ICOG FOGSI Recommendations for Good Clinical Practice

Management of Acute Pelvic Inflammatory Disease

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1. Introduction

Acute Pelvic Inflammatory Disease (PID) is a common cause of morbidity in women of reproductive age group (15-45 yrs). PID is usually the result of infection ascending from the endocervix causing endometritis, salpingitis, parametritis, oophoritis, tubo-ovarian abscess and / or pelvic peritonitis.[1] It has a poly-microbial etiology. These recommendations apply to women requiring treatment for confirmed or suspected acute PID being treated in an outpatient or inpatient setting by primary and secondary care practitioners.

2. Transmission

In women aged less than 25 years, PID is usually caused by sexually transmitted infections (STIs) like gonorrhoea and / or chlamydia plus anaerobic genital flora[1-6]. PID may occur occasionally by ascending spread of genital commensals including gram negative organisms, often following spontaneous or induced abortions, delivery, gynaecological procedures or surgeries etc. Causative organisms also include Gardnerella vaginalis, peptostreptococcus, bacteroides, ureaplasma, mycoplasma species etc. The predominant aerobes (found in the Pouch of Douglas aspirate in a study on Indian women with acute PID) include Escherichia coli, Coagulase Negative Staphylococcus (CONS), Staphylococcus and Klebsiella pneumonia.[7] Sexually active women in their childbearing years are most at risk, and those under age 25 years are more likely to develop PID, because the cervix of adolescent girls and young women is immature, increasing its susceptibility to the STIs that are linked to PID. Multiple sexual partners, having a partner who has multiple partners put the women at a higher risk of acquiring PID. Women who douche have a higher risk as douching changes the vaginal flora and can force bacteria into the upper reproductive organs from the vagina. Women who have IUD inserted may have a slightly increased risk of PID immediately post-insertion. Poor housing facilities and lack of sanitation may lead to poor menstrual hygiene in turn leading to PID.

3. Diagnosis

3.1 Symptoms and Signs

B Because of the lack of definitive clinical diagnostic criteria, a low threshold for empirical treatment of PID is recommended. Where there is diagnostic doubt or in clinically severe cases, admission to hospital for treatment and further investigations is advisable.

PID may cause a range of signs and symptoms from mild lower abdominal pain, leucorrhoea, dyspareunia, dysuria to even an acute abdomen. Symptoms may remain mild (particularly with chlamydia) or may become more severe over time. The diagnosis of PID is a clinical one[8]. It should always be considered when diagnosing chlamydial and / or gonococcal cervical infection.

Minimum criteria for the diagnosis of Acute PID are:

Lower abdominal pain and tenderness, pain elicited on moving the cervix, adnexal tenderness / mass where other causes (especially ectopic pregnancy) have been excluded.

Other additional criteria may be present but their absence does not exclude PID.

These additional criteria[1] include

Dyspareunia, abnormal vaginal or cervical discharge, positive chlamydia or gonorrhoea test result, change in menstrual bleeding pattern or abnormal bleeding in hormonal contraception use, fever (> 38°C), white blood cells on vaginal wet preparation[9,10], elevated ESR, elevated c-reactive proteins[5], lab documentation of cervical infection with N. gonorrhoea or chlamydia, USG findings of adnexal masses and free fluid in PID[11,12]; histopathology evidence of endometritis on endometrial biopsy; laparoscopic abnormalities consistent with PID.

3.2 Microbiological evaluation

Women with suspected PID should be screened for gonorrhoea and chlamydia.

Evidence of more than 10 WBCs / HPF on microscopic evaluation of a saline preparation of vaginal secretions is easy, cost-effective and favours a diagnosis of PID strongly. Endocervical swabs should be sent for microscopy, culture and sensitivity. Testing for gonorrhoea should be done with an endocervical specimen and tested via culture (direct inoculation on to a culture plate or transport of the swab to the laboratory within 24 hrs) or using a nucleic acid amplification test (NAAT). Screening for chlamydia should also be from the endocervix, preferably using a NAAT (e.g. PCR, strand displacement amplification). Taking an additional sample from the urethra increases the diagnostic yield for gonorrhoea and chlamydia. High vaginal swab also can be sent for culture. If a speculum examination cannot be done then self collected first catch urine or low vaginal swab for PCR testing and wet preparation can be sent. Diagnosis of PID remains a clinical one on the basis of signs elicited on bimanual pelvic examination, regardless of swab results. **Also, it should be noted that screening for gonorrhoea and chlamydia may not be feasible and economical in Indian setting.**

It is important to rule out presence of intra or extra uterine pregnancy or retained products of conception in women of child bearing age presenting with lower abdominal pain. In certain cases acute appendicitis should be ruled out. Laparoscopy enables specimens to be taken from the fallopian tubes and the pouch of Douglas and can provide information on the severity of the condition.[13,14] Although it has been considered the gold standard in many studies of treatment regimens, 15-30% of suspected cases may have no laparoscopic evidence of acute infection despite organisms being isolated from the fallopian tubes, thus giving rise to false-negative results.[15] When there is diagnostic doubt, however, laparoscopy may be useful to exclude alternative pathologies.[5,15] The differential diagnosis of lower abdominal pain in a young woman includes ectopic pregnancy, acute appendicitis, endometriosis, irritable bowel syndrome, rupture/torsion of an ovarian cyst, urinary tract infection, functional pain.

4. Treatment for Acute PID

4.1 The aims of treatment are relief of acute symptoms and prevention of long term sequelae like infertility, ectopic pregnancy, chronic pelvic pain and spontaneous abortions. Fertility is enhanced if the patients are treated within 48 hrs of onset of symptoms. Treatment should be initiated if the minimum criteria are met and no other causes are identified. The diagnosis is enhanced by the additional criteria, but their absence does not exclude PID. Hospital admission is recommended for all patients except those with mild disease.

4.2 Outpatient treatment

Ⓐ Outpatient antibiotic treatment should be commenced as soon as the diagnosis is suspected. In mild or moderate PID (in the absence of a tubo-ovarian abscess), there is no difference in outcome when patients are treated as outpatients or admitted to hospital[16]. It is likely that delaying treatment, especially in chlamydial infections, increases the severity of the condition and the risk of long-term sequelae such as ectopic pregnancy, subfertility and pelvic pain.[5,17,18]

PID treatment regimens must provide empiric, broad spectrum coverage of likely pathogens. Several anti microbial regimens have been effective in achieving clinical and microbiologic cure. All treatment regimens should be effective against N. Gonorrhoea and C. trachomatis because negative endocervical screening for these organisms does not rule out upper reproductive tract infection.

Ⓑ Outpatient antibiotic treatment should be based on one of the following regimens:[1,8]

Recommended Regimen A

- Oral Ofloxacin 400 mg twice a day plus oral Metronidazole 400mg twice a day for 14 days.
- Oral Levofloxacin 500 mg once daily with oral Metronidazole 400mg twice daily for 14 days is also a good alternative as it has better compliance than twice daily dosage of Ofloxacin.

Recently, however, there has been a concern about the increasing reports of fluoroquinolone resistance in Neisseria gonorrhoea.[19] Ofloxacin should be avoided in patients who are at high risk of gonococcal PID (e.g. avoid when the patient's partner has gonorrhoea [or is from a high prevalence area] or the patient has clinically severe disease).[19,20]

The addition of a cephalosporin (e.g. ceftriaxone 250mg i.m. single dose or Cefixime 400 mg orally in a single dose) should be considered, if gonococcal PID is suspected.[1,19,20] Alternatively, Spectinomycin 2 gm intramuscularly in a single dose can be given.[19]

Regimen B

- IM Ceftriaxone 250mg single dose or IM Cefoxitin 2gm single dose with oral probenecid 1 gm followed by oral doxycycline 100mg twice a day plus Metronidazole 400mg twice a day for 14 days.

Although the combination of oral doxycycline and metronidazole is in common use, there are no clinical trials assessing its effectiveness.[21] There is insufficient evidence for including Azithromycin 1 gm orally as one stat dose in the treatment of PID but this is a common medication prescribed. Other regimens include amoxycillin + clavulinic acid 2-3g/day along with doxycycline 200mg/day or ofloxacin 400mg/day. [22]

A randomized, un-blinded study on the frequently used short-course antibiotic therapy for acute PID suggested that ciprofloxacin (500mg) + tinidazole (600mg) twice daily for 7 days showed slightly higher cure rates and resolution of inflammatory mass than the single doses of azithromycin(1g)-secnidazole(2g)-fluconazole(150mg).[23]

- **Concomitant vaginal discharge should be treated by suitable local medications.** The patient should be re-evaluated after 48-72 hrs to determine response to the outpatient treatment. Antibiotics should be revised according to clinical response and microbiological results.
- **Patients should be provided with a detailed explanation of their condition, with particular emphasis on the long-term implications on the health of themselves and their partner(s), reinforced with clear and accurate written information.**

4.3 Inpatient treatment

Criteria for hospitalization in women with PID[24]

- Inability to exclude surgical emergency (e.g. appendicitis)
- Presence of tubo-ovarian abscess
- PID in pregnancy
- Clinically severe disease
- Failure to respond to outpatient oral therapy
- Intolerance to oral therapy (e.g. severe nausea / vomiting)

In more severe cases inpatient antibiotic treatment should be based on intravenous therapy which should be continued until 24 hours after clinical improvement and followed by oral therapy. Duration of treatment depends on the severity of disease and the response to the therapy. It should continue until symptoms and cervical tenderness have resolved, and for a minimum of 14 days. Laparoscopy is indicated if the diagnosis is doubtful or if rapid resolution of symptoms does not occur.

Ⓑ Recommended Regimens[8,24] are:

Parenteral Regimen A

Cefotetan 2gm IV 12 hrly

Or

Cefoxitin 2gm IV 6 hrly

Or

Ceftriaxone 2gm IV infusion daily[1]

+

Doxycycline 100mg oral / IV every 12hrly for 48hrs followed by oral Doxycycline 100mg twice a day plus oral metronidazole 400 mg twice a day for 14 days.

The clinical trial data support the use of cefoxitin for the treatment of PID but this agent is not easily available. So ceftriaxone, which has a similar spectrum of activity, is recommended.[1] An alternative third-generation cephalosporin would also be acceptable.[1]

Parenteral Regimen B

Clindamycin 900 mg IV 8 hrly

+

Gentamicin IV / IM (2mg/kg load; then 1.5mg/kg 8 hrly) for 48 hrs followed by T.Doxycycline 100 mg BD plus oral metronidazole 400 mg BD for 14 days.

Or

T. Clindamycin 450mg QID for 14 days

If parenteral gentamicin is used, then serum drug levels and renal function should be monitored.

The combination of Inj. Ampicillin 500mg IV 6 hrly + Inj. Gentamicin 1.5mg/kg IV/IM 8 hrly + Inj. Metronidazole 500mg IV 8 hrly is sometimes used in India, but hardly any scientific evidence exists.

Alternative regimens recommended are:

IV ofloxacin 400 mg twice daily plus intravenous metronidazole 500 mg three times daily for 14 days[1].

IV ciprofloxacin 200mg twice daily plus IV (or oral) doxycycline 100mg twice daily plus i.v.metronidazole 500mg three times daily.[20]

When selecting a treatment regimen, local antimicrobial sensitivity patterns, availability of drugs, their cost and patient acceptance should be considered.

4.4. Treatment in pregnancy

A pregnancy test should be performed in all women suspected of having PID to help exclude an ectopic pregnancy. In an ongoing intrauterine pregnancy, PID is extremely rare, except in the case of septic abortion. Cervicitis may occur, however, and is associated with increased maternal and fetal morbidity including pre-term delivery. Treatment regimens will be dependent upon the organisms isolated. Drugs known to be toxic in pregnancy should be avoided e.g.- Tetracyclines.[1] Erythromycin and amoxycillin are not known to be harmful in pregnancy. A combination of cefotaxime, azithromycin and metronidazole for 14 days may be used. The risks associated with metronidazole are uncertain but no confirmed associations with adverse outcomes have been reported.

4.5. Treatment in children

Acute PID is rarely seen in very young girls. Clinicians should be aware that the safety of quinolones has not been established for children <18 years of age.[8] In girls over the age of 12 years, Doxycycline can be safely used.[1]

4.6. Treatment in a woman with an intrauterine contraceptive device

Ⓑ An intrauterine contraceptive device (IUCD) may be left in-situ in women with clinically mild PID but should be removed in cases of severe disease and, especially, if symptoms have not resolved within 72 hours.

4.7. Treatment in a woman with HIV

Women with PID who are also infected with HIV should be treated with the same antibiotic regimens as women who are HIV negative. Potential interactions between antibiotics and anti-retroviral medication needs to be considered on an individual basis. Low CD4 count is an indication for hospitalization.

5. *Management of sexual partners of women with PID, which may be sexually acquired*

Ⓑ Current sexual partners of women with PID should be contacted and offered health advice and screening for gonorrhoea and chlamydia.

If adequate screening is not possible, empirical therapy for both gonorrhoea and chlamydia should be given to the partner. [1,8,25]

6. *Other modes of treatment*

Ⓑ Surgical treatment should be considered in severe cases or where there is clear evidence of a pelvic abscess.

Laparotomy / Laparoscopy may help early resolution of the disease by division of adhesions and drainage of pelvic abscesses.[26,27] Ultrasound-guided aspiration of pelvic fluid collections is less invasive and may be equally effective.[27,28] It is also possible to perform adhesiolysis in cases of peri-hepatitis due to chlamydia although there is no evidence as to whether this is superior to antibiotic therapy alone.

7. *Follow up of patients with PID*

In the outpatient setting, review at 72 hours is recommended[1,24], particularly for those with a moderate or severe clinical presentation.

Failure to improve suggests the need for further investigations, parenteral therapy and / or surgical intervention.

Further review four weeks after therapy may be useful to ensure:

- Adequate clinical response to treatment
- Compliance with oral antibiotics
- Screening and treatment of sexual contacts
- Awareness of the significance of PID and its sequelae.

If PCR is used as a test of cure, it should not be repeated before 3 weeks as persistent gonococcal and chlamydial DNA may lead to false positive results. If microscopy and culture are used as a test of cure, specimens should be taken at least 72 hrs after completion of treatment.

A full screen for all STDs including Hepatitis B & HIV should be offered for persistent infections.

8. *Counseling issues*

1. Importance of compliance with medication and completing the full course of treatment.
2. Regular follow-up in case of persistent symptoms.
3. Treatment of the partner is essential.
4. Avoid sexual intercourse until both patient and partner are fully treated.
5. Encouraged to use barrier contraceptives or dual protection.
6. Regular PAP smear as women with STI are also prone for HPV infection leading to CIN and cervical cancer.

9. Preventive Measures

- Reproductive Health Education to be given to young girls.
- Importance of menstrual hygiene to be reinforced.
- Safe sexual practices to be advocated.
- Pamphlets / Brochures regarding PID.
- Awareness programmes through mass media.

Grades of recommendations

A Requires at least one randomized controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation.

B Requires the availability of well controlled clinical studies but no randomized clinical trials on the topic of recommendations.

C Requires evidence obtained from expert committee reports or opinions and / or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality.

Good Practice point

4 Recommended best practice based on the clinical experience of the guideline development group.

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