

2001 Guidelines for the Management of Pelvic Infection and Perihepatitis

Clinical Effectiveness Group (Association for Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases)

Aetiology

- Pelvic inflammatory disease (PID) is usually the result of infection ascending from the endocervix causing endometritis, salpingitis, parametritis, oophoritis, tuboovarian abscess and/or pelvic peritonitis.
- *Neisseria gonorrhoeae* and *Chlamydia trachomatis* have been identified as causative agents^{1,2}, whilst *Gardnerella vaginalis*, anaerobes and other organisms commonly found in the vagina may also be implicated.

Clinical Features

Symptoms

The following features are suggestive of a diagnosis of PID¹⁻⁵:

- lower abdominal pain
- dyspareunia
- abnormal bleeding
- abnormal vaginal or cervical discharge

Signs

- lower abdominal tenderness
- adnexal tenderness on bimanual vaginal examination
- cervical motion tenderness on bimanual vaginal examination
- fever (>38°C)

Complications

- Women with HIV may have more severe symptoms associated with PID but respond well to antibiotic therapy⁶. Parenteral regimens are recommended. (Grade B [III])
- The Fitz-Hugh-Curtis syndrome comprises right upper quadrant pain associated with perihepatitis which occurs in up to 10-20% of women with PID. Although laparoscopic division of hepatic adhesions has been performed, there is insufficient clinical trial evidence to make specific recommendations for treatment beyond those for PID.
- Women with an intrauterine contraceptive device in situ, who have clinically severe PID, may require it removed (Grade C [IV]). Two retrospective studies^{7,8} and a small prospective clinical trial⁹ have however shown no difference in short term outcomes following removal of the intrauterine contraceptive device in women with PID.

Diagnosis

- PID may be symptomatic or asymptomatic. Even when present, clinical symptoms and signs lack sensitivity and specificity (the positive predictive value of a clinical diagnosis is 65-90% compared to laparoscopic diagnosis)^{1,3,4}.
- Testing for gonorrhoea and chlamydia in the lower genital tract is recommended since a positive result supports the diagnosis of PID. The absence of infection at this site does not exclude PID however^{1,3-5}.
- An elevated ESR or C reactive protein also supports the diagnosis¹⁰.
- Laparoscopy may strongly support a diagnosis of PID but is not justified routinely on the basis of cost and the potential difficulty in identifying mild intra-tubal inflammation or endometritis^{1,3,4}.

- Endometrial biopsy and ultrasound scanning may also be helpful when there is diagnostic difficulty but there is insufficient evidence to support their routine use at present.

The differential diagnosis of lower abdominal pain in a young woman includes:

- ectopic pregnancy
- acute appendicitis
- endometriosis
- complications of an ovarian cyst
- functional pain

Management

It is likely that delaying treatment increases the risk of long term sequelae such as ectopic pregnancy, infertility and pelvic pain^{3,5}. Because of this, and the lack of definitive diagnostic criteria, a low threshold for empiric treatment of PID is recommended. Broad spectrum antibiotic therapy is required to cover *N. gonorrhoeae*, *C. trachomatis* and anaerobic infection¹⁻³.

The recommendation to cover *N. gonorrhoeae* in patients presenting with suspected PID in the UK is based on the following:

- much of the evidence supporting the use of antibiotics active against *N. gonorrhoeae* is from the United States. Although anecdotally *N. gonorrhoeae* is a less common cause of PID in the UK, the only recent British study found gonococcal infection in 14% of PID patients¹. The absence of endocervical gonorrhoea does not exclude gonococcal PID.

- most published studies relate to patients presenting with acute PID in a gynaecological setting. PID presenting in other areas, such as primary care and genitourinary medicine clinics, may be less clinically severe, but again there is no published evidence to support the use of less intensive regimens.
- the need for the guidelines to be evidence based. At present there are no large controlled trials from the UK which support the use of regimens which do not cover *N. gonorrhoeae*.
- the increasing incidence of gonorrhoea in the UK¹¹

The agents suggested in the guidelines as cover for *N. gonorrhoeae* are based on the published evidence. Other oral antibiotics, such as ciprofloxacin, have not at present been evaluated as extensively in combination regimens.

Evidence of long term effectiveness in preventing the complications of PID is currently lacking. A small study reported infertility in 43% (6/14) patients treated with doxycycline and metronidazole¹². There are comparatively fewer data on oral than parenteral regimens.

The choice of an appropriate treatment regimen may be influenced by:

- robust evidence on local antimicrobial sensitivity patterns
- robust evidence on the local epidemiology of specific infections in this setting
- cost
- patient preference and compliance
- severity of disease

General Advice

- Rest is advised for those with severe disease. (Grade C [IV])
- If there is a possibility that the patient could be pregnant, a pregnancy test should be performed. (Grade C [IV])
- Appropriate analgesia should be provided. (Grade C [IV])
- Intravenous therapy is recommended for patients with more severe clinical disease (Grade C [IV])
- Patients should be advised to avoid unprotected intercourse until they, and their partner(s), have completed treatment and follow-up (Grade C [IV]).
- A detailed explanation of their condition with particular emphasis on the long term implications for the health of themselves and their partner(s) should be provided, reinforced with clear and accurate written information (Grade C [IV]).

Admission for parenteral therapy, observation, further investigation and/or possible surgical intervention should be considered in the following situations³:

- diagnostic uncertainty
- clinical failure with oral therapy
- severe symptoms or signs
- presence of a tuboovarian abscess
- immunodeficiency
- inability to tolerate an oral regimen

Further Investigation

All patients should be offered screening for sexually transmitted infections.

Treatment

The following antibiotic regimens are evidence based.

Intravenous therapy should be continued until 24 hours after clinical improvement and then switched to oral.

Recommended Regimens

- i.v. cefoxitin 2g TID **plus** i.v. doxycycline 100mg BD (oral doxycycline may be used if tolerated)

followed by

oral doxycycline 100mg BD **plus** oral metronidazole 400mg BD for a total of 14 days

Grade B (III)^{3,13-16}

- i.v. clindamycin 900mg TID **plus** i.v. gentamicin (2mg/kg loading dose followed by 1.5mg/kg TID [a single daily dose may be substituted])

followed by either

oral clindamycin 450mg QID

oral doxycycline 100mg BD

to complete 14 days

plus oral metronidazole 400mg BD

to complete 14 days

Grade B (III)^{3,13,15,16}

- oral ofloxacin 400mg BD **plus** oral metronidazole 400mg BD for 14 days

Grade B (III)^{3,14,16-18}

- i.m. ceftriaxone 250mg stat. *or* i.m. cefoxitin 2g stat. with oral probenecid 1g

followed by

oral doxycycline 100mg BD *plus* metronidazole 400mg BD for 14 days

Grade B (III)^{3,13-16}

Alternative Regimens

- i.v. ofloxacin 400mg BD *plus* i.v. metronidazole 500mg TID

Grade B (III)^{3,14,16-18}

- i.v. ciprofloxacin 200mg BD *plus* i.v. (or oral) doxycycline 100mg BD *plus* i.v. metronidazole 500mg TID

Grade B (III)^{3,16,19}

Allergy

There is no evidence of the superiority of any one of the suggested regimens over the others.

Therefore patients known to be allergic to one of the suggested regimens should be treated with an alternative.

Pregnancy and Breastfeeding

- In pregnancy PID is associated with an increase in both maternal and fetal morbidity, therefore parenteral therapy is advised although none of the suggested evidence based regimens are of proven safety in this situation.
- There is insufficient data from clinical trials to recommend a specific regimen and empirical therapy with agents effective against gonorrhoea, chlamydia and anaerobic infections should be considered taking into account local antibiotic sensitivity patterns (e.g. i.v.

cefoxitin 2g TID plus i.v. erythromycin 50mg/kg continuous infusion, with the possible addition of i.v. metronidazole 500mg TID) (Grade C [IV]).

Sexual Partners

- Current male partners of women with PID should be contacted and offered health advice and screening for gonorrhoea and chlamydia. Other recent sexual partners may also be offered screening - tracing of contacts within a 6 month period of onset of symptoms is recommended (Grade C [IV]) but this time period may be influenced by the sexual history.
- Partners should be advised to avoid intercourse until they and their partner have completed the treatment course.
- Gonorrhoea diagnosed in the male partner should be treated appropriately and concurrently with the index patient. (Grade C [IV])
- Concurrent empirical treatment for chlamydia is recommended for all sexual contacts due to the variable sensitivity of currently available diagnostic tests. (Grade C [IV])
- If adequate screening for gonorrhoea and chlamydia in the sexual partner(s) is not possible, empirical therapy for gonorrhoea and chlamydia should be given. (Grade C [IV])

Follow Up

Review at 72 hours is recommended³, particularly for those with a moderate or severe clinical presentation, and should show a substantial improvement in clinical symptoms and signs.

Failure to do so suggests the need for further investigation, parenteral therapy and/or surgical intervention.

Further review 4 weeks after therapy may be useful to ensure:

- adequate clinical response to treatment
- compliance with oral antibiotics
- screening and treatment of sexual contacts

Repeat testing for gonorrhoea after treatment is recommended in those initially found to be infected. Repeat testing for chlamydia may be appropriate in those in whom persisting symptoms, compliance with antibiotics and/or tracing of sexual contacts indicate the possibility of persisting or recurrent infection.

Auditable Outcome Measures

Little is known about the long term outcome, in relation to future fertility, ectopic pregnancy and chronic pelvic pain, following the treatment of PID. Appropriate short term audit outcomes include:

- proportion of women receiving treatment with a recommended regimen
- proportion of named male contacts screened for infection and/or treated

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Conflict of Interest

No known conflict of interest.

Evidence Base

Five reference sources were used as the basis for the guidelines:

1. Medline Search

1987 – April 2000

The search strategy comprised the following terms in the title or abstract: ‘pelvic inflammatory disease’, ‘adnexitis’, ‘oophoritis’, ‘parametritis’, ‘salpingitis’ or ‘adnexal disease’. 2610 citations were identified.

1963 - 1986

The search strategy comprised the following terms in the title or abstract: ‘pelvic inflammatory disease’, ‘adnexitis’, ‘oophoritis’, ‘parametritis’, ‘salpingitis’ or ‘adnexal disease’. The dataset was then limited to AIM journals and human subjects, identifying 349 citations.

2. 1998 CDC STD Treatment Guidelines

3. 1997 Netherlands STD Management Guidelines

4. Royal College of Obstetrics and Gynaecology Working Group on PID Report 1996

5. Cochrane Collaboration

a) Cochrane database of systematic reviews

No directly relevant reviews were identified.

b) Cochrane controlled trials register

Using a search strategy of 'pelvic inflammatory disease', 'adnexitis', 'oophoritis', 'parametritis', 'salpingitis' or 'adnexal disease', 312 citations were identified.

References

1. Bevan CD, Johal BJ, Mumtaz G, Ridgway GL, Siddle NC. Clinical, laparoscopic and microbiological findings in acute salpingitis: report on a United Kingdom cohort. *British Journal of Obstetrics & Gynaecology* 1995; 102:407-414.
2. Anonymous. Recommendations arising from the 31st Study Group: The Prevention of Pelvic Infection. In: Templeton A, editor. *The Prevention of Pelvic Infection*. London: RCOG Press, 1996:267-270.
3. Centers for Disease Control. 1998 Guidelines for Treatment of Sexually Transmitted Diseases. 1998; <http://www.cdc.gov/epo/mmwr/preview/mmwrhtml/00050909.htm>.
4. Morcos R, Frost N, Hnat M, Petrunak A, Caldito G. Laparoscopic versus clinical diagnosis of acute pelvic inflammatory disease. *Journal of Reproductive Medicine* 1993; 38:53-56.
5. Netherlands Association for Dermatology and Venereology. 1997 STD Diagnosis and Therapy Guidelines. 1997;
6. Kamenga MC, De Cock KM, St.Louis ME, Toure CK, Zakaria S, N'gbichi JM, et al. The impact of human immunodeficiency virus infection on pelvic inflammatory disease: a case-control study in Abidjan, Ivory Coast. *Am.J.Obstet.Gynecol.* 1995; 172:919-925.
7. Teisala K. Removal of an intrauterine device and the treatment of acute pelvic inflammatory disease. *Annals of Medicine* 1989; 21:63-65.
8. Larsson B, Wennergren M. Investigation of a copper-intrauterine device (Cu-IUD) for possible effect on frequency and healing of pelvic inflammatory disease. *Contraception* 1977; 15:143-149.
9. Soderberg G, Lindgren S. Influence of an intrauterine device on the course of an acute salpingitis. *Contraception* 1981; 24:137-143.

10. Miettinen AK, Heinonen PK, Laippala P, Paavonen J. Test performance of erythrocyte sedimentation rate and C- reactive protein in assessing the severity of acute pelvic inflammatory disease. *Am.J.Obstet.Gynecol.* 1993; 169:1143-1149.
11. Anonymous. Gonorrhoea incidence in England rises again. *Communicable Disease Report Weekly* 2000; 10:107-107.
12. Brunham RC, Binns B, Guijon F, Danforth D, Kosseim ML, Rand F, et al. Etiology and outcome of acute pelvic inflammatory disease. *Journal of Infectious Diseases* 1988; 158:510-517.
13. Hemsell DL, Little BB, Faro S, Sweet RL, Ledger WJ, Berkeley AS, et al. Comparison of three regimens recommended by the Centers for Disease Control and Prevention for the treatment of women hospitalized with acute pelvic inflammatory disease. *Clin.Infect.Dis.* 1994; 19:720-727.
14. Martens MG, Gordon S, Yarborough DR, Faro S, Binder D, Berkeley A. Multicenter randomized trial of ofloxacin versus cefoxitin and doxycycline in outpatient treatment of pelvic inflammatory disease. Ambulatory PID Research Group. *Southern Medical Journal* 1993; 86:604-610.
15. Anonymous. Comparative evaluation of clindamycin/gentamicin and cefoxitin/doxycycline for treatment of pelvic inflammatory disease: a multi-center trial. The European Study Group. *Acta Obstetricia et Gynecologica Scandinavica* 1992; 71:129-134.
16. Walker CK, Kahn JG, Washington AE, Peterson HB, Sweet RL. Pelvic inflammatory disease: metaanalysis of antimicrobial regimen efficacy. *Journal of Infectious Diseases* 1993; 168:969-978.
17. Wendel GD, Jr., Cox SM, Bawdon RE, Theriot SK, Heard MC, Nobles BJ. A randomized trial of ofloxacin versus cefoxitin and doxycycline in the outpatient treatment of acute salpingitis. *Am.J.Obstet.Gynecol.* 1991; 164:1390-1396.

18. Witte EH, Peters AA, Smit IB, van der Linden MC, Mouton RP, van der Mee, et al. A comparison of pefloxacin/metronidazole and doxycycline/metronidazole in the treatment of laparoscopically confirmed acute pelvic inflammatory disease. *European Journal of Obstetrics, Gynecology, & Reproductive Biology* 1993; 50:153-158.
19. Heinonen PK, Teisala K, Miettinen A, Aine R, Punnonen R, Gronroos P. A comparison of ciprofloxacin with doxycycline plus metronidazole in the treatment of acute pelvic inflammatory disease. *Scandinavian Journal of Infectious Diseases - Supplementum* 1989; 60:66-73.