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Review

A review of antibiotic therapy for pelvic inflammatory disease

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ABSTRACT

Pelvic inflammatory disease (PID) is a gynaecological inflammatory disorder with a high incidence that can lead to sequelae such as infertility, ectopic pregnancy and chronic pelvic pain. The International Union against Sexually Transmitted Infections (IUSTI) and the US Centers for Disease Control and Prevention (CDC) have issued treatment recommendations for the management of PID. The purpose of this review is to summarise the available evidence for the use of IUSTI- and CDC-recommended antibiotic therapies for PID. The main differences between recommendations concern alternative regimens for inpatient treatment and the use of oral moxifloxacin as an alternative outpatient regimen in the IUSTI guidelines. There is evidence supporting the use of the recommended antibiotic regimens, although with some variation in reported cure rates. This variation can be explained, in part, by the different diagnostic and evaluation criteria used in different trials. Adverse events that require discontinuation of antibiotic therapy are rarely observed. The main limitation of the current available evidence is the short-term follow-up, which does not allow full evaluation of the risks of long-term sequelae.

1. Introduction

Pelvic inflammatory disease (PID) is an inflammatory disorder that affects the female upper genital tract. It is usually an ascending infection originating in the vagina and endocervix resulting in endometritis, salpingitis, tubo-ovarian abscess, parametritis, oophoritis and/or pelvic peritonitis [1–3]. A variety of causative agents have been implicated, including sexually transmitted organisms such as *Neisseria gonorrhoeae* and *Chlamydia trachomatis* as well as micro-organisms found in the vaginal flora (e.g. anaerobes, *Gardnerella vaginalis*, *Haemophilus influenzae*, enteric Gram-negative rods and *Streptococcus agalactiae*) [4–6]. The high incidence of PID, and its sequelae of infertility, ectopic pregnancy and chronic pelvic pain, are important public health issues. In the USA it is the most common gynaecological cause for hospital admission, and in England, even though the incidence is decreasing, 1.1% of young women attending primary care services are diagnosed with PID [7–9].

The diagnosis of PID is imprecise, lacks sensitivity and specificity, and there is no gold-standard diagnostic tool [3,4,10]. A clinical diagnosis of acute PID has a positive predictive value of 65% (compared with 90% for laparoscopy) but is still the most common approach in practice [3]. The clinical symptoms and signs of PID have a wide variation and range from asymptomatic to severe systemic illness [3]. The clinical features include lower abdominal pain, abnormal vaginal bleeding (postcoital, intermenstrual and menorrhagia), deep dyspareunia, lower abdominal tenderness, adnexal tenderness, cervical motion tenderness and fever [3,4,10]. The consequences of PID can be severe, and a delay in diagnosis and treatment probably increases the chance of impaired fertility [3,11]. Of those women with PID, 10–20% are subsequently infertile, 40% develop chronic pelvic pain and 10–20% of those who conceive will have an ectopic pregnancy [12,13].

2. Diagnosing and choosing an antibiotic regimen for pelvic inflammatory disease

The most common criteria used to initiate empirical treatment for PID are the presence of pelvic or lower abdominal pain in a sexually active young woman in whom no other cause has been identified, and where one or more of the following criteria are present on examination: cervical motion tenderness; uterine tenderness; or adnexal tenderness [3]. Additional criteria can be used to increase the specificity of a PID diagnosis (but decrease the sensitivity): oral temperature >38.3 °C; presence of numerous

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white blood cells on saline microscopy of vaginal fluid; abnormal cervical or vaginal mucopurulent discharge; elevated erythrocyte sedimentation rate/C-reactive protein; and laboratory documentation of cervical infection with *N. gonorrhoeae* or *C. trachomatis*. The absence of these additional findings does not exclude PID [1,3,4,10,14,15]. Further tests may assist in making a diagnosis but are not commonly used in clinical practice, e.g. endometrial biopsy, transvaginal sonography, pelvic magnetic resonance imaging (MRI) and laparoscopy [1,3,4,10]. A pregnancy test should be performed to help exclude ectopic pregnancy [1].

The choice of treatment regimen should consider drug costs, drug availability, patient acceptance/preference, antimicrobial susceptibility, local epidemiology of specific pathogens and severity of the disease [1,3,16]. Initial empirical treatment should cover *N. gonorrhoeae* and *C. trachomatis*. Resistance to third-generation cephalosporins in *N. gonorrhoeae* is emerging but varies between different populations and is less common in women compared with men [17–19]. *Mycoplasma genitalium* is emerging as a cause of PID [20], and although both azithromycin and moxifloxacin have in vitro activity against *M. genitalium*, resistant cases are increasingly being detected [21,22]. There is a lack of consensus about the need to routinely cover anaerobes in women with pelvic infection, but they are commonly associated with tubal and epithelial damage, and some guidelines recommend the routine inclusion of specific cover, typically with metronidazole or a cephalosporin such as cefoxitin [3].

PID may be assessed clinically as being mild, moderate or severe, and a number of scoring systems have been developed to assess the response to treatment (e.g. McCormack score, Westrom score) although their use is largely confined to clinical trials [23,24]. Mild and moderate disease can be treated on an outpatient basis with oral therapy since long-term outcomes are not improved with parenteral antibiotics [25]. Hospitalisation for intravenous therapy should be considered where there is diagnostic uncertainty, severe signs or symptoms, potential tubo-ovarian abscess, clinical failure with oral treatment, in pregnancy and if the patient is unable to tolerate oral medication. Parenteral treatment should be continued for at least 24 h after clinical improvement [1,3]. Most PID studies have evaluated a 10–14-day course of treatment and this is the length of therapy currently recommended [1].

Treatment of acute PID typically has a response rate of 90–95% as assessed by resolution of acute symptoms but unfortunately there is a poor correlation between short-term response and long-term sequelae such as infertility [26].

3. Current treatment recommendations

Recommendations have been developed both in the USA and Europe for the management of PID with antibiotic therapy (Table 1). These recommendations were based on the available evidence at the time, and the European guideline published in 2014 currently represent the most up-to-date evidence-based guidance.

First- and second-line inpatient treatment for PID differ between the guidelines. In the International Union against Sexually Transmitted Infections (IUSTI) guideline [1] it is suggested that doxycycline should be given with oral metronidazole, whilst the

Table 1
US and European current pelvic inflammatory disease treatment guidelines.

	US Centers for Disease Control and Prevention	International Union against Sexually Transmitted Infections
Inpatient regimens		
Regimen 1	Cefotetan 2 g i.v. q12h (*OR* cefoxitin 2 g i.v. q6h) *PLUS* doxycycline 100 mg orally or i.v. q12h *FOLLOWED BY*[a] oral therapy with doxycycline (100 mg twice daily)	Cefoxitin 2 g i.v. q6h (*OR* cefotetan 2 g i.v. q12h *OR* ceftriaxone 1 g i.v./i.m. once daily) *PLUS* doxycycline 100 mg i.v. q12h (oral doxycycline may be used if tolerated) *FOLLOWED BY*[a] oral doxycycline 100 mg twice daily plus oral metronidazole 400 mg q12h
Regimen 2	Clindamycin 900 mg i.v. q8h *PLUS* gentamicin loading dose i.v. or i.m. (2 mg/kg of body weight) followed by a maintenance dose (1.5 mg/kg) q8h. Single daily dosing (3–5 mg/kg) can be substituted. *FOLLOWED BY*[a] doxycycline 100 mg orally twice daily or clindamycin 450 mg orally four times a day	Clindamycin 900 mg i.v. q8h *PLUS* gentamicin i.v. [2 mg/kg loading dose followed by 1.5 mg/kg q8h (a single daily dose may be substituted)] *FOLLOWED BY*[a] either oral clindamycin 450 mg four times daily *OR* oral doxycycline 100 mg twice daily *PLUS* oral metronidazole 400 mg twice daily
Alternative inpatient regimens		
Regimen 3	Ampicillin/sulbactam 3 g i.v. q6h *PLUS* doxycycline 100 mg orally or i.v. q12h	Ofloxacin 400 mg i.v. q12h *PLUS* metronidazole 500 mg i.v. q8h for 14 days
Regimen 4	Azithromycin, either as monotherapy for 1 week (500 mg i.v. for one or two doses followed by 250 mg orally for 5–6 days) or combined with a 12-day course of metronidazole	Ciprofloxacin 200 mg i.v. q12h *PLUS* doxycycline 100 mg i.v. (or oral) q12h *PLUS* metronidazole 500 mg i.v. q8h for 14 days
Outpatient regimens		
Regimen 1	Ceftriaxone 250 mg i.m. in a single dose *PLUS* doxycycline 100 mg orally twice daily for 14 days *WITH* or *WITHOUT* metronidazole 500 mg orally twice daily for 14 days	Ceftriaxone 500 mg i.m. single dose *FOLLOWED BY* oral doxycycline 100 mg q12h *PLUS* metronidazole 400 mg q12h for 14 days
Regimen 2	Cefoxitin 2 g i.m. in a single dose and probenecid 1 g orally administered concurrently in a single dose *PLUS* doxycycline 100 mg orally twice daily for 14 days *WITH* or *WITHOUT* metronidazole 500 mg orally twice daily for 14 days	Cefoxitin 2 g i.m. single dose and oral probenecid 1 g *FOLLOWED BY* oral doxycycline 100 mg q12h *PLUS* metronidazole 400 mg q12h for 14 days
Regimen 3	Other parenteral third-generation cephalosporin (e.g. ceftizoxime or cefotaxime) *PLUS* doxycycline 100 mg orally twice daily for 14 days *WITH* or *WITHOUT* metronidazole 500 mg orally twice daily for 14 days	Oral ofloxacin 400 mg q12h *PLUS* oral metronidazole 500 mg q12h for 14 days (ofloxacin may be replaced by levofloxacin 500 mg once daily)
Alternative outpatient regimens		
Regimen 4	Levofloxacin 500 mg orally once daily or ofloxacin 400 mg twice daily for 14 days *WITH* or *WITHOUT* metronidazole 500 mg orally twice daily for 14 days	Ceftriaxone 500 mg i.m. single dose *PLUS* oral azithromycin 1 g single dose followed by a second dose of oral azithromycin 1 g after 1 week
Regimen 5	Ceftriaxone 250 mg i.m. single dose *PLUS* oral azithromycin 1 g single dose followed by a second dose of oral azithromycin 1 g after 1 week	Oral moxifloxacin 400 mg q24h for 14 days

i.v., intravenous; q12h, every 12 h; q6h, every 6 h; i.m., intramuscular; q8h, every 8 h; q24h, every 24 h.
[a] Parenteral therapy should be continued until 24 h after clinical improvement; oral therapy to continue to complete 14 days of therapy in total.

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