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Main Revisions:

- consider removal of an intra uterine contraceptive in a woman with a diagnosis of PID
- metronidazole may be discontinued in women with mild to moderate PID who cannot tolerate it
- in women at high risk of gonococcal PID a cephalosporin based regimen is preferred to the use of a quinolone

United Kingdom National Guideline for the Management of Pelvic Inflammatory Disease

Introduction

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.

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}, whilst *Gardnerella vaginalis*, anaerobes 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
- dyspareunia
- abnormal vaginal bleeding
- abnormal vaginal or cervical discharge

Signs

- lower abdominal tenderness which is usually bilateral
- 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 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 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.
- 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 {Altunyurt, Demir, et al. 2003 4420 /id}{Soderberg & Lindgren 1981 4132 /id}. Removal of the IUD should be considered and may be associated with better short term clinical outcomes {Altunyurt, Demir, et al. 2003 4420 /id}. 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)^{1;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^{1;4;5}.
- An elevated ESR or C reactive protein also supports the diagnosis¹¹.
- Laparoscopy may strongly support a diagnosis of PID but is not justified routinely on the basis of cost, the potential difficulty in identifying mild intra-tubal inflammation or endometritis and high rates of intra- and inter-observer variation in diagnosing PID^{1;4;5;12}.
- 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 presence of histological endometritis is not associated with higher rates of infertility, chronic pelvic pain nor recurrent PID¹³.
- 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%)¹⁴.

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^{15;16}
- endometriosis – the relationship between symptoms and the menstrual cycle may be helpful in establishing a diagnosis
- complications of an ovarian cyst – often of sudden onset
- 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 pain^{5;17}. 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;5}.

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^{13;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 currently being produced by the Royal College of Obstetrics and Gynaecology, which will be consistent with these guidelines, and will be available at www.rcog.org.uk.

Outpatient therapy is as effective as inpatient treatment for patients with mild to moderate PID as assessed clinically¹⁸. Admission for parenteral therapy,

observation, further investigation and/or possible surgical intervention should be considered in the following situations^{5;19}:

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

Further Investigation

All patients should be offered:

- a pregnancy test when required to exclude pregnancy
- 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. Intravenous doxycycline is not currently licensed in the UK but is available from IDIS world medicines (0208 410 0700).

Recommended Regimens

All the recommended regimens are of similar efficacy.

Outpatient Regimens

- 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 A (Ib) ^{5;18;20-24}

- oral ofloxacin 400mg BD **plus** oral metronidazole 400mg BD for 14 days
Grade A (Ib) ^{5;22;24-27}

In both recommended outpatient regimens metronidazole is included 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 should be avoided in patients who are at high risk of gonococcal PID because of increasing quinolone resistance in the UK (e.g. patients's partner has gonorrhoea, clinically severe disease, sexual contact abroad). Levofloxacin is the L isomer of ofloxacin²⁸ and has the advantage of once daily dosing (500mg OD for 14 days). It may provide a more convenient alternative to ofloxacin but no clinical trials in women with PID have been published for this agent⁵.

Inpatient 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 A (Ib) ^{5;18;21-24}

- i.v. clindamycin 900mg TID plus i.v. gentamicin (2mg/kg loading dose

followed by

1.5mg/kg TID [a single daily dose of 7mg/kg may be substituted])

followed by either

oral clindamycin 450mg QID for 14 days

or

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

Grade A (Ib) ^{5;21;23;24}

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

Alternative Regimens

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

Grade B (III) ^{5;22;24;25;29}

- 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) ^{5;24;30}

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.m. ceftriaxone plus oral/i.v. erythromycin, with the possible addition of oral/i.v. metronidazole 500mg TID in clinically severe disease) (Grade C [IV]).

- The risk of giving any of the recommended antibiotic regimens in very early pregnancy (prior to a positive pregnancy test) is low with any significant drug toxicity resulting in failed implantation (personal communication, UK National Teratology Information Service).

Surgical Management

- Laparoscopy may help early resolution of the disease by division of adhesions and drainage of pelvic abscesses³¹ but ultrasound guided aspiration of pelvic fluid collections is less invasive and may be equally effective.^{32;33}
- It is also possible to perform adhesiolysis in cases of perihepatitis although there is no evidence whether this is superior to only using 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]).
- Partners should be advised to avoid intercourse until they and the index patient have completed the treatment course (Grade C [IV]).
- 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 recommended⁵, 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 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 testing for gonorrhoea or chlamydia 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%
- proportion of named male contacts screened for infection and/or treated – target 40% (large urban centres) or 60% (other centres)³⁴

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.

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Conflict of Interest

The author has not declared any conflict of interest. This guideline was commissioned and edited by the CEG of the BASHH, without external funding being sought or obtained.

Rigour of development

Stakeholder Involvement

Prior to submission this guideline was distributed to three consultants in Genitourinary Medicine. They were asked to use the guideline as an aid to the management of patients presenting with PID. Their comments were noted and incorporated into the current document.

Prior to publication the final draft of the guideline was placed on the BASHH website, and copies circulated to the Genitourinary Medicine regional audit, GUNA and SHAS chairs for comment and peer review. After a period of three months any comments received were reviewed by the guideline authors, and acted on appropriately, before final authorisation by the CEG was given and publication was undertaken.

Rigour of Development

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

1. Medline and Embase Search

1987 – February 2004

The search strategy comprised the following terms in the title or abstract:

'pelvic inflammatory disease', 'adnexitis', 'oophoritis', 'parametritis', 'salpingitis' or 'adnexal disease'. 9884 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 2321 citations.

2. 2002 CDC STD Treatment Guidelines (www.cdc.gov/std/)

3. 2003 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 1996²

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

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.

Timescale for next revision

2008

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