboratory documentation may reveal cervical infection with *Neisseria gonorrhoeae* or *Chlamydia trachomatis*
- Imaging; vaginal ultrasound (US) to rule out a tubo-ovarian abscess or ectopic pregnancy
- Serologic testing for syphilis
- Human immunodeficiency virus (HIV) testing (e.g., enzyme-linked immunosorbent assay [ELISA] or Western blot) and counseling should be offered to all patients with suspected PID or sexually transmitted disease (STD)
- Endometrial biopsy
- Laparoscopy; it should be noted that direct visualization of the pelvic cavity is generally the only way to confirm PID diagnosis.

Differential Diagnosis

- Ovarian conditions (see the Intracorp guideline Ovarian Cyst):
    - Cyst
    - Cyst rupture
    - Torsion

- Ectopic pregnancy; ruptured or non-ruptured
- Endometriosis
- Menstrual disorders (see the Intracorp guideline Abnormal Uterine Bleeding):
    - Myomas
    - Abnormal uterine bleeding
    - Mittelschmerz
- UTI (see the Intracorp guideline Urinary Tract Infection)
- Appendicitis
- Gallbladder conditions:
    - Colic
    - Cholecystitis
- Renal conditions:
    - Colic
    - Cystitis
    - Pyelonephritis
- Hepatitis
- Gastrointestinal conditions:
    - Gastroenteritis
    - Diverticulitis
    - Inflammatory bowel disease
- Intestinal conditions:
    - Ischemic bowel
    - Ruptured viscous
    - Bowel obstruction
- Infertility

Treatment

Treatment Options

- Antibiotic therapy; choices vary in regard to inpatient versus outpatient regimens, allergies, compliance needs, and the gravid status of the patient
- Pelvic ultrasound
- Laparoscopy
- Surgery for the following:
    - Life-threatening infections
    - Ruptured tuboovarian abscesses
    - Pelvic abscesses
    - Persistent symptomatic mass
- Hysterectomy may be suggested for individuals who are older (see the Intracorp guideline Hysterectomy). NOTE: should be referred to physician advisor for review

Duration of Medical Treatment

- Medical - Optimal: 2 day(s), Maximal: 14 day(s)

Additional information regarding primary care visit schedules, referral options, and specialty care is provided in the original guideline document.

The original guideline document also provides a list of red flags that may affect disability duration, and return to work goals, including

- Resolving symptoms of pelvic pain, fever without hospitalization
- Resolving nausea, vomiting, hydration with hospitalization
- After hospitalization for surgery

GUIDELINE TITLE

Pelvic inflammatory disease. Sexually transmitted diseases treatment guidelines

MAJOR RECOMMENDATIONS

Note from the National Guideline Clearinghouse and the Centers for Disease Control and Prevention: When more than one therapeutic regimen is recommended, the sequence is alphabetized unless the choices for therapy are prioritized based on efficacy, convenience, or cost. For sexually transmitted diseases (STDs) with more than one recommended regimen, almost all regimens have similar efficacy and similar rates of intolerance or toxicity unless otherwise specified.

Pelvic inflammatory disease (PID) comprises a spectrum of inflammatory disorders of the upper female genital tract, including any combination of endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis. Sexually transmitted organisms, especially *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, are implicated in many cases; however, microorganisms that comprise the vaginal flora (e.g., anaerobes, *Gardnerella vaginalis, Haemophilus influenzae*, enteric Gram-negative rods, and *Streptococcus agalactiae*) also have been associated with PID. In addition, cytomegalovirus (CMV), *Mycoplasma hominis*, and *Ureaplasma urealyticum* may be the etiologic agents in some cases of PID.

Diagnostic Considerations

Acute PID is difficult to diagnose because of the wide variation in the symptoms and signs. Many women with PID have subtle or mild symptoms. Delay in diagnosis and effective treatment probably contributes to inflammatory sequelae in the upper reproductive tract. Laparoscopy can be used to obtain a more accurate diagnosis of salpingitis and a more complete bacteriologic diagnosis. However, this diagnostic tool often is not readily available, and its use is not easy to justify when symptoms are mild or vague. Moreover, laparoscopy will not detect endometritis and may not detect subtle inflammation of the fallopian tubes. Consequently, a diagnosis of PID usually is based on clinical findings.

The clinical diagnosis of acute PID is imprecise. Data indicate that a clinical diagnosis of symptomatic PID has a positive predictive value (PPV) for salpingitis of 65%--90% compared with laparoscopy. The positive predictive value of a clinical diagnosis of acute PID differs depending on epidemiologic characteristics and the clinical setting, with higher positive predictive value among sexually active young women (particularly adolescents) and among patients attending STD clinics or from settings in which rates of gonorrhea or chlamydia are high. In all settings, however, no single historical, physical, or laboratory finding is both sensitive and specific for the diagnosis of acute PID (i.e., can be used both to detect all cases of PID and to exclude all women without PID). Combinations of diagnostic findings that improve either sensitivity (i.e., detect more women who have PID) or specificity (i.e., exclude more women who do not have PID) do so only at the expense of the other. For example, requiring two or more findings excludes more women who do not have PID but also reduces the number of women with PID who are identified.

Many episodes of PID go unrecognized. Although some cases are asymptomatic, others are undiagnosed because the patient or the health-care provider fails to recognize the implications of mild or nonspecific symptoms or signs (e.g., abnormal bleeding, dyspareunia, and vaginal discharge). Because of the difficulty

of diagnosis and the potential for damage to the reproductive health of women even by apparently mild or atypical PID, health-care providers should maintain a low threshold for the diagnosis of PID.

The optimal treatment regimen and long-term outcome of early treatment of women with asymptomatic or atypical PID are unknown. The following recommendations for diagnosing PID are intended to help health-care providers recognize when PID should be suspected and when they need to obtain additional information to increase diagnostic certainty. Diagnosis and management of other common causes of lower abdominal pain (e.g., ectopic pregnancy, acute appendicitis, and functional pain) are unlikely to be impaired by initiating empiric antimicrobial therapy for PID.

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(s) for the illness can be identified:

- uterine/adnexal tenderness
- cervical motion tenderness

Requiring all minimum criteria may result in low sensitivity in patients at high risk for infection. In patients with both pelvic tenderness and signs of lower genital tract inflammation, the diagnosis of PID should be considered. Treatment may be indicated based on a patient's risk profile.

More elaborate diagnostic evaluation often is needed, because incorrect diagnosis and management might cause unnecessary morbidity. These additional criteria may be used to enhance the specificity of the minimum criteria. Additional criteria that support a diagnosis of PID include the following:

- oral temperature >101 degrees F (>38.3 degrees C)
- abnormal cervical or vaginal mucopurulent discharge
- presence of white blood cells (WBCs) on saline microscopy of vaginal secretions
- elevated erythrocyte sedimentation rate
- elevated C-reactive protein
- laboratory documentation of cervical infection with *N. gonorrhoeae* or *C. trachomatis*

Most women with PID have either mucopurulent cervical discharge or evidence of white blood cells on a microscopic evaluation of a saline preparation of vaginal fluid. If the cervical discharge appears normal and no white blood cells are found on the wet prep, the diagnosis of PID is unlikely, and alternative causes of pain should be investigated.

The most specific criteria for diagnosing PID include the following:

- endometrial biopsy with histopathologic evidence of endometritis
- transvaginal sonography or magnetic resonance imaging techniques showing thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex
- laparoscopic abnormalities consistent with PID

A diagnostic evaluation that includes some of these more extensive studies may be warranted in certain cases.

Treatment

PID treatment regimens must provide empiric, broad-spectrum coverage of likely pathogens. Antimicrobial coverage should include *N. gonorrhoeae*, *C. trachomatis*, anaerobes, Gram-negative facultative bacteria, and streptococci. Several antimicrobial regimens have been effective in achieving clinical and microbiologic cure in randomized clinical trials with short-term follow-up. However, few investigations have assessed and compared these regimens with regard to elimination of infection in the endometrium and fallopian tubes or determined the incidence of long-term complications (e.g., tubal infertility and ectopic pregnancy) of antimicrobial regimens.

All regimens should be effective against *N. gonorrhoeae* and *C. trachomatis*, because negative endocervical screening does not preclude upper reproductive tract infection. The need to eradicate anaerobes from women who have PID has not been determined definitively. Anaerobic bacteria have been isolated from the upper reproductive tract of women who have PID, and data from in vitro studies have revealed that certain anaerobes (e.g., *Bacteroides fragilis*) can cause tubal and epithelial destruction. In addition, bacterial vaginosis also is present in many women who have PID. Until treatment regimens that do not adequately cover these microbes have been demonstrated to prevent sequelae as successfully as the regimens that are effective against these microbes, the recommended regimens should provide anaerobic coverage. Treatment should be initiated as soon as the presumptive diagnosis has been made, because prevention of long-term sequelae has been linked directly with immediate administration of appropriate antibiotics. When selecting a treatment regimen, health-care providers should consider availability, cost, patient acceptance, and antimicrobial susceptibility.

In the past, many specialists recommended that all patients who had PID be hospitalized so that bed rest and supervised treatment with parenteral antibiotics could be initiated. However, hospitalization is no longer synonymous with parenteral therapy. No currently available data compare the efficacy of parenteral with oral therapy or inpatient with outpatient treatment settings. The decision of whether hospitalization is necessary should be based on the discretion of the health-care provider.

The following criteria for hospitalization are based on observational data and theoretical concerns:

- surgical emergencies (e.g., appendicitis) cannot be excluded
- the patient is pregnant
- the patient does not respond clinically to oral antimicrobial therapy
- the patient is unable to follow or tolerate an outpatient oral regimen
- the patient has severe illness, nausea and vomiting, or high fever
- the patient has a tubo-ovarian abscess

No data are available that suggest that adolescent women benefit from hospitalization for treatment of PID. Whether women in their later reproductive years benefit from hospitalization for treatment of PID is also

unclear, although women aged ≥35 years who are hospitalized with PID are more likely than are younger women to have a complicated clinical course.

Parenteral Treatment

No efficacy data compare parenteral with oral regimens. Many randomized trials have demonstrated the efficacy of both parenteral and oral regimens. Although most trials have used parenteral treatment for at least 48 hours after the patient demonstrates substantial clinical improvement, this time designation is arbitrary. Clinical experience should guide decisions regarding transition to oral therapy, which usually can be initiated within 24 hours of clinical improvement. Most clinicians recommend at least 24 hours of direct inpatient observation for patients who have tubo-ovarian abscesses, after which time home antimicrobial therapy is adequate.

Parenteral Regimen A

- **Cefotetan** 2 g intravenously every 12 hours

  OR

- **Cefoxitin** 2 g intravenously every 6 hours

  PLUS

- **Doxycycline** 100 mg orally or intravenously every 12 hours

Note: Because of pain associated with infusion, doxycycline should be administered orally when possible, even when the patient is hospitalized. Both oral and intravenous administration of doxycycline provide similar bioavailability.

Parenteral therapy may be discontinued 24 hours after a patient improves clinically, and oral therapy with doxycycline (100 mg twice a day) should continue to complete 14 days of therapy. When tubo-ovarian abscess is present, many health-care providers use clindamycin or metronidazole with doxycycline for continued therapy rather than doxycycline alone, because it provides more effective anaerobic coverage.

Clinical data are limited regarding the use of other second- or third-generation cephalosporins (e.g., ceftizoxime, cefotaxime, and ceftriaxone), which also may be effective therapy for PID and may replace cefotetan or cefoxitin. However, these cephalosporins are less active than cefotetan or cefoxitin against anaerobic bacteria.

Parenteral Regimen B

- **Clindamycin** 900 mg intravenously every 8 hours

  PLUS

- **Gentamicin** loading dose intravenously or intramuscularly (2 mg/kg of body weight) followed by a maintenance dose (1.5 mg/kg) every 8 hours. Single daily dosing may be substituted.

Although use of a single daily dose of gentamicin has not been evaluated for the treatment of PID, it is efficacious in other analogous situations. Parenteral therapy can be discontinued 24 hours after a patient

improves clinically; continuing oral therapy should consist of doxycycline 100 mg orally twice a day or clindamycin 450 mg orally four times a day to complete a total of 14 days of therapy. When tubo-ovarian abscess is present, many health-care providers use clindamycin for continued therapy rather than doxycycline, because clindamycin provides more effective anaerobic coverage.

Alternative Parenteral Regimens

Limited data support the use of other parenteral regimens, but the following three regimens have been investigated in at least one clinical trial, and they have broad spectrum coverage.

- **Ofloxacin** 400 mg intravenously every 12 hours

  OR

- **Levofloxacin** 500 mg intravenously once daily

  WITH or WITHOUT

- **Metronidazole** 500 mg intravenously every 8 hours

  OR

- **Ampicillin/Sulbactam** 3 g intravenously every 6 hours

  PLUS

- **Doxycycline** 100 mg orally or intravenously every 12 hours

Intravenous ofloxacin has been investigated as a single agent; however because of concerns regarding its spectum, metronidazole may be included in the regimen. Preliminary data suggest that levofloxacin is as effective as ofloxacin and may be substituted; its single daily dosing makes it advantageous from a compliance perspective. Ampicillin/sulbactam plus doxycycline has good coverage against *C. trachomatis*, *N. gonorrhoeae*, and anaerobes and is effective for patients who have tubo-ovarian abscess.

Oral Treatment

As with parenteral regimens, clinical trials of outpatient regimens have provided minimal information regarding intermediate and long-term outcomes. The following regimens provide coverage against the frequent etiologic agents of PID, but evidence from clinical trials supporting their use is limited. Patients who do not respond to oral therapy within 72 hours should be reevaluated to confirm the diagnosis and should be administered parenteral therapy on either an outpatient or inpatient basis.

Regimen A

- **Ofloxacin** 400 mg orally twice a day for 14 days

  OR

- **Levofloxacin** 500 mg orally once daily for 14 days

  WITH or WITHOUT

- **Metronidazole** 500 mg orally twice a day for 14 days

Oral ofloxacin has been investigated as a single agent in two well-designed clinical trials, and it is effective against both *N. gonorrhoeae* and *C. trachomatis*. Despite the results of these trials, lack of anaerobic coverage with ofloxacin is a concern; the addition of metronidazole to the treatment regimen provides this coverage. Preliminary data suggest that levofloxacin is as effective as ofloxacin and may be substituted; its single daily dosing makes it advantageous from a compliance perspective.

Regimen B

- **Ceftriaxone** 250 mg intramuscularly in a single dose

  OR

- **Cefoxitin** 2 g intramuscularly in a single dose and **Probenecid**, 1 g orally administered concurrently in a single dose

  OR

- Other parenteral third-generation **cephalosporin** (e.g., **ceftizoxime** or **cefotaxime**)

  PLUS

- **Doxycycline** 100 mg orally twice a day for 14 days

  WITH or WITHOUT

- **Metronidazole** 500 mg orally twice a day for 14 days

The optimal choice of a cephalosporin for Regimen B is unclear; although cefoxitin has better anaerobic coverage, ceftriaxone has better coverage against *N. gonorrhoeae*. Clinical trials have demonstrated that a single dose of cefoxitin is effective in obtaining short-term clinical response in women who have PID; however, the theoretical limitations in its coverage of anaerobes may require the addition of metronidazole to the treatment regimen. The metronidazole also will effectively treat bacterial vaginosis, which is frequently associated with PID. No data have been published regarding the use of oral cephalosporins for the treatment of PID. Limited data suggest that the combination of oral metronidazole plus doxycycline after primary parenteral therapy is safe and effective.

Alternative Oral Regimens

Although information regarding other outpatient regimens is limited, one other regimen has undergone at least one clinical trial and has broad spectrum coverage. Amoxicillin/clavulanic acid plus doxycycline was effective in obtaining short-term clinical response in a single clinical trial; however, gastrointestinal symptoms might limit compliance with this regimen. Several recent investigations have evaluated the use of azithromycin in the treatment of upper reproductive tract infections; however, the data are insufficient to recommend this agent as a component of any of the oral treatment regimens for PID.

Follow-Up

Patients should demonstrate substantial clinical improvement (e.g., defervescence; reduction in direct or rebound abdominal tenderness; and reduction in uterine, adnexal, and cervical motion tenderness) within 3

days after initiation of therapy. Patients who do not improve within this period usually require hospitalization, additional diagnostic tests, and surgical intervention.

If the health-care provider prescribes outpatient oral or parenteral therapy, a follow-up examination should be performed within 72 hours using the criteria for clinical improvement described previously. If the patient has not improved, hospitalization for parenteral therapy and further evaluation are recommended. Some specialists also recommend rescreening for *C. trachomatis* and *N. gonorrhoeae* 4--6 weeks after therapy is completed in women with documented infection with these pathogens.

Management of Sex Partners

Male sex partners of women with PID should be examined and treated if they had sexual contact with the patient during the 60 days preceding the patient's onset of symptoms. Evaluation and treatment are imperative because of the risk for reinfection of the patient and the strong likelihood of urethral gonococcal or chlamydial infection in the sex partner. Male partners of women who have PID caused by *C. trachomatis* and/or *N. gonorrhoeae* often are asymptomatic.

Sex partners should be treated empirically with regimens effective against both of these infections, regardless of the etiology of PID or pathogens isolated from the infected woman. Even in clinical settings in which only women are treated, arrangements should be made to provide care for male sex partners of women who have PID. When this is not feasible, health-care providers should ensure that sex partners are referred for appropriate treatment.

Prevention

Prevention of chlamydial infection by screening and treating high-risk women reduces the incidence of PID. Theoretically, most cases of PID can be prevented by screening all women or those determined to be at high-risk (based on age or other factors) using deoxyribonucleic acid (DNA) amplification on cervical specimens (in women receiving pelvic exams) and on urine (in women not undergoing exams). Although bacterial vaginosis is associated with PID, whether the incidence of PID can be reduced by identifying and treating women with bacterial vaginosis is unclear.

Special Considerations

Pregnancy

Because of the high risk for maternal morbidity, fetal wastage, and preterm delivery, pregnant women who have suspected PID should be hospitalized and treated with parenteral antibiotics.

HIV Infection

Differences in the clinical manifestations of PID between HIV-infected women and HIV-negative women have not been well delineated. In early observational studies, HIV-infected women with PID were more likely to require surgical intervention. In recent, more comprehensive observational and controlled studies, HIV-infected women with PID had similar symptoms when compared with uninfected controls. They were more likely to have a tubo-ovarian abscess, but responded equally well to standard parenteral and oral antibiotic regimens when compared with HIV-negative women. The microbiologic findings for HIV-positive and HIV-negative women were similar, except for a) higher rates of concomitant *M. hominis*,

candida, streptococcal, and human papilloma virus (HPV) infections and b) human papilloma virus-related cytologic abnormalities among those with HIV infection. Whether the management of immunodeficient HIV-infected women with PID requires more aggressive interventions (e.g., hospitalization or parenteral antimicrobial regimens) has not been determined.