MANAGEMENT OF ACUTE PELVIC INFLAMMATORY DISEASE

This is the second edition of this guideline, which was previously published in 2003 under the same title.

1. Purpose and scope

Pelvic inflammatory disease (PID) is usually the result of infection ascending from the endocervix causing endometritis, salpingitis, parametritis, oophoritis, tubo-ovarian abscess and/or pelvic peritonitis. While sexually transmitted infections (STIs) such as Chlamydia trachomatis and Neisseria gonorrhoeae have been identified as causative agents, additional STIs including Mycoplasma genitalium, anaerobes and other organisms may also be implicated.1–5

PID is a common cause of morbidity and accounts for one in 60 general practitioner consultations by women under the age of 45 years.6 Delays of only a few days in receiving appropriate treatment markedly increase the risk of sequelae, which include infertility, ectopic pregnancy and chronic pelvic pain.7,8 Sequelae may also have significant healthcare costs.9 This guideline applies to women requiring treatment for confirmed or suspected acute PID being treated in an outpatient or inpatient setting by primary and secondary care practitioners.

There are marked variations in the antimicrobial regimens used in the treatment of PID, reflecting uncertainty in the optimal treatment schedule.10 The guideline contains recommendations for treatment and graded evidence to support their use.

2. Identification and assessment of evidence

A Medline search was performed covering 1963 to August 2007 looking for the following terms in the title or abstract: ‘pelvic inflammatory disease’, ‘adnexitis’, ‘oophoritis’, ‘parametritis’, ‘salpingitis’ or ‘adnexal disease’ (the dataset for 1963–86 was limited to Argonne Information Management journals and human subjects); 7211 citations were identified. A search of the Cochrane database revealed no directly relevant systematic reviews. A search of the Cochrane controlled trials register using a search strategy of ‘pelvic inflammatory disease’, ‘adnexitis’, ‘oophoritis’, ‘parametritis’, ‘salpingitis’ or ‘adnexal disease’ identified 356 citations. The following guidelines and reports were also reviewed: 2006 US Centers for Disease Control STD treatment guidelines,11 Royal College of Obstetrics and Gynaecology Study Group proceedings on PID 1996,12 2004 Health Technology Assessment report, The Clinical Effectiveness and Cost Effectiveness of Antibiotic Regimens for Pelvic Inflammatory Disease,13 2005 UK National Guidelines on Sexually Transmitted Diseases14 and 2007 European guidelines for the management of pelvic inflammatory disease.15

The recommendations given in this guideline have been graded according to the guidance for the development of RCOG Green-top Guidelines.
3. Making a diagnosis of acute PID

3.1 Clinical

A low threshold for empiric treatment of PID is recommended because of the lack of definitive clinical diagnostic criteria and because the potential consequences of not treating of PID are significant. In clinically severe cases, referral to hospital for treatment and further investigation is advisable.

The following clinical features are suggestive of a diagnosis of PID:

- bilateral lower abdominal tenderness (sometimes radiating to the legs)
- abnormal vaginal or cervical discharge
- fever (greater than 38°C)
- abnormal vaginal bleeding (intermenstrual, postcoital or ‘breakthrough’)
- deep dyspareunia
- cervical motion tenderness on bimanual vaginal examination
- adnexal tenderness on bimanual vaginal examination (with or without a palpable mass).

Clinical symptoms and signs lack sensitivity and specificity (the positive predictive value of a clinical diagnosis is 65–90% compared with laparoscopic diagnosis but laparoscopy may also lack sensitivity).15–18 The presence of excess leucocytes on a wet-mount vaginal smear is associated with PID19,20 but is also found in women with isolated lower genital tract infection.

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.2,21 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 identified from the fallopian tubes.2,16,17 When there is diagnostic doubt laparoscopy may, however, be useful to exclude alternative pathologies.2,17

Transvaginal ultrasound scanning may be helpful when there is diagnostic difficulty. When supported by power Doppler, it can identify inflamed and dilated tubes and tubo-ovarian masses. It may differentiate PID from acute appendicitis in a minority of cases but there is insufficient evidence to support its routine use.22,23 Computed tomography24 and magnetic resonance imaging25–27 can assist in making a diagnosis but the evidence is limited. A peripheral blood leucocytosis, elevated erythrocyte sedimentation rate or C-reactive protein also support the diagnosis and can provide a useful measure of disease severity28 but these are non-specific findings. There is insufficient evidence to support endometrial biopsy as a routine diagnostic test at present.29,30

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

- ectopic pregnancy
- acute appendicitis
- endometriosis
- irritable bowel syndrome (and, less commonly, other gastrointestinal disorders)
- complications of an ovarian cyst, such as rupture or torsion
- urinary tract infection
- functional pain (pain of unknown physical origin).
3.2 Microbiological

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

Although not a prerequisite to justify initial treatment decisions, testing for gonorrhoea and chlamydia in the lower genital tract is recommended. A positive result gives support to the clinical diagnosis of PID and reinforces the need to treat sexual partners. The absence of confirmed infection in the lower genital tract site does not exclude PID.\(^2,11,16\)

Testing for gonorrhoea should be with an endocervical specimen and tested via culture (direct inoculation on to a culture plate or transport of swab to laboratory within 24 hours) or using a nucleic acid amplification test (NAAT). If gonorrhoea is detected using a NAAT, an additional endocervical swab should be taken for gonococcal culture to allow the reporting of antibiotic sensitivities and revision of therapy if required (women at high risk of gonorrhoea should have an endocervical swab for gonococcal culture taken at their first examination; for example, where the woman’s partner has gonorrhoea, clinically severe disease, sexual contact abroad).

Testing for chlamydia should also be from the endocervix, preferably using a NAAT (such as polymerase chain reaction, strand displacement amplification).

Taking an additional sample from the urethra can increase the diagnostic yield for gonorrhoea and chlamydia but is only recommended if the more sensitive NAAT is not available. A first catch urine or self-taken vulvovaginal swab sample provides an alternative sample for some NAATs.\(^31\)

The absence of endocervical or vaginal pus cells on a wet-mount smear has a good negative predictive value (95%) for a diagnosis of PID but their presence is non-specific (poor positive predictive value (17%).\(^19,20,32\)

Other organisms, including \(M.\) genitalium,\(^4,33–35\) have been associated with PID but routine screening is not yet justified because of limited information on prevalence, natural history, treatment and cost effectiveness.\(^36\)

Further advice on the appropriate testing for STIs is available from the National Screening and Testing Guidelines for Sexually Transmitted Infections (www.bashh.org/guidelines).

4. Starting treatment

4.1 How should PID be managed in the outpatient setting?

Information on current and recent medication should be obtained.

Interactions between antibiotic therapy and hormonal contraception and other patient medications should be assessed and appropriate action taken.\(^48\)

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 women are treated as outpatients or admitted to hospital.\(^9\) It is likely that delaying treatment, especially in chlamydia infections, increases the severity of the condition and the risk of long-term sequelae such as ectopic pregnancy, subfertility and pelvic pain.\(^7,8\)
Outpatient antibiotic treatment should be based on one of the following regimens:

- oral ofloxacin 400 mg twice daily plus oral metronidazole 400 mg twice daily for 14 days.38–41
- intramuscular ceftriaxone 250 mg single dose,* followed by oral doxycycline 100 mg twice daily plus metronidazole 400 mg twice daily for 14 days.38,39,42–44

* Cefoxitin has a better evidence base for the treatment of PID than ceftriaxone but is not easily available in the UK. Ceftriaxone is therefore recommended.

Broad-spectrum antibiotic therapy is generally required to cover N. gonorrhoeae, C. trachomatis and anaerobic infection.1,2,11 Ofloxacin should be avoided in women who are at high risk of gonococcal PID because of increasing quinolone resistance in the UK. Those women at high risk of acquiring gonorrhoea include those whose partner has gonorrhoea, in clinically severe disease or if there is a history of sexual contact abroad.

Metronidazole may be discontinued in those women with mild or moderate PID who are unable to tolerate it, since its addition provides uncertain additional efficacy in this patient group.

Clinical trial evidence for the following regimen is less strong but it may be used as an alternative to the treatments above:
- intramuscular ceftriaxone 250 mg immediately, followed by azithromycin 1 g/week for 2 weeks.45,46

Although the combination of oral doxycycline and metronidazole (without ceftriaxone) has been used to treat PID in the UK, there are no clinical trials adequately assessing its effectiveness and its use in isolation is not recommended.10,39,47 Data supporting azithromycin monotherapy for PID is also limited at present and its use without the addition of ceftriaxone is not recommended.

There are currently no randomised controlled trial data to support the use of an oral (rather than parenteral) cephalosporin as part of the treatment regimen. Tissue levels of the antibiotic are likely to be lower following oral administration.

A detailed explanation of their condition should be provided to women, with particular emphasis on the long-term implications for their health and the health of their partner(s). This should be reinforced with clear and accurate written information.

When giving information to patients, the clinician should consider the following:

- an explanation of what treatment is being given and its possible adverse effects
- that following treatment fertility is usually maintained but there remains a risk of future infertility, chronic pelvic pain or ectopic pregnancy
- repeat episodes of PID are associated with an exponential increase in the risk of infertility
- future use of barrier contraception will significantly reduce the risk of PID
- the need to screen her sexual contacts for infection to prevent her becoming reinfected
- clinically more severe disease is associated with a greater risk of sequelae
- the earlier treatment is given the lower the risk of future fertility problems.


4.2 What hospital treatment should be given and when should it be recommended?

Admission to hospital would be appropriate in the following circumstances:11

Evidence level 1–
● surgical emergency cannot be excluded
● clinically severe disease
● tubo-ovarian abscess
● PID in pregnancy
● lack of response to oral therapy
● intolerance to oral therapy.

Inpatient antibiotic treatment should be based on intravenous therapy which should be continued until 24 hours after clinical improvement and followed by oral therapy.

Recommended regimens are:

● ceftriaxone 2 g by intravenous infusion daily plus intravenous doxycycline 100 mg twice daily,* followed by oral doxycycline 100 mg twice daily plus oral metronidazole 400 mg twice daily for a total of 14 days.13,35-37,44
   * Oral doxycycline may be used if tolerated.
● intravenous clindamycin 900 mg three times daily plus intravenous gentamicin,* followed by either
   ● oral clindamycin 450 mg four times daily to complete 14 days
   OR
   ● oral doxycycline 100 mg twice daily plus oral metronidazole 400 mg twice daily to complete 14 days.13,35-37,44
   * Gentamicin should be given as a 2 mg/kg loading dose followed by 1.5 mg/kg three times daily [or a single daily dose of 7 mg/kg may be substituted].
● intravenous ofloxacin 400 mg twice daily plus intravenous metronidazole 500 mg three times daily for 14 days.38,39,49

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

Intravenous doxycycline is available from IDIS World Medicines (+44 [0] 1932 824000). If parenteral gentamicin is used then serum drug levels and renal function should be monitored.

The choice of an appropriate treatment regimen will be influenced by robust evidence on local antimicrobial sensitivity patterns, robust evidence on the local epidemiology of specific infections, cost, the woman’s preference and compliance and severity of disease.

Evidence of the efficacy of antibiotic therapy in preventing the long-term complications of PID is currently limited.

4.3 Treatment in pregnancy and in young women

A pregnancy test should be performed in all women suspected of having PID to help exclude an ectopic pregnancy. When the risk of ectopic pregnancy is judged clinically to be high, the pregnancy test should be repeated 21 days after the date of last unprotected intercourse.

The risk of giving any of the recommended antibiotic regimens in very early pregnancy (before a positive pregnancy test) is low, since significant drug toxicity results in failed implantation (UK National Teratology Information Service).

PID is rare in women with an intrauterine pregnancy except in the case of septic abortion. In septic abortion, the infective organism is unlikely to be a sexually transmitted pathogen. Cervicitis may, however, occur in a pregnancy and is associated with increased maternal and fetal morbidity. Treatment regimens will be dependent upon the organisms isolated. Drugs known to be toxic in pregnancy, such as tetracyclines, should be avoided.
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.

Ofloxacin should be avoided, where possible, in young women, when bone development is still occurring. However, this recommendation is based on data from animal studies and no problems have been reported in human subjects, so the British National Formulary currently recommends that ofloxacin may be used in children where other options are limited. Doxycycline can be safely used in children over the age of 12 years.

A particularly low threshold for diagnosing and treating PID in women under the age of 25 years is appropriate, owing to the higher incidence of disease in this group and the potential impact on future fertility.

4.4 Treatment in a woman with an intrauterine contraceptive device

Consideration should be given to removing an intrauterine contraceptive device (IUD) in women presenting with PID, especially if symptoms have not resolved within 72 hours.

The randomised controlled trial evidence for whether an IUD should be left in place or removed in women presenting with PID is limited.\textsuperscript{50,51} Removal of the IUD should be considered and may be associated with better short-term clinical outcomes but the decision to remove it needs to be balanced against the risk of pregnancy in those who have had otherwise unprotected intercourse in the preceding 7 days. Hormonal emergency contraception may be appropriate for some women in this situation.

5. Other modes of treatment

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

Consider drainage of an abscess and in noting its position, the possibility that the abscess may have arisen from the appendix or colon.

Laparoscopy may help early resolution of the disease by division of adhesions and drainage of pelvic abscesses.\textsuperscript{52} Ultrasound-guided aspiration of pelvic fluid collections is less invasive and may be equally effective.\textsuperscript{53,54}

6. Management of sexual partner(s) of women with PID

When a sexually transmitted infection is either proven or likely to be the cause of PID, the current sexual partner(s) should be contacted and offered health advice and screening for gonorrhoea and chlamydia.

Other recent sexual partners may also be offered screening. Tracing of sexual partners within a 6-month period of the onset of symptoms is recommended but this time period may be influenced by the sexual history. The risk of detecting STIs in the partners of women with PID is high.\textsuperscript{2} Women should be advised to avoid intercourse until they and their partner have completed the treatment course. Gonorrhoea diagnosed in their sexual partner should be treated appropriately and concurrently with the index woman. Concurrent empirical treatment for chlamydia is recommended for all sexual partners, owing to the variable sensitivity of currently available diagnostic tests. If adequate screening for gonorrhoea and chlamydia in the sexual partner(s) is not possible, empirical therapy for both gonorrhoea and chlamydia should be given.\textsuperscript{55,56} Currently recommended regimens are available at www.bashh.org. Tracing of sexual partners is not required where a non-sexually transmitted pathogen has been clearly identified as the cause of infection.
Referral of the index woman and her partner to a genitourinary medicine/sexual health clinic is recommended to facilitate contact tracing and infection screening.

7. Review of women with PID

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

Failure to improve clinically suggests the need for further investigation, to exclude competing diagnoses, and may require admission for parenteral therapy and/or surgical intervention.

Further review 4–6 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
- that a repeat pregnancy test is negative, if clinically indicated.

Repeat testing for gonorrhoea after treatment is recommended in those initially found to be infected unless sensitivity testing of the isolate confirms sensitivity to the prescribed antibiotic.

Repeat testing for chlamydia and gonorrhoea is appropriate in those in whom persisting symptoms, compliance with antibiotics and/or tracing of sexual contacts indicate the possibility of persisting or recurrent infection.

A repeat chlamydia and gonorrhoea test is not otherwise required.

8. Women who are infected 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.

Women who are infected with HIV may have clinically more severe PID but respond equally well to treatment as women who are not infected. Standard antibiotic treatment as outlined above is therefore appropriate and hospital admission is only required for those with clinically severe disease. Potential interactions between antibiotics and antiretroviral medication need to be considered on an individual basis (information on drug interactions with antiretroviral drugs is available at www.hiv-druginteractions.org).

Women with HIV should be managed in conjunction with their HIV physician.

9. Contraception options and PID

Women on hormonal contraception presenting with breakthrough bleeding should be screened for genital tract infection, especially *C. trachomatis*.

The use of the combined oral contraceptive pill has usually been regarded as protective against symptomatic PID. Retrospective case–control and prospective studies have, however, shown an association with an increased incidence of asymptomatic cervical infection with *C. trachomatis*. This has led to the suggestion that the oral contraception may mask endometritis.
An IUD only increases the risk of developing PID in the first few weeks after insertion. One European randomised trial compared efficacy and continuation rates of copper-containing IUDs and the levonorgestrel-releasing intrauterine system (LNG-IUS). At 3 years, there were significantly fewer removals for PID in the LNG-IUS group.

All women diagnosed with PID should be provided with information about future contraceptive options and should be assisted in making an informed choice.

If a woman is likely to be at risk of future PID and requests an IUD for contraception, the LNG-IUS would be the most appropriate choice.

10. Auditable standards

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

1. Proportion of women receiving treatment with a recommended regimen – target 95%.
2. Proportion of women referred for tracing of sexual contacts – target 95%.
3. Proportion of named male contacts in STI associated PID confirmed to have been screened for infection and/or treated – target 60%.
4. Proportion of women having an adequate sexual history documented – target 95%.
5. Proportion of women in whom microbiological investigations have been taken – target 90%.


References


APPENDIX

Clinical guidelines are: ‘systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions’. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No. 1: Development of RCOG Green-top Guidelines (available on the RCOG website at www.rcog.org.uk/index.asp?PageID=75). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

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<tr>
<th>Classification of evidence levels</th>
<th>Grades of recommendations</th>
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<tr>
<td>1+++ High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias</td>
<td><strong>A</strong> At least one meta-analysis, systematic reviews or randomised controlled trial rated as 1+++ and directly applicable to the target population; or A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results</td>
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<td>1+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias</td>
<td><strong>B</strong> A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+</td>
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<td>1- Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias</td>
<td><strong>C</strong> A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++</td>
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<td>2+++ High-quality systematic reviews of case-control or cohort studies or high-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal</td>
<td><strong>D</strong> Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+</td>
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<tr>
<td>2+ Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal</td>
<td>Good practice point</td>
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<tr>
<td>2- Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal</td>
<td>Recommended best practice based on the clinical experience of the guideline development group</td>
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<tr>
<td>3 Non-analytical studies; e.g. case reports, case series</td>
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<tr>
<td>4 Expert opinion</td>
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This guideline was produced on behalf of the Guidelines Committee of the Royal College of Obstetricians and Gynaecologists and the British Association for Sexual Health and HIV (BASHH) by:

Prof J Ross MD FRCP, Birmingham (BASHH) and Mr P Stewart FRCOG, Sheffield (RCOG)

and peer-reviewed by:
BASHH, Ms J Birch, J Birch, Pelvic Pain Support Network; Mr CD Bevan FRCOG, Weston Super Mare; RCOG Consumers' Forum; Dr GE Forster FRCOG, London; Dr PE Munday FRCOG, Watford; Professor J Paavonen, Helsinki; Dr J Paton, Consultant Microbiologist, Queens Hospital, Burton upon Trent; Dr JT Preston FRCOG, Great Yarmouth.

The Guidelines Committee lead reviewers were:
Dr MR Gazvani FRCOG, Liverpool; Ms T Belfield, Consumers' Forum Representative, Family Planning Association, and Mr S Leeson FRCOG, Bangor, Wales.

The final version is the responsibility of the Guidelines Committee of the RCOG.

The guideline review process will commence in 2011 unless otherwise indicated

The following changes were made to the published document January 2009:

Section 4.4 Treatment in a woman with an intrauterine contraceptive device
Consideration should be given to removing an intrauterine contraceptive device (IUD) in women presenting with PID, especially if symptoms have not resolved within 72 hours.

Section 5. Other modes of treatment
Consider drainage of an abscess and in noting its position, the possibility that the abscess may have arisen from the appendix or colon.

DISCLAIMER
The Royal College of Obstetricians and Gynaecologists produces guidelines as an educational aid to good clinical practice. They present recognised methods and techniques of clinical practice, based on published evidence, for consideration by obstetricians and gynaecologists and other relevant health professionals. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor or other attendant in the light of clinical data presented by the patient and the diagnostic and treatment options available.

This means that RCOG Guidelines are unlike protocols or guidelines issued by employers, as they are not intended to be prescriptive directions defining a single course of management. Departure from the local prescriptive protocols or guidelines should be fully documented in the patient’s case notes at the time the relevant decision is taken.