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Review

A review of antibiotic therapy for pelvic inflammatory disease

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A B S T R A C T

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.

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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, Cardinergella 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
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

**Table 1**

<table>
<thead>
<tr>
<th>US Centers for Disease Control and Prevention</th>
<th>International Union against Sexually Transmitted Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inpatient regimens</strong></td>
<td></td>
</tr>
<tr>
<td>Regimen 1</td>
<td>Cefotetan 2 g i.v. q12h (OR cefixitin 2 g i.v. q6h) PLUS doxycycline 100 mg orally or i.v. q12h FOLLOWED BY oral therapy with doxycycline (100 mg twice daily)</td>
</tr>
<tr>
<td>Regimen 2</td>
<td>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 oral doxycycline 100 mg orally twice daily or clindamycin 450 mg orally four times a day</td>
</tr>
<tr>
<td><strong>Alternative inpatient regimens</strong></td>
<td></td>
</tr>
<tr>
<td>Regimen 3</td>
<td>Ampicillin/sulbactam 3 g i.v. q6h PLUS doxycycline 100 mg orally or i.v. q12h</td>
</tr>
<tr>
<td>Regimen 4</td>
<td>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</td>
</tr>
<tr>
<td><strong>Outpatient regimens</strong></td>
<td></td>
</tr>
<tr>
<td>Regimen 1</td>
<td>Ceftriaxone 250 mg i.m. in a single dose PLUS doxycycline 100 mg orally twice daily for 14 days OR metronidazole 500 mg orally twice daily for 14 days</td>
</tr>
<tr>
<td>Regimen 2</td>
<td>Cefoxitin 2 g i.m. in a single dose plus probenecid 1 g orally administered concurrently in a single dose PLUS doxycycline 100 mg orally twice daily for 14 days OR metronidazole 500 mg orally twice daily for 14 days</td>
</tr>
<tr>
<td>Regimen 3</td>
<td>Other parenteral third-generation cephalosporin (e.g. cefotaxime or cefoxaxime) PLUS doxycycline 100 mg orally twice daily for 14 days OR metronidazole 500 mg orally twice daily for 14 days</td>
</tr>
<tr>
<td><strong>Alternative outpatient regimens</strong></td>
<td></td>
</tr>
<tr>
<td>Regimen 4</td>
<td>Levofloxacin 500 mg orally once daily or ofloxacin 400 mg twice daily for 14 days OR metronidazole 500 mg orally twice daily for 14 days</td>
</tr>
<tr>
<td>Regimen 5</td>
<td>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</td>
</tr>
</tbody>
</table>

i.v., intravenous; q12h, every 12 h; q6h, every 6 h; i.m., intramuscular; q8h, every 8 h; q24h, every 24 h.

* Parenteral therapy should be continued until 24 h after clinical improvement; oral therapy to continue to complete 14 days of therapy in total.
doxycycline should be given with oral metronidazole, whilst the US Centers for Disease Control and Prevention (CDC) recommends this only if a tubo-ovarian abscess is present [3].

For outpatient regimens there are differences in the recommended dosage of intramuscular ceftriaxone between the European and CDC guidelines [1,3]. The higher dose of intramuscular ceftriaxone is recommended in the European guideline to reduce the risk of resistance developing in N. gonorrhoeae. Metronidazole is part of the recommended regimen in the European guideline, whilst for the CDC metronidazole is optional due to uncertainty as to the importance of treating anaerobes. Oral ofloxacin or levofloxacin plus oral metronidazole is a recommend outpatient antibiotic regimen in the European and CDC guidelines as long as the risk of gonococcal PID is low reflecting the relatively high risk of quinolone resistance in gonorrhoea in many areas of the world. Oral moxifloxacin is not recommended in the CDC guideline but is suggested as an option in the European guideline if gonococcal PID is considered unlikely [1].

The strengths and weaknesses of commonly used regimens are shown in Table 2.

3.1. Ceftriaxone (or cefoxitin) plus doxycycline and metronidazole

Several studies have investigated the effectiveness of ceftriaxone, cefoxitin, doxycycline and metronidazole in a variety of combinations, but the effectiveness of the specific regimen of ceftriaxone (or cefoxitin) plus doxycycline and metronidazole for the treatment of PID has not yet been evaluated. The majority of published studies have looked at parenteral cefoxitin followed by oral doxycycline [27–34]. Cure rates for the different antibiotic regimens are presented in Table 3, although comparisons between studies should be interpreted with caution as the definition of cure, timing of outcome evaluation, and the use of per-protocol versus intention-to-treat analyses differ between studies, and several trials also have small patient numbers.

The use of cefoxitin as a single antibiotic agent [35,36], doxycycline alone [37], doxycycline plus metronidazole [38] and ceftriaxone plus doxycycline [39,40] for the treatment of PID have been less extensively explored. As a simpler alternative with a lower tablet burden, a study investigating the use of ceftriaxone plus two doses of weekly azithromycin found a cure rate of 56/62 (90%) [40].

Commonly observed side effects associated with the use of ceftriaxone (or cefoxitin), doxycycline and metronidazole are presented in Table 4. Two studies have reported withdrawals due to side effects. One patient (1/69; 1.4%) administered ceftriaxone plus doxycycline withdrew from treatment due to severe pruritus and moderate rash [39], and one patient (1/114; 0.9%) withdrew from treatment due to hives subsequent to administration of cefoxitin plus doxycycline [27].

3.2. Ofloxacin (plus metronidazole)

Ofloxacin can be administered on an inpatient or outpatient basis with the addition of either oral or parenteral metronidazole. There is a reasonable evidence base for this regimen, with cure rates

Table 2
Strengths and limitations of currently recommended antibiotic regimens for pelvic inflammatory disease (PID).

<table>
<thead>
<tr>
<th>Antibiotic regimen</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone (or cefoxitin) + doxycycline + metronidazole</td>
<td>Good evidence base, can be administered on an inpatient or outpatient basis</td>
<td>Reluctance of patients to receive antibiotic intramuscularly, limited mycoplasma cover</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Inexpensive</td>
<td>Ceftriaxone provides less effective cover for anaerobic infection than cefoxitin</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Levofloxacin as once-daily alternative to ofloxacin</td>
<td>Well tolerated but occasional quinolone or metronidazole side effects</td>
</tr>
<tr>
<td>Clindamycin (plus gentamicin)</td>
<td>Inpatient care including pelvic abscesses</td>
<td>Limited efficacy against chlamydia</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>Four large RCTs showing effectiveness</td>
<td>Limited to inpatient administration</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Covers anaerobes</td>
<td>Not appropriate for possible gonococcal PID</td>
</tr>
</tbody>
</table>


Table 4
Commonly observed side effects according to antibiotic regimen.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Antibiotic regimen</th>
<th>At least one side effect</th>
<th>Gastrointestinal*</th>
<th>Rash</th>
<th>Pruritus</th>
<th>Infection site reaction*</th>
<th>Vaginal or vulvar symptoms</th>
<th>Withdrawals and reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arredondo et al., 1997</td>
<td>Ceftriaxone plus doxycycline</td>
<td>52/69 (75%)</td>
<td>46/69 (66.6%)</td>
<td>1/69</td>
<td>1/69</td>
<td>–</td>
<td>–</td>
<td>1/69 (1.4%) severe pruritus and moderate rash</td>
</tr>
<tr>
<td>Hernsell et al., 1994</td>
<td>Cefoxitin plus doxycycline</td>
<td>–</td>
<td>26/114 (22.8%)</td>
<td>–</td>
<td>2/114</td>
<td>–</td>
<td>–</td>
<td>9/114 (7.9%) 1/114 (0.9%) hives</td>
</tr>
<tr>
<td>Landers et al., 1991</td>
<td>Cefoxitin plus doxycycline</td>
<td>–</td>
<td>2/75 (2.6%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>European Study Group, 1992</td>
<td>Cefoxitin plus doxycycline</td>
<td>–</td>
<td>10/82 (12.2%)</td>
<td>–</td>
<td>–</td>
<td>6/82 (7.3%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Martens et al., 1993</td>
<td>Cefoxitin plus doxycycline</td>
<td>20/134 (14.9%)</td>
<td>19/134 (14.2%)</td>
<td>1/134</td>
<td>1/134</td>
<td>–</td>
<td>–</td>
<td>6/134 (4.5%) –</td>
</tr>
<tr>
<td>Walters and Gibbs, 1990</td>
<td>Cefoxitin plus doxycycline</td>
<td>–</td>
<td>2/56 (3.6%)</td>
<td>1/56</td>
<td>1/56</td>
<td>–</td>
<td>–</td>
<td>11/56 (19.6%) –</td>
</tr>
<tr>
<td>Wendel Jr et al., 1991</td>
<td>Cefoxitin plus doxycycline</td>
<td>9/35 (25.7%)</td>
<td>3/35 (8.6%)</td>
<td>–</td>
<td>–</td>
<td>2/35 (5.7%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Heinonen et al., 1989</td>
<td>Doxycycline plus metronidazole</td>
<td>–</td>
<td>2/20 (10%)</td>
<td>–</td>
<td>–</td>
<td>6/20 (30%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Martens et al., 1993</td>
<td>Ofloxacin</td>
<td>9/138 (6.5%)</td>
<td>3/138 (2.2%)</td>
<td>2/138</td>
<td>2/138</td>
<td>–</td>
<td>5/138 (3.6%)</td>
<td>–</td>
</tr>
<tr>
<td>Wendel Jr et al., 1991</td>
<td>Ofloxacin</td>
<td>6/37 (16.2%)</td>
<td>2/37 (5.4%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1/37 (2.7%)</td>
<td>1/37 (2.7%) severe nausea and vomiting 10/578 (1.7%)</td>
</tr>
<tr>
<td>Asçiçlio glu et al., 2013</td>
<td>Ofloxacin plus metronidazole</td>
<td>252/543 (46.4%)</td>
<td>202/543 (37.2%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ross et al., 2006</td>
<td>Ofloxacin plus metronidazole</td>
<td>200/363 (55.1%)</td>
<td>71/363 (19.6%)</td>
<td>8/363</td>
<td>4/363</td>
<td>7/363 (1.9%)</td>
<td>17/363 (4.7%)</td>
<td>18/363 (5.0%) –</td>
</tr>
<tr>
<td>Hernsell et al., 1994</td>
<td>Clindamycin plus gentamicin</td>
<td>–</td>
<td>26/116 (22.4%)</td>
<td>–</td>
<td>–</td>
<td>6/116 (5.2%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hernsell et al., 1997</td>
<td>Clindamycin plus gentamicin</td>
<td>41/256 (16.0%)</td>
<td>13/256 (5.1%)</td>
<td>–</td>
<td>1/256</td>
<td>6/256 (2.3%)</td>
<td>–</td>
<td>1/256 (0.4%) persistent temperature spikes</td>
</tr>
<tr>
<td>European Study Group, 1992</td>
<td>Clindamycin plus gentamicin</td>
<td>–</td>
<td>15/88 (17.0%)</td>
<td>–</td>
<td>–</td>
<td>9/88 (10.2%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Walters and Gibbs, 1990</td>
<td>Clindamycin plus gentamicin</td>
<td>–</td>
<td>2/46 (4.3%)</td>
<td>1/46</td>
<td>1/46</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Asçiçlio glu et al., 2013</td>
<td>Moxifloxacin</td>
<td>210/560 (37.3%)</td>
<td>143/560 (25.5%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>7/578 (1.2%) –</td>
</tr>
<tr>
<td>Heystek and Ross, 2009</td>
<td>Moxifloxacin</td>
<td>151/343 (44.0%)</td>
<td>100/343 (29.2%)</td>
<td>8/343</td>
<td>4/343</td>
<td>8/343 (2.3%)</td>
<td>10/343 (2.9%)</td>
<td>–</td>
</tr>
<tr>
<td>Judin et al, 2010</td>
<td>Moxifloxacin</td>
<td>106/228 (46.5%)</td>
<td>57/228 (25.0%)</td>
<td>–</td>
<td>–</td>
<td>9/228 (3.9%)</td>
<td>9/228 (3.9%)</td>
<td>–</td>
</tr>
<tr>
<td>Ross et al., 2006</td>
<td>Moxifloxacin</td>
<td>179/378 (47.4%)</td>
<td>54/378 (14.3%)</td>
<td>6/378</td>
<td>2/378</td>
<td>13/378 (3.4%)</td>
<td>11/378 (2.9%)</td>
<td>24/378 (6.3%) –</td>
</tr>
</tbody>
</table>

* Gastrointestinal side effects include diarrhoea, constipation, flatulence, nausea and vomiting.

* Infection site reaction includes inflammation and pain.
3.3. Clindamycin (plus gentamicin)

Clindamycin (plus gentamicin) is a second option antibiotic regimen recommended for inpatients in both guidelines. Several studies have investigated the effectiveness of clindamycin plus gentamicin in the treatment of PID [27,28,30,35,43–48], and the effectiveness of clindamycin alone was investigated in a single study [49]. Cure rates ranged from 39% to 100%. This wide range in cure rates may be related to the limited number of patients (<40 patients in 8 of the 11 studies). Cover for C. trachomatis is limited with this combination and repeat testing after 4 weeks may be advisable if Chlamydia is detected at baseline.

The most commonly observed side effect was gastrointestinal intolerance. One (1/256; 0.4%) patient receiving clindamycin plus gentamicin stopped therapy due to persistent temperature spikes [47].

3.4. Moxifloxacin

Oral moxifloxacin is recommended as an alternative regimen in the European guideline for outpatient treatment. Although not included in the CDC recommendations, four large randomised controlled trials have demonstrated the effectiveness of moxifloxacin for the management of PID [41,42,50,51]. The total number of patients receiving moxifloxacin in clinical studies is larger than for any of the other recommended antibiotic regimens, the studies are amongst the most recent available for PID, and fulfil most of the CONSORT (Consolidated Standards of Reporting Trials) recommendations for reporting. The main limitation in the use of moxifloxacin is its limited cover for gonococcal PID.

In one of the studies, 9/228 (3.9%) of the patients receiving moxifloxacin withdrew from treatment after experiencing a drug-related side effect [51]. In the Ross et al. study, 24/378 patients (6.3%) ceased moxifloxacin administration due to side effects [42], whilst 7/578 (1.2%) withdrew from treatment in the Aşıcıoğlu et al. trial [41].

4. Additional considerations

PID in pregnancy, although uncommon, has been associated with an increase in maternal and foetal morbidity and preterm delivery [1,3]. Management should be as an inpatient with parenteral antibiotics (e.g. ceftriaxone plus erythromycin plus metronidazole), although there is limited evidence to support any specific antibiotic regimen.

The partners of patients diagnosed with PID should be referred for screening for gonorrhoea and chlamydia and given appropriate empirical treatment (usually with azithromycin 1g single dose). The time interval for seeking partners is arbitrary, with the IUSTI recommending review of sexual partners within a 6-month period of onset of symptoms [1] and the CDC suggesting assessment of partners within 60 days (or the most recent sexual partner if longer than 60 days) [3]. Unprotected intercourse should be avoided until both partners have completed their course of antibiotics in order to avoid re-infection.

The risk of impaired fertility approximately doubles with each new presentation of PID [52] and the use of condoms is advised to reduce the risk of recurrent infection.

5. Criteria for pelvic inflammatory disease cure

Reported cure rates for PID may be difficult to interpret and depend on the definition used for clinical cure and the type of analysis performed (per-protocol versus intention-to-treat). For example, Heystek and Ross report cure rates for oral moxifloxacin that range from 60% to 77% in a single trial: clinical cure rate 63.7% (defined as reduction of >70% in severity score, normal temperature and leucocyte count 2–14 days post-treatment); clinical success rate 77% (defined as clinical cure or improvement, i.e. <70% reduction in severity score but >30%, plus normal temperature and leucocyte count 2–14 days post-treatment); or clinical cure or improvement 60% (<70% reduction in severity score but >30%, plus normal temperature and leucocyte count 21–35 days post-treatment) [50]. Savaris et al. report cure rates ranging from 31% to 72%, depending on the definition of cure, following the use of ceftriaxone plus doxycycline [40]. A consensus needs to be agreed on the criteria for clinical cure following treatment to allow comparisons to be made between different studies.

Future analyses based on the severity of PID at presentation would be useful since it is likely that this influences short- and long-term response rates.

6. Conclusions

There is good evidence to support the antibiotic regimens recommended in international guidelines for the management of PID. However, comparisons of efficacy between studies should be interpreted with caution due to the lack of a standardised approach to diagnosis and evaluation. Most published studies provide only short-term follow-up, which does not correlate well with the risk of long-term sequelae. Side effects do not appear to differ substantially between antibiotic regimens and the most commonly observed side effect is gastrointestinal intolerance. Side effects requiring discontinuation of therapy are relatively rare. Early diagnosis and treatment of PID before irreversible damage to the Fallopian tubes occurs should be prioritised, and prompt and effective therapy with appropriate antibiotics can preserve fertility in the majority of women.

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Competing interests

None declared.

Ethical approval

Not required.

References


