Pelvic Inflammatory Disease (PID)

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PELVIC INFLAMMATORY DISEASE (PID)

Definition

- PID is an infection of the female upper genital tract involving any combination of the endometrium, fallopian tubes, pelvic peritoneum and contiguous structures.

Etiology

- There are multiple causes of lower abdominal pain in women, including gynecologic disease or dysfunction (complications of pregnancy, acute infections, endometriosis, adnexal disorders, menstrual disorders), as well as gastrointestinal (appendicitis, gastroenteritis, inflammatory bowel disease), genitourinary (cystitis, pyelonephritis, nephrolithiasis), musculoskeletal and neurologic causes.
- The most common infectious cause of lower abdominal pain in women is pelvic inflammatory disease (PID).[1]
- PID is a polymicrobial infection with multiple microbial etiologies.
- Most cases of PID are associated with more than one organism.
- Pathogens can be categorized as sexually transmitted or endogenous organisms.

Table 1. Microbial causes

Sexually transmitted organisms	• *Chlamydia trachomatis* • *Neisseria gonorrhoeae* • Viruses and protozoa (rare) – Herpes simplex virus – *Trichomonas vaginalis*
Endogenous organisms	• Genital-tract mycoplasmas – *Mycoplasma genitalium* – *Mycoplasma hominis* – *Ureaplasma urealyticum*
Anaerobic bacteria	• *Bacteroides* spp. • *Peptostreptococcus* spp. • *Prevotella* spp.
Facultative (aerobic) bacteria	• *Escherichia coli* • *Gardnerella vaginalis* • *Haemophilus influenzae* • *Streptococcus* spp.

Epidemiology

- PID is a very significant public health problem.
- Up to two-thirds of cases go unrecognized, and underreporting is common.
- There are approximately 100,000 cases of symptomatic PID annually in Canada, although PID is not nationally reportable, so exact numbers are unknown.
- It is estimated that 10–15% of women of reproductive age have had one episode of PID.[2]
- In recent years, hospitalization rates for PID have declined (118/100,000 women in 1995 and 55/100,000 women in 2001, data from Health Canada) because increasing numbers of patients are treated as outpatients, but the number of patient visits to physician offices for PID has remained stable.
- The incidence of long-term sequelae of PID (tubal factor infertility, ectopic pregnancy, chronic pelvic pain) is directly related to the number of episodes of PID.[3]
- In jurisdictions with long-standing chlamydia control programs, PID rates and ectopic pregnancy rates have declined.

Prevention

- At the community level, health-promotion and education programs are essential to promote screening for sexually transmitted infections (STIs).
- Health care providers should assume responsibility for primary prevention activities, such as risk-reduction counselling and patient education.
- At the time of diagnosis of infection, health care providers should reinforce prevention and safer sex practices. They should also identify barriers to prevention practices and ways to overcome them.
- Patients and contacts should be counselled to abstain from unprotected sexual contact until treatment of both partners is complete.

Manifestations and Diagnosis

- Abdominal pain may be a clinical feature of many disorders, and the symptoms of PID may overlap with other gynecologic disorders or disorders of the gastrointestinal, urinary and musculoskeletal systems.
- There is no single historical, physical or laboratory finding that is both sensitive and specific for the diagnosis of PID.[4]
- Only one-third of women with acute PID have a temperature above 38°C.[5]
- Common findings on physical examination of patients with acute PID include bilateral lower abdominal, uterine, adnexal and cervical motion tenderness, but these findings may be present with a variety of other conditions as well.
- The clinical diagnosis of PID is imprecise, and clinicians should have a high index of suspicion.

Table 2. Criteria for diagnosis

Minimum diagnostic criteria	Additional diagnostic criteria	Definitive diagnostic criteria
• Lower abdominal tenderness • Adnexal tenderness • Cervical motion tenderness	• Oral temperature >38.3°C. • Presence of white blood cells on saline microscopy of vaginal secretions/wet mount • Elevated erythrocyte sedimentation rate • Elevated C-reactive protein • Laboratory documentation of cervical infection with *Neisseria gonorrhoeae* or *Chlamydia trachomatis*	• Endometrial biopsy with histopathologic evidence of endometritis (at least 1 plasma cell per x120 field and at least 5 neutrophils per x400 field) • Transvaginal sonography or other imaging techniques showing thickened fluid-filled tubes, with or without free pelvic fluid or tubo-ovarian complex • Gold standard: Laparoscopy demonstrating abnormalities consistent with PID, such as fallopian tube erythema and/or mucopurulent exudates

PID = pelvic inflammatory disease

Physical examination and specimen collection

- A complete abdominal and pelvic examination should be performed in any patient with lower abdominal pain.
- Pelvic examination should include speculum and bimanual examinations.
- The external genital area, vagina and cervix should all be inspected.

- **Stat serum beta HCG to rule out ectopic pregnancy.**
- With the aid of a speculum, endocervical swabs should be obtained for diagnostic tests for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*.
- Cervical lesions should be sampled with swabs for diagnostic tests for herpes simplex virus, if suspected.
- Vaginal swabs should be obtained for culture; pH testing; amine odour whiff testing; normal saline and potassium hydroxide wet preparations; and Gram stain. Clinical assessment for bacterial vaginosis includes three of four Amsel criteria (vaginal discharge, elevated pH, amine odour whiff test and clue cells* on microscopy).[6] An aerobic and anaerobic culture may assist with the detection of unusual vaginal pathogens, such as Group A streptococcus.

* Clue Cells are vaginal epithelial cells covered with numerous coccobacillia

Laboratory diagnosis

- Negative laboratory results do not rule out a diagnosis of PID.
- A normal ultrasound study does not rule out a diagnosis of PID.
- Ultrasound may aid in the diagnosis, especially if tubo-ovarian abscess is suspected.
- A STAT beta HCG pregnancy test should be done to exclude ectopic pregnancy from the differential diagnosis.
- Detection of Gram-negative intracellular diplococci on a stained smear of endocervical secretions; positive results of a diagnostic test for *N. gonorrhoeae* or *C. trachomatis*; or both.
- Detection of *N. gonorrhoeae* or *C. trachomatis* may be enhanced by using nucleic acid amplification tests (NAAT).
- Other tests that may be helpful in the diagnosis of acute PID include complete blood count, erythrocyte sedimentation rate, C-reactive protein and endometrial biopsy.

Management

- **Early diagnosis and treatment are crucial to the maintenance of fertility.**
- Antibiotic therapy can be administered orally or parenterally, and in inpatient or outpatient settings.
- Data suggest that efficacy and long-term complication rates are not significantly different between parenteral and oral therapy or inpatient and outpatient treatment.[7]
- Individuals treated as outpatients need careful follow-up and should be re-evaluated 2 to 3 days after therapy is initiated.
- **If no clinical improvement has occurred, hospital admission for parenteral therapy, observation and consideration for laparoscopy is required; consultation with colleagues experienced in the care of these patients should be considered.**

Table 3. Criteria for hospitalization

- Surgical emergencies such as 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.

Consider hospitalization for observed oral or parenteral therapy in the following cases:

- HIV infection
- Youth/adolescents (particularly if compliance is an issue)

Treatment

- Goals of treatment are to control the acute infection and to prevent long-term sequelae such as infertility, ectopic pregnancy and chronic pelvic pain.
- Treatment regimens should provide empiric broad-spectrum coverage of likely etiologic pathogens and take into account the polymicrobial nature of PID.
- Treatment regimens should provide coverage for *N. gonorrhoeae*, *C. trachomatis*, Gram-negative facultative bacteria and streptococci.[8] Anaerobic coverage should be considered, but whether elimination of anaerobes from the upper tract is necessary remains to be answered even though anaerobes are detected in the majority of PID cases.
- Although quinolones are no longer recommended for the treatment of gonococcal infections in Canada, due to the polymicrobial nature of PID, they still can be useful in the treatment of acute infection that does not involve quinolone resistant *N. gonorrhoeae*. Recent clinical trials have shown that quinolones are very effective at producing cure of acute PID.[9-11]
- **For patients with contraindications to treatment with cephalosporins or quinolones,** recent evidence suggests that short course **azithromycin** at a dose of either 250 mg PO daily for one week OR 1 gram PO weekly for two weeks combined with oral **metronidazole** is effective in producing a clinical cure for acute PID.[12]
- Discontinuation of parenteral therapy may be considered 24 hours after a patient improves clinically.[8]
- Oral step-down therapy should then begin and continue for a total of 14 days of treatment.[8]
- If recovery does not occur, other differential diagnoses and a laparoscopy need to be considered.

Table 4. Recommended parenteral treatment regimens

Regimen A[13] ***[A-I]***	• **Cefoxitin** 2 g IV every 6 hours PLUS **doxycycline** 100 mg IV or PO every 12 hours – Parenteral therapy may be discontinued 24 hours after a patient improves clinically, and oral therapy with **doxycycline** (100 mg bid) should continue for a total of 14 days – Most authorities recommend administering doxycycline in oral form even in hospitalized patients, because IV administration is painful and more costly, and because oral and IV administration provide similar bioavailability
Regimen B ***[A-I]***	• **Clindamycin** 900 mg IV every 8 hours PLUS **gentamicin*** loading dose IV or IM (2 mg/kg of body weight), followed by a maintenance dose (1.5 mg/kg) every 8 hours. Once-daily dosing may be substituted (5mg/kg of body weight IV every 24h) – Parenteral therapy may be discontinued 24 hours after a patient improves clinically, and oral therapy with **doxycycline** (100 mg bid) OR **clindamycin** (450 mg PO qid) should continue for a total of 14 days
Alternative regimens[14] ***[A-II]***	• **Ofloxacin** 400 mg IV every 12 hours† PLUS/MINUS **metronidazole** 500 mg IV every 8 hours‡ OR • **Levofloxacin** 500 mg IV once daily† PLUS/MINUS **metronidazole** 500 mg IV every 8 hours‡ OR • **Ampicillin/sulbactam** 3 g IV every 6 hours PLUS **doxycycline** 100 mg IV or PO every 12 hours OR • **Ciprofloxacin** 200 mg IV every 12 hours† PLUS **doxycycline** 100 mg IV or PO every 12 hours PLUS/MINUS **metronidazole** 500 mg IV every 8 hours‡ – Because ciprofloxacin has poor coverage against *C trachomatis*, it is recommended that doxycycline be added routinely – Because of concerns regarding the anaerobic coverage of quinolones, metronidazole should be included with each regimen‡

Notes:

- **Patients should not drink alcohol during and for 24 hours following treatment with metronidazole because of a possible disulfiram (antabuse) reaction.**
- **The use of ofloxacin, ciprofloxacin, levofloxacin, and doxycycline is contraindicated for pregnant and lactating women. Pregnant women should not be treated with quinolones or tetracyclines.**

* These recommendations apply for those patients with normal renal function; gentamicin dosage to be adjusted for renal impairment. Renal function and gentamicin levels should be monitored during treatment.

† Due to the rapid increase in quinolone resistant *Neisseria gonorrhoeae*, quinolones such as ciprofloxacin and ofloxacin are no longer preferred drugs for the treatment of gonococcal infections in Canada.

- **Quinolones may be considered as an alternative treatment option ONLY IF** :
  – antimicrobial susceptibility testing is available and quinolone susceptibility is demonstrated;
  OR
  – where antimicrobial testing is not available, a test of cure is essential.

‡ Anaerobic coverage should be considered, but whether elimination of anaerobes from the upper tract is necessary remains to be answered even though anaerobes are detected in the majority of PID cases.

Table 5. Recommended outpatient treatment regimens

Regimen A[15] *[A-II]*	• **Ceftriaxone** 250 mg IM in a single dose[§ ‖] PLUS **doxycycline** 100 mg PO bid for 14 days OR • **Cefoxitin** 2 g IM PLUS **probenecid** 1 g PO in a single dose concurrently once PLUS **doxycycline** 100 mg PO bid for 14 days OR • Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime) PLUS **doxycycline** 100 mg PO bid for 14 days • Many authorities recommend the addition of **metronidazole** 500 mg PO bid for 14 days to this regimen for additional anaerobic coverage and the treatment of bacterial vaginosis[‡] *[B-III]*
Regimen B[16] *[A-II]*	• **Ofloxacin** 400 mg PO bid for 14 days[†] PLUS/MINUS **metronidazole** 500 mg PO bid for 14 days[‡] *[A-I]* OR • **Levofloxacin** 500 mg PO qd[†] PLUS/MINUS **metronidazole** 500 mg PO bid for 14 days[‡] *[B-II]* – Metronidazole is added to provide anaerobic coverage[‡] – Preliminary data suggest that oral levofloxacin is as effective as oral ofloxacin, with the advantage of once-daily dosing[9]

Notes:

- **Patients should not drink alcohol during and for 24 hours following treatment with oral metronidazole because of a possible disulfiram (antabuse) reaction.**
- **The use of ofloxacin, ciprofloxacin, levofloxacin, and doxycycline is contraindicated for pregnant and lactating women. Pregnant women should not be treated with quinolones or tetracyclines.**

† Due to the rapid increase in quinolone resistant *Neisseria gonorrhoea*, quinolones such as ciprofloxacin and ofloxacin are no longer preferred drugs for the treatment of gonococcal infections in Canada.

- **Quinolonesmay be considered as an alternative treatment option ONLY IF** :
  - antimicrobial susceptibility testing is available and quinolone susceptibility is demonstrated;

  OR
  - where antimicrobial testing is not available, a test of cure is essential.

§ Ceftriaxone should not be given to persons with a cephalosporin allergy or a history of immediate and/or anaphylactic reactions to penicillins.

‖ The preferred diluent for ceftriaxone is 1% lidocaine without epinephrine (0.9 mL/250 mg, 0.45 mL/125 mg) to reduce discomfort.

‡ Anaerobic coverage should be considered, but whether elimination of anaerobes from the upper tract is necessary remains to be answered even though anaerobes are detected in the majority of PID cases.

Consideration for Other STIs

- Individuals infected with one STI are at risk of concurrent infection with one or more other STIs.
- Following a diagnosis of PID, testing and counselling should be performed for other infections, including HIV and syphilis.
- Immunization against hepatitis B is recommended if not already immune.
- Discuss HPV vaccine as per the recommendations outlined in the Canada Communicable Disease Report, Volume 33 ACS-2, (2007) *National Advisory Committee on Immunization (NACI) statement on Human papillomavirus vaccine*.

Reporting and Partner Notification

- Patients with conditions that are notifiable according to provincial and territorial laws and regulations should be reported to local public health authorities.
- The management of women with PID is considered inadequate unless their sexual partners are also evaluated and treated.
- Evaluation should occur if there was sexual contact with the patient during the 60 days prior to symptom onset or date of diagnosis (if asymptomatic).
- After evaluation, sexual partners should be empirically treated with regimens effective against both gonorrhea and chlamydia regardless of clinical findings and without waiting for test results.
- Local public health authorities are available to assist with partner notification and appropriate referral for clinical evaluation, testing, treatment and health education when the causative organism is identified as a reportable STI.

Follow-up

- Pain and tenderness resulting from acute PID should begin to resolve within 48 to 72 hours of initiating antibiotics.[17]
- If no improvement is observed, further work-up is essential.
- Individuals treated as outpatients need careful follow-up and should be re-evaluated 2 to 3 days after treatment is initiated.
- If no clinical improvement has occurred, hospital admission for parenteral therapy and observation is required.
- Following a diagnosis of PID, patients should be informed that they are at risk of both short-term consequences such as Fitz-Hugh-Curtis syndrome (perihepatitis) and tubo-ovarian abscess, and long-term sequelae, including infertility, ectopic pregnancy and chronic pelvic pain.

Special Considerations

Pregnancy

- PID is uncommon in pregnancy, especially after the first trimester.
- Pregnant patients with suspected PID should be hospitalized for evaluation and treatment with parenteral therapy because of an increased risk of adverse outcomes for both the mother and the pregnancy.
- There is a large differential diagnosis of acute abdominal pain in pregnancy, and consultation with an expert should be sought.

HIV infection

- HIV-positive women with PID may represent a subgroup of patients with a more difficult clinical course.
- Some studies have suggested that HIV-positive women with PID have longer hospital stays and are at higher risk for the development of tubo-ovarian abscesses and are more likely to require surgical intervention.[18,19]
- These women should be followed closely and managed aggressively, and consideration should be given to hospitalization.
- Consultation with a colleague experienced in HIV care is recommended.

Adolescents

- Consideration should be given to hospitalization for adolescents with suspected PID if compliance is expected to be an issue.

Patients with an intrauterine contraceptive device in situ

- In patients with an intrauterine device (IUD) in situ, the device should not be removed until after therapy has been initiated and at least two doses of antibiotics have been given.