INTERNATIONAL JOURNAL OF STD & AIDS

International Journal of STD & AIDS
0(0) 1–7

DOI: 10.1177/0956462417744099
journals.sagepub.com/home/std
SAGE

2017 European guideline for the management of pelvic inflammatory disease

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Abstract

The European guideline for the management of pelvic inflammatory disease includes evidence-based advice on the investigation and treatment of pelvic inflammatory disease (PID). It has been updated to acknowledge the role of *Mycoplasma genitalium* as an important cause of PID with testing now recommended for women presenting with possible PID and for the male partners of women with confirmed *M. genitalium* infection. Recent evidence suggests that serious adverse events are uncommon when using moxifloxacin and its use is now recommended as a first-line therapy, especially in those women with *M. genitalium* PID. The potential utility of MRI scanning of the pelvis in excluding differential diagnoses has been highlighted. The use of doxycycline is now suggested as empirical treatment for male partners of women with PID to reduce exposure to macrolide antibiotics, which has been associated with increased resistance in *M. genitalium*.

Keywords

Pelvic infection, pelvic inflammatory disease, salpingitis, treatment, antibiotics, guideline

Date received: 16 October 2017; accepted: 1 September 2017

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 agents,[1] *Mycoplasma genitalium* is a likely cause[2] and anaerobes are also implicated. Microorganisms from the vaginal flora including streptococci, staphylococci, *Escherichia coli* and *Haemophilus influenzae* can be associated with upper genital tract inflammation. Mixed infections are common.
- The relative importance of different pathogens varies between 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 three 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 six weeks
- hysterosalpingography
- hysteroscopy
- saline infusion sonography
- in vitro fertilisation

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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).[1,3,4]

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, postcoital 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

The following 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.
- Right upper quadrant pain associated with perihepatitis (Fitz-Hugh–Curtis syndrome) can occur and may be the dominant symptom.
- 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 are 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. ceftriaxone 2 g once daily plus i.v. erythromycin 50 mg/kg once daily, with the addition of metronidazole given orally [500 mg twice daily], per rectum [1 g three times daily] or i.v. [500 mg 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 required.[5–8]
- 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 a single randomised controlled trial suggests that this may be associated with better short-term improvement in symptoms and signs.[9] However, a subsequent systematic review concluded that there is little difference in outcomes for women with mild-to-moderate PID who retain their IUD in situ during treatment.[10]
  (Evidence level Ib, A)

Diagnosis

- Testing for gonorrhoea, Chlamydia and *M. genitalium* 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 PID.[1–4]
- 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%).[11]
- An elevated ESR or C-reactive protein supports the diagnosis[12] but is non-specific and often normal in mild/moderate PID.

- Elevation of the white cell count can occur in women with PID but it is usually 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 endometritis.[1,3,4,13]
- Ultrasound scanning may be useful to confirm a pelvic abscess while computed tomography (CT) or magnetic resonance imaging (MRI) can help rule out other causes of peritonitis. However, routine ultrasound scanning is not recommended for all women with suspected PID.
- Endometrial biopsy may also be helpful when there is diagnostic difficulty but there is insufficient evidence to support its 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 symptoms have resolved (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 antimicrobial therapy
  - the risk of impaired fertility increases significant ly with each subsequent episode of PID (approximately doubling with each new presentation[14])
  - 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%
- Although laparoscopic division of hepatic adhesions has been performed in women with perihepatitis, there is insufficient clinical trial evidence to make specific recommendations for treatment beyond antibiotic therapy.
- A patient information leaflet is available at http://www.iusti.org/regions/europe/PatientInformation.htm
  (Evidence level IV, C)

Therapy

Broad spectrum antibiotic therapy is required to cover *N. gonorrhoeae*, *C. trachomatis* and anaerobic infection.[1,3] It is also desirable to include microbiological cover for other possible pathogens (e.g. *M. genitalium*, streptococci, staphylococci, *E. coli*, *H. influenzae*).[15]

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

- local antimicrobial sensitivity patterns
- 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 IV, C)
- if there is a possibility that the patient could be pregnant, a pregnancy test should be performed (Evidence level IV, C)
- appropriate analgesia should be provided (Evidence level IV, C)

Admission for parenteral therapy, observation, further investigation and/or possible surgical intervention should be considered in the following situations[3] (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 white cell count. In severe cases and cases with failure of the initial treatment, tuboovarian abscess should be excluded by vaginal ultrasonography, CT or MRI.

All patients should be offered testing for Chlamydia, gonorrhoea, *M. genitalium*, syphilis and HIV (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.[16] Because of this, and the lack of

definitive diagnostic criteria, a low threshold for empiric treatment of PID is recommended (Evidence level IV, C).

Recommended regimens

Choice of treatment regimen should be influenced by the following:

- Mild and moderate cases should be treated as outpatients with oral therapy[17] (Evidence level Ib, A).
- Intravenous therapy, when given, should be continued until 24 h after clinical improvement and then switched to oral (Evidence level IV, C).
- Dosage recommendations may need to be adjusted depending on local licensing regulations and the availability of drug formulations, e.g. metronidazole may be dosed at 400 or 500 mg.
- 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. It should be noted, however, that the changing spectrum of antimicrobial resistance over time and in different geographical areas may overestimate the efficacy of some regimens which were evaluated several years ago.

Outpatient regimens

- i.m. ceftriaxone 500 mg single dose

followed by

oral doxycycline 100 mg twice daily ***plus*** metronidazole 500 mg twice daily for 14 days[18–21]
(Evidence level Ia, A)

- oral ofloxacin[a] 400 mg twice daily ***plus*** oral metronidazole 500 mg twice daily for 14 days[19,21–23]
(ofloxacin may be replaced by levofloxacin[a] 500 mg once daily[24])
(Evidence level Ib, A)
- oral moxifloxacin[a] 400 mg once daily for 14 days[24–26] (Evidence level Ia, A)

Inpatient regimens

- i.v./i.m. ceftriaxone 1 g once daily ***plus*** i.v. doxycycline 100 mg twice daily (oral doxycycline may be used if tolerated)

followed by

oral doxycycline 100 mg twice daily ***plus*** oral metronidazole 500 mg twice daily to complete 14 days[18,19,21]
(Evidence level Ia, A)

- i.v. clindamycin 900 mg three times daily ***plus*** i.m./i.v. gentamicin (3–6 mg/kg as a single daily dose with renal monitoring)

followed by either

(oral clindamycin 450 mg four times daily to complete 14 days) or (oral doxycycline 100mg twice daily ***plus*** oral metronidazole 500 mg twice daily to complete 14 days)[18,21]
(Evidence level Ia, A)

Alternative regimens

The evidence for alternative regimens is less robust than the regimens above.

- i.v. ofloxacin[a] 400 mg twice daily ***plus*** i.v. metronidazole 500 mg three times daily for 14 days[19,21–23]
(Evidence level Ib, A)
- i.m. ceftriaxone 500 mg single dose plus oral azithromycin 1 g single dose followed by a second dose of oral azithromycin 1 g after one week[27]
(Evidence level Ib, A)

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

- *N. gonorrhoeae*, e.g. cephalosporins
- *C. trachomatis*, e.g. tetracyclines, macrolides
- anaerobic bacteria, e.g. metronidazole

Metronidazole is included in some regimens to improve coverage for anaerobic bacteria that may have a role in the pathogenesis of PID.[3,28] 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.

In women who are positive for *M. genitalium* treatment with moxifloxacin is recommended.

Partner notification

- Current partners of women with PID should be contacted and offered health advice and screening

for gonorrhoea and Chlamydia (and *M. genitalium* if the index patient is infected). Other recent sexual partners may also be offered screening – tracing of contacts within a six-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.
- Gonorrhoea, Chlamydia and *M. genitalium* diagnosed in the male partner should be treated appropriately (see European Guidelines at www.iusti.org) and concurrently with the index patient.
- Because many cases of PID are not associated with gonorrhoea, Chlamydia or *M. genitalium*, broad spectrum empirical therapy should also be offered to male partners, e.g. doxycycline 100 mg twice daily for one week.
- Partners should be advised to avoid unprotected intercourse until they and their partner have completed the treatment course.

Follow-up

Review at 72 h is recommended[3] for those with a moderate or severe clinical presentation and should show a substantial improvement in clinical symptoms and signs. Failure to improve suggests the need for further investigation, parenteral therapy and/or surgical intervention.

(Evidence level IV, C)

Repeat microbiology testing is appropriate in women who are positive for gonorrhoea, Chlamydia or *M. genitalium* at baseline:

- in those with persistent symptoms
- where antibiotic sensitivities are unknown or resistance is present (gonorrhoea or *M. genitalium* 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 in person, by phone or via email four 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

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Note

a. High levels of quinolone resistance in *N. gonorrhoeae* occur in many areas of Europe. Therefore in women who are at high risk of gonococcal PID (e.g. when the patient's partner has gonorrhoea, in clinically severe disease, following sexual contact abroad) a regimen containing i.m. ceftriaxone 500 mg should be used.

References

1. Bevan CD, et al. Clinical, laparoscopic and microbiological findings in acute salpingitis: report on a United Kingdom cohort. *Br J Obstet Gynaecol* 1995; 102: 407–414.
2. Lis R, Rowhani-Rahbar A and Manhart LE. *Mycoplasma genitalium* infection and female reproductive tract disease: a meta-analysis. *Clin Infect Dis* 2015; 61: 418–426.
3. Centers for Disease Control and Prevention. Sexually Transmitted diseases treatment guidelines 2015, http://www.cdc.gov/std/tg2015/default.htm (2015, accessed 15 November 2017).
4. Morcos R, et al. Laparoscopic versus clinical diagnosis of acute pelvic inflammatory disease. *J Reprod Med* 1993; 38: 53–56.
5. Kamenga MC, 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.
6. Mugo NR, et al. Effect of human immunodeficiency virus-1 infection on treatment outcome of acute salpingitis. *Obstet Gynecol* 2006; 107: 807–812.
7. Bukusi EA, et al. Effects of human immunodeficiency virus 1 infection on microbial origins of pelvic inflammatory disease and on efficacy of ambulatory oral therapy. *Am J Obstet Gynecol* 1999; 181: 1374–1381.
8. Irwin KL, et al. Influence of human immunodeficiency virus infection on pelvic inflammatory disease. *Obstet Gynecol* 2000; 95: 525–534.
9. Altunyurt S, Demir N and Posaci C. A randomized controlled trial of coil removal prior to treatment of pelvic inflammatory disease. *Eur J Obstet Gynecol Reprod Biol* 2003; 107: 81–84.
10. Tepper NK, et al. Retention of intrauterine devices in women who acquire pelvic inflammatory disease: a systematic review. *Contraception* 2013; 87: 655–660.

11. Yudin MH, et al. Vaginal polymorphonuclear leukocytes and bacterial vaginosis as markers for histologic endometritis among women without symptoms of pelvic inflammatory disease. *Am J Obstet Gynecol* 2003; 188: 318–323.
12. Miettinen AK, et al. 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.
13. Molander P. Observer agreement with laparoscopic diagnosis of pelvic inflammatory disease using photographs. *Obstet Gynecol* 2003; 101: 875–880.
14. Westrom L. Incidence, prevalence, and trends of acute pelvic inflammatory disease and its consequences in industrialized countries. *Am J Obstet Gynecol* 1980; 138: 880–892.
15. Judlin P. Current concepts in managing pelvic inflammatory disease. *Curr Opin Infect Dis* 2010; 23: 83–87.
16. Hillis SD, et al. Delayed care of pelvic inflammatory disease as a risk factor for impaired fertility. *Am J Obstet Gynecol* 1993; 168: 1503–1509.
17. Ness RB, et al. Effectiveness of treatment strategies of some women with pelvic inflammatory disease: a randomized trial. *Obstet Gynecol* 2005; 106: 573–580.
18. Hemsell DL, 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.
19. Martens MG, et al. Multicenter randomized trial of ofloxacin versus cefoxitin and doxycycline in outpatient treatment of pelvic inflammatory disease. Ambulatory PID Research Group. *South Med J* 1993; 86: 604–610.
20. Ness RB, et al. Effectiveness of inpatient and outpatient treatment strategies for women with pelvic inflammatory disease: results from the Pelvic Inflammatory Disease Evaluation and Clinical Health (PEACH) Randomized Trial. *Am J Obstet Gynecol* 2002; 186: 929–937.
21. Duarte R, Fuhrich D and Ross JD. A review of antibiotic therapy for pelvic inflammatory disease. *Int J Antimicrob Agents* 2015. doi: 10.1016/j.ijantimicag.2015.05.004
22. Wendel GD Jr, et al. A randomized trial of ofloxacin versus cefoxitin and doxycycline in the outpatient treatment of acute salpingitis. *Am J Obstet Gynecol* 1991; 164: 1390–1396.
23. Witte EH, et al. A comparison of pefloxacin/metronidazole and doxycycline/metronidazole in the treatment of laparoscopically confirmed acute pelvic inflammatory disease. *Eur J Obstet Gynecol Reprod Biol* 1993; 50: 153–158.
24. Judlin P, et al. Efficacy and safety of moxifloxacin in uncomplicated pelvic inflammatory disease: the MONALISA study. *Br J Obstet Gynaecol* 2010; 117: 1475–1484.
25. Heystek M, Ross JD and PID Study Group. A randomized double-blind comparison of moxifloxacin and doxycycline/metronidazole/ciprofloxacin in the treatment of acute, uncomplicated pelvic inflammatory disease. *Int J STD AIDS* 2009; 20: 690–695.
26. Ross JD, et al. Moxifloxacin versus ofloxacin plus metronidazole in uncomplicated pelvic inflammatory disease: results of a multicentre, double blind, randomised trial. *Sex Transm Infect* 2006; 82: 446–451.
27. Savaris RF, et al. Comparing ceftriaxone plus azithromycin or doxycycline for pelvic inflammatory disease: a randomized controlled trial. *Obstet Gynecol* 2007; 110: 53–60.
28. Walker CK, et al. Anaerobes in pelvic inflammatory disease: implications for the Centers for Disease Control and Prevention's guidelines for treatment of sexually transmitted diseases. *Clin Infect Dis* 1999; 28: S29–S36.

Appendix 1

Search strategy

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

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

1. Medline and Embase Search
   a. 1987–July 2017

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'. Ten thousand four hundred and twenty-two 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. 2015 CDC STD Treatment Guidelines (www.cdc.gov/std/)
3. 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 controlled 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 has received speaker fees from Becton Dickinson Diagnostics and consultancy fees from Glaxo Smith Kline pharma.

Secondo Guaschino has received speaker fees from Pierre Fabre.

Marco Cusini has no interests to declare.

Jorgen Jensen has no interests to declare.

Appendix 4

European STI guidelines editorial board and list of contributing organisations

Membership of the European STI Guidelines Editorial Board is available at:

http://iusti.org/regions/Europe/euroguidelines.htm

This guideline has been produced on behalf of the following organisations: the European Branch of the International Union against Sexually Transmitted Infections, the European Academy of Dermatology and Venereology, the European Dermatology Forum, the Union of European Medical Specialists, International Society for Infectious Diseases in Obstetrics and Gynaecology. The European Centre for Disease Prevention and Control and the European Office of the World Health Organisation also contributed to its development.