

2012 European Guideline for the Management of Pelvic Inflammatory Disease

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Authors:

Prof. Jonathan Ross MB ChB MD FRCP
University Hospital Birmingham
Whittall Street Clinic
Whittall Street
Birmingham B4 6DH
UK
Tel. 0121 237 5721 Fax. 0121 237 5729
email: jonathan.ross@uhb.nhs.uk

Prof. Philippe Judlin MD, FACOG
Clinique Universitaire de Gynécologie-Obstétrique
Maternite Regionale de Nancy
France
email: p.judlin@maternite.chu-nancy.fr

Lead Editor :

Jorgen Jensen
Statens Serum Institut
Artillerivej 5
DK-2300 Copenhagen S
Denmark

This guideline refers to ascending infections in the female genital tract unrelated to delivery and surgery and does not include actinomyces related infection.

Aetiology and Transmission

- 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 agents¹ whilst *Mycoplasma genitalium* and anaerobes can also be implicated. Micro-organisms from the vaginal flora including streptococci, staphylococci, *E. coli* and *H. influenzae* are also associated with upper genital tract inflammation.
- The relative importance of different pathogens varies in different countries and regions within Europe.

A number of factors are associated with PID:

- Factors related to sexual behaviour
 - young age
 - multiple partners
 - recent new partner (within previous 3 months)
 - past history of sexually transmitted infections (STIs) in the patient or their partner
- Instrumentation of the uterus / interruption of the cervical barrier
 - termination of pregnancy
 - insertion of intrauterine device within the past 6 weeks
 - hysterosalpingography
 - in vitro fertilisation

Clinical Features

Symptoms

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.

The following symptoms are suggestive of a diagnosis of PID^{1-3;4}:

- lower abdominal pain – usually bilateral
- deep dyspareunia – particularly of recent onset
- abnormal bleeding – intermenstrual bleeding, post coital bleeding and menorrhagia can occur secondary to associated cervicitis and endometritis
- abnormal vaginal or cervical discharge – as a result of associated cervicitis, endometritis or bacterial vaginosis

Physical signs

These signs are associated with PID:

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

PID should be considered in a patient with the clinical signs and/or symptoms outlined above.

Differential Diagnosis

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

- ectopic pregnancy
- acute appendicitis
- endometriosis
- irritable bowel syndrome
- complications of an ovarian cyst i.e. rupture, torsion
- functional pain (pain of unknown physical origin)

Complications

- Tuboovarian abscesses and pelvic peritonitis account for the main complications. Acute lower abdominal pain and fever are usually present. Ultrasound scanning may be useful to confirm a pelvic abscess while computed tomography may rule out other peritonitis.
- The Fitz-Hugh-Curtis syndrome comprises right upper quadrant pain associated with perihepatitis and may be the dominant symptom. 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
- In pregnancy PID is uncommon but has been 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 for pregnant women with PID 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 three times daily plus i.v. erythromycin 50mg/kg continuous infusion, with the possible addition of i.v. metronidazole 500mg three times daily)

(Evidence level III, B)

- Women with HIV may have more severe symptoms associated with PID but respond well to antibiotic therapy, although parenteral regimens may be required⁵⁻⁸.
- There is no evidence of the superiority of any one of the recommended regimens over the others. Therefore patients known to be allergic to one of the recommended regimens should be treated with an alternative.
- In women with an intrauterine contraceptive device (IUD) in situ, consider removing the IUD since this may be associated with better short term improvement in symptoms and signs⁹.

(Evidence level Ib, A)

Diagnosis

- Testing for gonorrhoea and chlamydia in the lower genital tract is recommended since a positive result supports the diagnosis of PID. However the absence of infection from the endocervix or urethra does not exclude PID¹⁻³.
- 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%)¹⁰.
- An elevated ESR or C reactive protein supports the diagnosis¹¹ but is non-specific and often normal in mild/moderate PID
- Elevation of the white cell count (WBC) supports the diagnosis but can be normal in mild cases.
- Laparoscopy may strongly support a diagnosis of PID but is not justified routinely on the basis of associated morbidity, cost and the potential difficulty in identifying mild intra-tubal inflammation or endometritis¹⁻³
- Endometrial biopsy and ultrasound scanning may also be helpful when there is diagnostic difficulty but there is insufficient evidence to support their routine use

- A pregnancy test should be performed to help exclude an ectopic pregnancy

Management

Information, explanation and advice for the patient

- Patients should be advised to avoid unprotected intercourse until they, and their partner(s), have completed treatment and follow-up (Evidence level IV, C)
- 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. Appropriate information should include:
 - fertility is usually well preserved in women with first episode PID who receive prompt appropriate anti-microbial therapy
 - the risk of impaired fertility increases significantly with each subsequent episode of PID (approximately doubling with each new presentation¹²)
 - the risk of impaired fertility is increased in clinically more severe PID
 - chronic pelvic pain of varying severity affects around 30% of women following PID
 - PID increases the relative risk of a subsequent pregnancy being an ectopic, but the absolute risk of ectopic pregnancy remains low at around 1%

A patient information leaflet is available at

<http://www.iusti.org/regions/europe/euroguidelines.htm#Current>.

(Evidence level IV, C)

Therapy

Broad spectrum antibiotic therapy is required to cover *N. gonorrhoeae*, *C. trachomatis* and anaerobic infection^{1,2}. It is also desirable to include microbiological cover for other possible pathogens (e.g. *Mycoplasma genitalium*, anaerobes, streptococci, staphylococci, *E. coli*, *H.*

influenzae)¹³. Recent data suggest that few antibiotics (azithromycin and moxifloxacin, mainly) are effective against *Mycoplasma genitalium*¹⁴. 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 measures include:

- Rest is advised for those with severe disease (Evidence level C)
- If there is a possibility that the patient could be pregnant, a pregnancy test should be performed (Evidence level C)
- Appropriate analgesia should be provided (Evidence level C)
- Intravenous therapy is recommended for patients with more severe clinical disease (Evidence level IV, C)

Admission for parenteral therapy, observation, further investigation and/or possible surgical intervention should be considered in the following situations² (Evidence level IV, C):

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

In inpatients the treatment response can be monitored by changes in C reactive protein and WBC .

In severe cases and cases with failure of the initial treatment tuboovarian abscess should be excluded by vaginal ultrasonography, CT or MRI imaging.

All patients should be offered screening for sexually transmitted infections including HIV testing (Evidence level IV, C) .

It is likely that delaying treatment increases the risk of long term sequelae such as ectopic pregnancy, infertility and pelvic pain ¹⁵. Because of this, and the lack of definitive diagnostic criteria, a low threshold for empiric treatment of PID is recommended (Evidence level IV, C).

In cases with suspected repeat PID, especially if it is of mild severity, other causes should be sought and treated accordingly, especially functional pain, pain originating in the ileopsoas muscles, the pelvic floor and urinary tract (Evidence level IV, C).

Recommended Regimens

Choice of treatment regime should be influenced by the following:

- Mild and moderate cases should be treated as outpatients with oral therapy¹⁶ (Evidence level Ib, A).

- Intravenous therapy, when given, should be continued until 24 hours after clinical improvement and then switched to oral (Evidence level IV, C).
- Dosage recommendations may need to be adjusted slightly depending on local licensing regulations and the availability of drug formulations.
- The optimal duration of treatment is not known but most clinical trials report a response to 10-14 days of therapy.
- No difference in efficacy has been demonstrated between the recommended regimens

The following antibiotic regimens are evidence based.

Outpatient Regimens

- i.m. ceftriaxone 500mg single dose. *or* [i.m. cefoxitin 2g single dose with oral probenecid 1g]
followed by
oral doxycycline 100mg twice daily *plus* metronidazole 400mg twice daily for 14 days^{2, 17, 18;16, 19}
(Evidence level Ia, A)
- oral ofloxacin 400mg twice daily *plus* oral metronidazole 500mg twice daily for 14 days²
18-21
(ofloxacin may be replaced by levofloxacin 500mg once daily²²)
(Evidence level Ib, A)

Inpatient Regimens

- i.v. cefoxitin 2g four times daily (or i.v. cefotetan 2g twice daily or i.v./i.m. ceftriaxone 1g once 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 to complete 14 days^{2, 17, 18;19}

(Evidence level Ia, A)

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

followed by either

[oral clindamycin 450mg four times daily
to complete 14 days]

[oral doxycycline 100mg twice daily
plus oral metronidazole 400mg twice daily
to complete 14 days]^{2, 17;19}

(Evidence level Ia, A)

Alternative Regimens

The evidence for alternative regimens is either less robust than the regimens above, or they have a poorer safety profile.

- i.v. ofloxacin 400mg twice daily **plus** i.v. metronidazole 500mg three times daily for 14 days^{2, 18-21}

(Evidence level Ib, B)

- i.v. ciprofloxacin 200mg twice daily *plus* i.v. (or oral) doxycycline 100mg twice daily *plus* i.v. metronidazole 500mg three times daily for 14 days^{2, 18, 23}

(Evidence level Ia, B)

- i.m. ceftriaxone 500mg single dose plus oral azithromycin 1g single dose followed by a second dose of oral azithromycin 1g after one week²⁴

(Evidence level Ia, A)

- oral moxifloxacin 400mg once daily for 14 days^{22, 25, 26}

(Evidence level Ia, A)

Where the above regimens are not available antibiotic therapy should be given for 14 days and attempt to cover:

- *Neisseria gonorrhoeae* e.g. cephalosporins
- *Chlamydia trachomatis* e.g. tetracyclines, macrolides
- anaerobic bacteria e.g. metronidazole

Metronidazole is included in the recommended outpatient regimens to improve coverage for anaerobic bacteria which may have a role in the pathogenesis of PID²⁷. Anaerobes are probably of relatively greater importance in patients with severe PID and some studies have shown good outcomes without the use of metronidazole. Metronidazole may therefore be discontinued in those patients with mild or moderate PID who are unable to tolerate it.

Ceftriaxone may be used when cefoxitin or cefotetan are not available since it offers a similar spectrum of activity, although with less effective cover for anaerobic infection.

Quinolones, including ofloxacin and moxifloxacin, should be combined with a single dose of ceftriaxone 500mg i.m. in patients who are at high risk of gonococcal PID because of increasing reports of quinolone resistance in *Neisseria gonorrhoeae* (e.g. avoid when the patient's partner has gonorrhoea [or is from a high prevalence area] or the patient has clinically severe disease). Moxifloxacin has a strong evidence base for effectiveness in the treatment of PID but has been associated with severe, although rare, liver and cardiac toxicity.

Partner notification

- 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 is not evidence based and may be influenced by the sexual history, available resources or local practice.
- Partners should be advised to avoid unprotected intercourse until they and their partner have completed the treatment course.
- Gonorrhoea diagnosed in the male partner should be treated appropriately (see European Guidelines at www.iusti.org) and concurrently with the index patient.
- Concurrent empirical treatment for chlamydia is recommended (see European Guidelines at www.iusti.org) for all sexual contacts due 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 gonorrhoea and chlamydia should be given (see European Guidelines at www.iusti.org).

Follow Up

Review at 72 hours is recommended², 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.

(Evidence level IV, C)

Repeat testing for gonorrhoea or chlamydia is appropriate:

- in those with persistent symptoms
- where antibiotic sensitivities are unknown or resistance is present (gonorrhoea only)
- history of poor compliance with antibiotics
- inadequate tracing of sexual contacts where there is a possibility of persisting or recurrent infection.

Prevention/health promotion

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
- advice on future use of condoms to prevent recurrent PID

Qualifying statement

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.

Authors

Prof. Jonathan D.C. Ross, Consultant Physician, University Hospital, Birmingham, UK

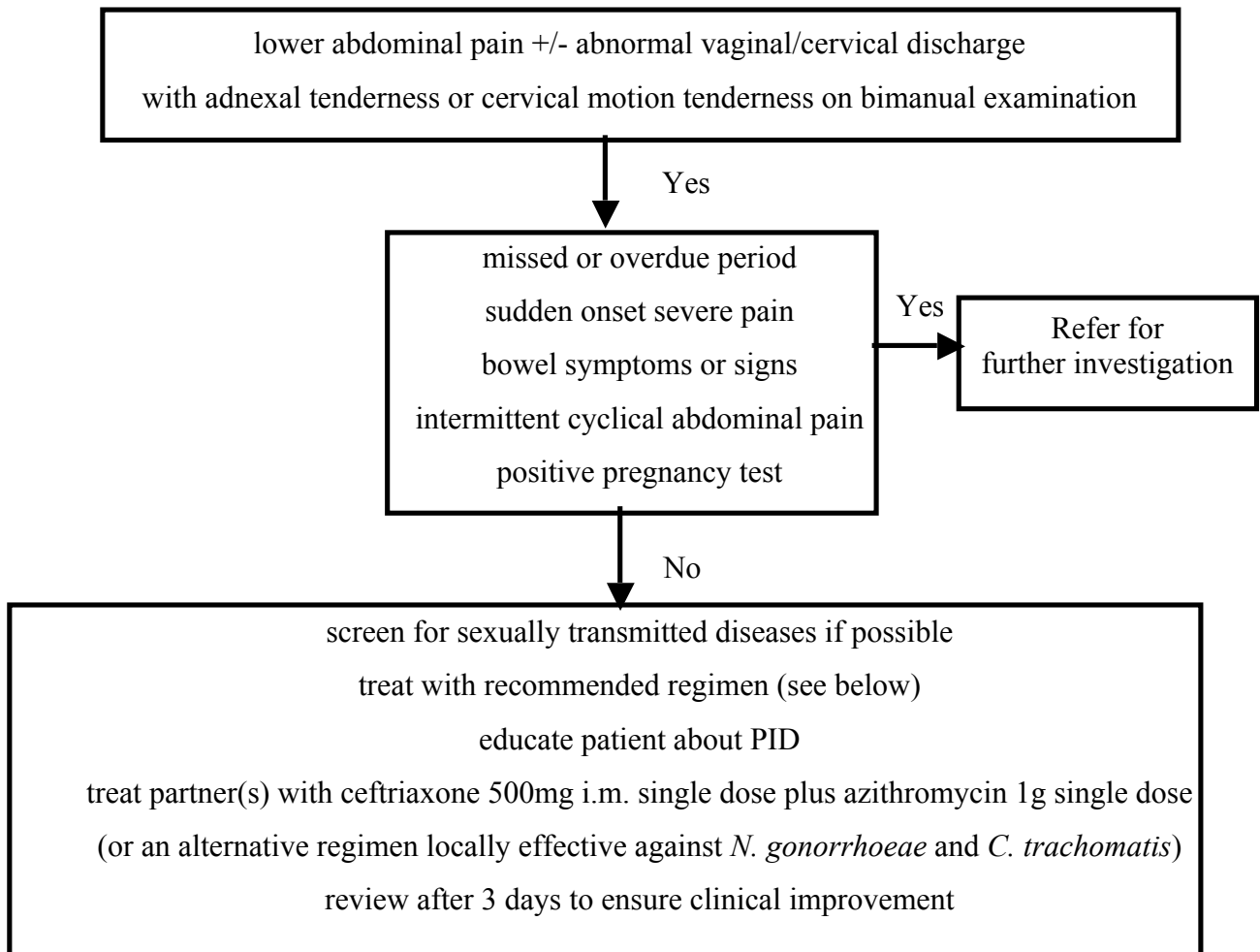
Prof. Philippe Judlin, Chairman, Clinique Universitaire de Gynécologie-Obstétrique Maternité
Regionale de Nancy, France

Date for review

January 2015

Syndromic Management of Pelvic Inflammatory Disease

(for use where initial investigations are not available)



Outpatient Regimens

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followed by
oral doxycycline 100mg twice daily **plus** metronidazole 400mg twice daily for 14 days^{2, 17, 18;16, 19}
(Evidence level Ia, A)

- oral ofloxacin 400mg twice daily **plus** oral metronidazole 500mg twice daily for 14 days²
18-21

(ofloxacin may be replaced by levofloxacin 500mg once daily²²)

(Evidence level Ib, A)

Inpatient Regimens

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[oral doxycycline 100mg twice daily
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to complete 14 days]^{2, 17;19}

(Evidence level Ia, A)

Appendix 1

Search strategy

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

1. Medline and Embase Search

a.1987 – September 2011

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. Cochrane Collaboration Databases (www.cochrane.org)

Appendix 2

Levels of evidence and grading of recommendations

Levels of Evidence

- Ia Evidence obtained from meta-analysis of randomised controlled trials.
- Ib Evidence obtained from at least one randomised controlled trial.
- IIa Evidence obtained from at least one well designed study without randomisation.
- IIb Evidence obtained from at least one other type of well designed quasi-experimental study.
- III Evidence obtained from well designed non-experimental descriptive studies such as comparative studies, correlation studies, and case control studies.
- IV Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Grading of Recommendations

- A (Evidence levels Ia, Ib) - Requires at least one randomised control trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.
- B (Evidence levels IIa, IIb, III) - Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.
- C (Evidence IV) - Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.

Appendix 3

Declarations of Interest

Jonathan Ross – no interests to declare

Philippe Judlin - no interests to declare

Jorgen Jensen – no interests to declare

Appendix 4

European STI Guidelines Editorial Board and List of contributing organisations

Dr Keith Radcliffe, UK – Editor-in-Chief

Dr Karen Babayan, Armenia (appointed 2009)
Dr Marco Cusini, Italy (app. 2010)
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Dr Marita van de Laar – ECDC representative, Netherlands (app. 2007)
Prof. Martino Neumann – EDF representative, Netherlands (app. 2007)
Dr Angela Robinson, - EADV representative, UK (app. 2009)

This guideline has been produced on behalf of the following organisations: the European Branch of the International Union against Sexually Transmitted Infections (IUSTI Europe); the European Academy of Dermatology and Venereology (EADV); the European Dermatology Forum (EDF); the Union of European Medical Specialists (UEMS). The European Centre for Disease Prevention and Control (ECDC) and the European Office of the World Health Organisation (WHO-Europe) also contributed to its development.

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