



**UK National Guideline
for the Management of Pelvic Inflammatory Disease
2011
(updated June 2011)**

**Clinical Effectiveness Group
British Association for Sexual Health and HIV**

Guideline development group:

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What is new in the June 2011 update?

- The dose of ceftriaxone has been increased to 500mg stat to reflect the reduced sensitivity of *Neisseria gonorrhoeae* to cephalosporins and the current UK treatment guidelines for uncomplicated gonorrhoea



NHS Evidence has accredited the process used by the British Association for Sexual Health & HIV (BASHH) to produce UK national guidelines. Accreditation is valid for 3 years from January 2011 and is retrospectively applicable to guidance produced using the processes described in the BASHH Framework for Guideline Development and Assessment dated September 2010. More information on accreditation can be viewed at www.evidence.nhs.uk

Introduction and methodology

Objectives

This guideline offers recommendations on the diagnostic tests, treatment regimens and health promotion principles needed for the effective management of pelvic inflammatory disease (PID) covering the management of the initial presentation, as well as how to reduce transmission and future infection.

It is aimed primarily at women aged 16 years or older (see specific guidelines for those under 16) presenting to health care professionals working in departments offering level 3 care in STI management within the United Kingdom. However, the principles of the recommendations should be adopted across all levels - level 1 and 2 providers may need to develop local care pathways where appropriate.

A PID patient information leaflet is currently being developed.

Search strategy

Five reference sources were used to provide a comprehensive basis for the guideline:

1. Medline and Embase Search

a.1987 – January 2010

The search strategy comprised the following terms in the title or abstract: 'pelvic inflammatory disease', 'adnexitis', 'oophoritis', 'parametritis', 'salpingitis', 'endometritis', 'PID' (excluding 'primary immune deficiency'), 'adnexal disease' or 'adnexal disease'. 10422 citations were identified.

b.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 2321 citations.

2. 2010 CDC STD Treatment Guidelines (www.cdc.gov/std/)

3. 2009 RCOG Green Top Guidelines – Management of Acute Pelvic Inflammatory Disease (www.rcog.org.uk)

4. Royal College of Obstetrics and Gynaecology Working Group on PID Report 1996¹

5. Cochrane Collaboration Databases (www.cochrane.org)

Methods

Article titles and abstracts were reviewed and if relevant the full text article obtained. Priority was given to randomised controlled trial and systematic review evidence, and recommendations made and graded on the basis of best available evidence.

Piloting and feedback

The initial draft of the guideline including the patient information leaflet was piloted for validation by the Clinical Effectiveness Group (CEG) of BASHH using a sample of UK genitourinary medicine clinics. A standardised feed back form was completed by each pilot site and the guideline amended by the CEG editor. The final guideline was then reviewed by the CEG using the AGREE instrument before posting it on the BASHH website for external peer review for a 3 month period. Comments received were collated by the CEG editor and sent to the guideline chair for review and action. The final guideline was approved by the CEG and a review date agreed before publication on the BASHH website.

Aetiology

- 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} but account for only a quarter of cases in the UK, whilst *Gardnerella vaginalis*, anaerobes (including *Prevotella*, *Atopobium* and *Leptotrichia*) and other organisms commonly found in the vagina may also be implicated. *Mycoplasma genitalium* has also been associated with upper genital tract infection in women³.

Clinical Features

Symptoms

The following features are suggestive of a diagnosis of PID^{1, 2, 4, 5}:

- lower abdominal pain which is typically bilateral

- deep dyspareunia
- abnormal vaginal bleeding, including post coital, inter-menstrual and menorrhagia
- abnormal vaginal or cervical discharge which is often purulent

Signs

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

A diagnosis of PID, and empirical antibiotic treatment, should be considered and usually offered in any young (under 25) sexually active woman who has recent onset, bilateral lower abdominal pain associated with local tenderness on bimanual vaginal examination, in whom pregnancy has been excluded.

Complications

- Women with HIV may have more severe symptoms associated with PID but respond well to standard antibiotic therapy⁶. No change in treatment recommendations compared to HIV uninfected patients is required⁷⁻⁹. (Grade B [III])
- The Fitz-Hugh-Curtis syndrome comprises right upper quadrant pain associated with perihepatitis which occurs in some 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 uncomplicated PID.
- The randomised controlled trial evidence for whether an intrauterine contraceptive device should be left in situ or removed in women presenting with PID is limited^{10, 11}. Removal of the IUD should be considered and may be associated with better short term clinical outcomes¹⁰. The decision to remove the IUD 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.

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^{2, 4, 5})
- 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^{2, 4, 5}
- An elevated ESR or C reactive protein also supports the diagnosis but is non-specific¹².
- The **absence** of endocervical or vaginal pus cells has a good negative predictive value (95%) for a diagnosis of PID but their **presence** is non-specific (poor positive predictive value – 17%)¹³.

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

- ectopic pregnancy – pregnancy should be excluded in all women suspected of having PID
- acute appendicitis – nausea and vomiting occurs in most patients with appendicitis but only 50% of those with PID. Cervical movement pain will occur in about a quarter of women with appendicitis^{14, 15}.
- endometriosis – the relationship between symptoms and the menstrual cycle may be helpful in establishing a diagnosis
- complications of an ovarian cyst e.g. torsion or rupture – often of sudden onset
- urinary tract infection – often associated with dysuria and/or urinary frequency
- functional pain – may be associated with longstanding symptoms

Management

It is likely that delaying treatment increases the risk of long term sequelae such as ectopic pregnancy, infertility and pelvic pain¹⁶. 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 a variety of aerobic and anaerobic bacteria commonly isolated from the upper genital tract in women with PID^{1,2}.

Some of the best evidence for the effectiveness of antibiotic treatment in preventing the long term complications of PID comes from the PEACH study where women were treated with cefoxitin followed by doxycycline – pregnancy rates after 3 years were similar or higher than those in the general population^{17,18}.

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])

Appropriate analgesia should be provided. (Grade C [IV])

Intravenous therapy is recommended for patients with more severe clinical disease (Grade C [IV]) e.g. pyrexia > 38°C, clinical signs of tubo-ovarian abscess, signs of pelvic peritonitis.

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]). A patient information leaflet is included in appendix 1 of this guideline.

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
- clinically more severe disease is associated with a greater risk of sequelae
- repeat episodes of PID are associated with an exponential increase in the risk of infertility
- the earlier treatment is given the lower the risk of future fertility problems.
- 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

Outpatient therapy is as effective as inpatient treatment for patients with clinically mild to moderate PID¹⁷. Admission for parenteral therapy, observation, further investigation and/or possible surgical intervention should be considered in the following situations¹⁹:

- a surgical emergency cannot be excluded
- lack of response to oral therapy
- clinically severe disease
- presence of a tuboovarian abscess
- intolerance to oral therapy
- pregnancy

Further Investigation

All sexually active patients should be offered:

- a pregnancy test
- screening for sexually transmitted infections including HIV²⁰

Treatment

The following antibiotic regimens are evidence based.

Recommended Regimens

All the recommended regimens are of similar efficacy.

Outpatient Regimens

i.m. ceftriaxone* 500mg single dose followed by oral doxycycline 100mg twice daily *plus* metronidazole 400mg twice daily for 14 days

Grade A (Ib) ²¹⁻²³

*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.

oral ofloxacin 400mg twice daily *plus* oral metronidazole 400mg twice daily for 14 days

Grade A (Ib) ²³⁻²⁷

Metronidazole is included in some regimens to improve coverage for anaerobic bacteria. Anaerobes are of relatively greater importance in patients with severe PID and metronidazole may be discontinued in those patients with mild or moderate PID who are unable to tolerate it.

Ofloxacin and moxifloxacin should be avoided in patients who are at high risk of gonococcal PID because of increasing quinolone resistance in the UK (e.g. when the patient's partner has gonorrhoea, in clinically severe disease, following sexual contact abroad). Quinolones should also be avoided as first line empirical treatment for PID in areas where >5% of PID is caused by quinolone resistant *Neisseria gonorrhoeae*.

Levofloxacin is the L isomer of ofloxacin²⁸ and has the advantage of once daily dosing (500mg OD for 14 days). It may be used as a more convenient alternative to ofloxacin.²⁹

Replacing intramuscular ceftriaxone with an oral cephalosporin (e.g. cefixime) is not recommended because there is no clinical trial evidence to support its use, and tissue levels are likely to be lower which might impact on efficacy. Reports of decreasing susceptibility of *Neisseria gonorrhoeae* to

cephalosporins also supports the use of parenteral based regimens when gonococcal PID is suspected (to maximise tissue levels and overcome low level resistance).

Alternative Regimens

intramuscular ceftriaxone 500 mg immediately, followed by azithromycin 1 g/week for 2 weeks

Grade A (Ib)^{30, 31}

Clinical trial evidence for this regimen is limited but it may be used when the treatments above are not appropriate e.g. allergy, intolerance:

oral moxifloxacin 400mg once daily for 14 days

Grade A (Ib)^{29, 32, 33}

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

Inpatient Regimens

Intravenous therapy should be continued until 24 hours after clinical improvement and then switched to oral. Intravenous doxycycline is not currently licensed in the UK but is available from IDIS world medicines (01932 824100).

i.v. ceftriaxone 2g daily *plus* i.v. doxycycline 100mg twice daily (oral doxycycline may be used if tolerated) followed by oral doxycycline 100mg twice daily *plus* oral metronidazole 400mg twice daily for a total of 14 days

Grade A (Ib) ^{22, 23}

i.v. clindamycin 900mg 3 times daily *plus* i.v. gentamicin (2mg/kg loading dose) followed by 1.5mg/kg 3 times daily [a single daily dose of 7mg/kg may be substituted] followed by either oral clindamycin 450mg 4 times daily or oral doxycycline 100mg twice daily *plus* oral metronidazole 400mg twice daily to complete 14 days

Grade A (Ib) ²²

Gentamicin levels need to be monitored if this regimen is used.

Alternative Regimens

Clinical trial evidence for the following regimens is more limited but they may be used when the treatments above are not appropriate e.g. allergy, intolerance:

i.v. ofloxacin 400mg BD *plus* i.v. metronidazole 500mg TID for 14 days

Grade B (III) ^{23-25, 34}

i.v. ciprofloxacin 200mg BD *plus* i.v. (or oral) doxycycline 100mg BD *plus* i.v. metronidazole 500mg TID for 14 days

Grade B (III) ^{24, 35}

Allergy

There is no clear 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

- PID in pregnancy 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 are 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.m. ceftriaxone plus oral or i.v. erythromycin, with the possible addition of oral or i.v. metronidazole 500mg 3 times daily in clinically severe disease) (Grade C [IV]).
- The risk of giving any of the recommended antibiotic regimens (listed above for non pregnant women) in very early pregnancy (prior to a pregnancy test becoming positive) is justified by the need to provide effective therapy and the low risk to the foetus (personal communication, UK National Teratology Information Service – 11.2.10).

Surgical Management

- Laparoscopy may help early resolution of the disease by dividing adhesions and draining pelvic abscesses³⁶ but ultrasound guided aspiration of pelvic fluid collections is less invasive and may be equally effective.^{37, 38}
- It is also possible to perform adhesiolysis in cases of perihepatitis although there is no evidence whether this is superior to using only antibiotic therapy

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 but this time period may be influenced by the sexual history (Grade C [IV]).
- Gonorrhoea or chlamydia diagnosed in the male partner should be treated appropriately and concurrently with the index patient. (Grade C [IV]).

- Because many cases of PID are not associated with gonorrhoea or chlamydia, broad spectrum empirical therapy should also be offered to male partners e.g. azithromycin 1g single dose (Grade C [IV]).
- If screening for gonorrhoea is not available additional specific antibiotics effective against *Neisseria gonorrhoeae* should be offered e.g. i.m. ceftriaxone 500mg single dose (see also UK National Guidelines for Gonorrhoea) (Grade C [IV]).
- Partners should be advised to avoid intercourse until they and the index patient have completed the treatment course (Grade C [IV]).

Follow Up

Review at 72 hours is recommended ⁵, particularly for those with a moderate or severe clinical presentation, and should show a substantial improvement in clinical symptoms and signs (Grade C [IV]). Failure to do so suggests the need for further investigation, parenteral therapy and/or surgical intervention.

Further review 2-4 weeks (Grade C [IV]) 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
- repeat pregnancy test, if clinically indicated

Repeat testing for gonorrhoea or chlamydia after 2 to 4 weeks is appropriate in those in whom persisting symptoms, antibiotic resistance pattern (gonorrhoea only), compliance with antibiotics and/or tracing of sexual contacts indicate the possibility of persisting or recurrent infection.

Auditable Outcome Measures

Appropriate short term audit outcomes include:

- proportion of women receiving treatment with a recommended regimen – target 95%

- number of named male contacts screened for infection and/or treated – target 0.4 (large urban centres) or 0.6 (other centres) per index case³⁹

Qualifying statement

The recommendations in this guideline may not be appropriate for use in all clinical situations. Decisions to follow these recommendations must be based on the professional judgement of the clinician and consideration of individual patient circumstances and available resources.

All possible care has been undertaken to ensure the publication of the correct dosage of medication and route of administration. However, it remains the responsibility of the prescribing physician to ensure the accuracy and appropriateness of the medication they prescribe.

Editorial independence

This guideline was commissioned, edited and endorsed by the BASHH CEG without external funding being sought or obtained.

Declarations of interest

All members of the guideline writing committee completed the BASHH conflict of interest declaration detailed below at the time the guideline's final draft was submitted to the CEG. JR has received consultancy fees from Bayer pharma.

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Timescale for next revision

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Appendix 1: Patient information leaflet on PID

See document on BASHH website (currently in preparation)