An Update on the Management of Acute Pelvic Inflammatory Disease

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Introduction

Pelvic inflammatory disease (PID) consists of a spectrum of infections of the upper genital tract including endometritis, salpingitis, pelvic peritonitis and/or tubo-ovarian abscess. Early diagnosis and treatment of this disease is important in the prevention of long-term sequelae which include tubal factor infertility, ectopic pregnancy and chronic pelvic pain.

PID is the result of ascending infection from the lower to the upper genital tract. Various organisms have been isolated from the upper genital tract of women with PID, suggesting a polymicrobial nature for the infections. However, it most frequently occurs secondary to sexually transmitted diseases (STDs) in the lower genital tract, especially *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, which is found in up to two thirds of women with PID[1]. Chlamydial infection is more common than gonococcal infection in PID. However gonococcal PID usually has a more acute presentation in terms of duration and severity of symptoms. Importantly, anaerobic organism like *Gardnerella vaginalis*, *Haemophilus influenza*, enteric Gram negative rods, and *Streptococcus agalactiae* from the vaginal flora have also been associated with PID[1].

Bacterial vaginosis is found in up to two thirds of women with PID[2]. It is an imbalance of the naturally occurring vaginal flora where the normal lactobacilli dominant environment is replaced by an anaerobic dominant environment in association with increasing Gardnerella vaginalis and genital mycoplasmas. Recently, *Mycolasma genitalium*, a sexually transmitted organism, has been associated with PID, and appears to present with mild clinical symptoms similar to chlamydial PID[3].

Diagnosis

The diagnosis of acute PID can be difficult due to the wide variation of symptoms and signs. Diagnosis should be based on clinical history, physical examination and to a lesser extent laboratory studies and imaging. The main clinical symptoms and signs suggestive of PID are listed in Table 1. These clinical symptoms and signs lack sensitivity and specificity for the diagnosis of PID. The positive predictive value of a clinical diagnosis is 65-90% compared with laparoscopic diagnosis[4]. While some cases of PID can be asymptomatic, many others are not diagnosed because of the mild or non-specific symptoms and signs of PID, such as abnormal bleeding, dyspareunia and vaginal discharge.

Table 1: Clinical features of women with clinically suspected pelvic inflammatory disease

Lower abdominal pain and tenderness
Abnormal vaginal or cervical discharge
Fever (>38°C)
Abnormal vaginal bleeding (intermenstrual bleeding / postcoital bleeding)
Deep dyspareunia
Urinary frequency
Low back pain
Nausea / vomiting
Cervical motion tenderness, uterine tenderness or adnexal tenderness

The Centres for Disease Control and Prevention (CDC) recommends that health care providers should maintain a low threshold for making the diagnosis of PID. Empiric treatment should be considered in sexually active young women and other women at risk for STDs if their symptoms could not be explained by other causes, particularly in the presence of cervical motion tenderness, uterine tenderness or adnexal tenderness.

Table 2: Investigations

Complete blood count (for leucocytosis)
Screening for sexually transmitted diseases • Endocervical swabs for Gonorrhoea and Chlamydia • High vaginal swab for Trichomonas • Serology for Syphilis (VDRL) and HIV infections
Cervical smear (for screening)
Blood or urine pregnancy test (to exclude ectopic pregnancy)

The investigations listed in Table 2 should be considered in women suspected of PID. Testing for *C. trachomatis* and *N. gonorrhoeae* is important as a positive result may support the clinical diagnosis. However, a negative result does not exclude PID. The peripheral white blood cell count is commonly normal in mild disease, and markers such as erythrocyte sedimentation rate or C-reactive protein, while correlating with the severity of PID, are non-specific findings. Although endometrial biopsy can provide histopathologic evidence of endometritis, there is insufficient evidence to support its routine use. Laparoscopy allows a more accurate diagnosis of salpingitis and tubo-ovarian abscess, and a more complete bacteriologic diagnosis. However, it is an invasive procedure and its routine use in the management of women with suspected PID may be difficult to justify. Imaging is useful when

there is a diagnostic uncertainty, such as the use of pelvic ultrasonography or computed tomography to rule out symptomatic ovarian cysts or appendicitis. Pelvic ultrasonography has limited sensitivity for the diagnosis of PID, but in the presence of thickened fluid filled tubes, the diagnosis of upper genital tract infection is likely. Imaging should be considered in women with severe PID because up to one third will have evidence of tubo-ovarian abscess.

Treatment

Treatment with antibiotics should be started as soon as possible, ideally within two days of the onset of symptoms. Studies have suggested that delaying treatment of PID increases the severity of the condition and the risk of long-term sequelae[5]. Broad spectrum antibiotic treatment is generally recommended to cover *C. trachomatis*, *N. gonorrhoeae* and anaerobic infection. Choice of the regimen may be influenced by severity of disease, history of allergy and patient preference. In mild or moderate PID (in the absence of tubo-ovarian abscess) there is no difference in outcome when women are treated as outpatients or admitted to hospitals[6]. The recommended regimens for mild or moderate PID are listed in Table 3[7,8].

Table 3: Outpatient antibiotic treatment for mild to moderate pelvic inflammatory diseases

Ceftriaxone 250mg IM in a single dose PLUS Doxycycline 100mg orally twice a day for 14 days AND Metronidazole 400mg orally twice a day for 14 days
Levofloxacin 500mg orally once a day for 14 days AND Metronidazole 400mg twice a day for 14 days
Ofloxacin 400mg orally twice a day for 14 days AND Metronidazole 400mg twice a day for 14 days
*Ceftriaxone 250mg IM in a single dose PLUS Azithromycin 1g/week for 2 weeks
#Moxifloxacin 400mg orally once a day for 14 days

**Clinical trial evidence is limited.*
#Three large RCTs support its efficacy but because of evidence of an increased risk of liver reactions and other serious risks (such as QT interval prolongation), this should be used only when it is considered inappropriate to use the other antibacterial agents recommended for PID or when these have failed.

Inpatient antibiotic treatment should be based on intravenous therapy (Table 4) and should be continued until 24 hours after clinical improvement, followed by oral therapy[7,8]. Admission to hospitals should be considered in situations listed in Table 5. Doxycycline should be administered orally when possible due to the pain associated with intravenous infusion, and both routes of administration provide similar bioavailability. The CDC recommends the use of cefotetan or cefoxitin for the treatment of PID but these agents are not easily available in Hong Kong. Therefore ceftriaxone, which has a similar spectrum of activity, is recommended. Alternatively, another third generation cephalosporin (e.g. ceftizoxime, cefotaxime) can also be used.

The CDC 2010 guidelines suggested optional addition of metronidazole for the treatment of PID. However, it indicates that anaerobes constitute a significant proportion of bacteria isolated in patients with PID and *in vitro* studies have identified that some anaerobes (e.g., *Bacteroides fragilis*) can cause tubal and epithelial damage. Therefore, in clinically severe diseases particularly in the presence of a tubo-ovarian abscess, proven or suspected infection with *Trichomonas vaginalis* or bacterial vaginosis, and recent history of uterine instrumentation, anaerobic cover should be considered.

Table 4: Inpatient antibiotic treatment

Ceftriaxone (Rocephin) 2g IV every 24 hours PLUS Doxycycline 100mg orally or IV every 12 hours FOLLOWED BY • Doxycycline 100mg orally twice a day AND Metronidazole 400mg orally twice a day to complete 14 days
Clindamycin 900mg IV every 8 hours PLUS *Gentamycin 2mg/kg loading dose followed by 1.5mg/kg every 8 hours (a single daily dose of 7mg/kg may be substituted) FOLLOWED BY • Doxycycline 100mg orally twice a day PLUS Metronidazole 400mg orally twice a day to complete 14 days OR • Clindamycin 450mg four times a day to complete 14 days
#Ofloxacin 400mg IV every 12 hours PLUS Metronidazole 500mg IV every 8 hours for 14 days
#Ciprofloxacin 200mg IV every 12 hours PLUS Doxycycline 100mg orally or IV every 12 hours PLUS Metronidazole 500mg IV every 8 hours for 14 days

**Gentamicin levels need to be monitored.*
#Clinical trial evidence is limited.

Table 5: Criteria for admission to hospitals

Surgical emergencies (e.g. appendicitis) cannot be excluded
Clinically severe disease (e.g. with nausea and vomiting or high fever)
Tubo-ovarian abscess
PID in pregnancy
Lack of response to oral therapy
Intolerance to oral therapy

75% of women with tubo-ovarian abscess will respond to antibiotic therapy alone. However, some will fail to respond and require surgical drainage[9]. The criteria for surgical drainage include failure to respond to antibiotic treatment within 48 to 72 hours as characterised by persistent fever, an increasing size of tubo-ovarian abscess and a persistent or increasing leukocytosis. Drainage of the tubo-ovarian abscess can be performed by laparoscopy, laparotomy or image guided percutaneous routes.

Due to the emergence of quinolone-resistant *N. gonorrhoeae* (QRNG), regimens that comprise of a quinolone agent are no longer recommended for the treatment of PID. In 2007-2008 the Gonococcal Antimicrobial Surveillance Programmes conducted by the World Health Organization in the Western Pacific and South East Asian Regions reported QRNG isolates in nearly 100% of isolates examined in Hong Kong and the Mainland China[10]. Recently, there are concerns expressed regarding the decreasing *in vitro* susceptibility of *N. gonorrhoeae* which was accompanied by clinical treatment failures with orally administered third-generation cephalosporins. Therefore, parenteral cephalosporin should be included in the treatment of gonococcal infections and PID in Hong Kong. If parenteral cephalosporin is not feasible (e.g. women with history of severe penicillin allergy), use of fluoroquinolones (levofloxaxin or ofloxaxin) with or without metronidazole can be considered if the community prevelance of gonorrhoea is <5%

or if the individual risk for gonorrhoea is low (e.g. in postmenopausal women who develop PID after uterine instrumentation). Alternatively, the addition of azithromycin 2g orally as a single dose to a quinolone-based PID regimen is recommended[11].

Patients should be advised to abstain from sexual intercourse until therapy is completed. Sex partners of women with PID caused by *C. trachomatis* and *N. gonorrhoeae* are often asymptomatic, and therefore should be screened and treated. Empirical treatment should be considered in their sex partners, regardless of the aetiology of PID or pathogens isolated from the infected woman, especially if adequate screening is not possible. In addition, referral of the sexual partners to a Social Hygiene Clinic can facilitate contact tracing and infection screening.

Special Considerations

Pregnancy

PID is rare in women with intrauterine pregnancy, except in cases of septic abortion. A pregnancy test should be done in all women suspected of having PID to exclude an ectopic pregnancy. There is no consensus on the optimal antibiotic regimen but treatment should cover the above mentioned organisms.

HIV Infection

HIV infected women with PID have similar symptoms to those women without HIV infection, except they were more likely to have tubo-ovarian abscess[12,13]. They respond equally well to the standard parenteral and oral antibiotic regimens.

Intrauterine Contraceptive Devices (IUCD)

The WHO expert Working Group on recommendations for contraceptive use concluded that removing the IUCD provides no additional benefit once PID is being treated with appropriate antibiotics[14]. Indeed, if a woman wants it to be removed, this should be done only after antibiotics have been started. However, removal should be considered if there is no clinical improvement or indeed deterioration despite antibiotic therapy.

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