EXPERT REVIEWS

Recommendations and rationale for the treatment of pelvic inflammatory disease

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Pelvic inflammatory disease (PID) is one of the most common serious infections of nonpregnant women of reproductive age. Management of PID is directed at containment of infection. Goals of therapy include the resolution of clinical symptoms and signs, the eradication of pathogens from the genital tract and the prevention of sequelae including infertility, ectopic pregnancy and chronic pelvic pain. The choice of an antibiotic regimen used to treat PID relies upon the appreciation of the polymicrobial etiology of this ascending infection including *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma genitalium* and other lower genital tract endogenous anaerobic and facultative bacteria, many of which are associated with bacterial vaginosis. Currently available evidence and the CDC treatment recommendations support the use of broad-spectrum antibiotic regimens that adequately cover the above named microorganisms. The outpatient treatment of mild-to-moderate PID should include tolerated antibiotic regimens consisting of an extended-spectrum cephalosporin in conjunction with either azithromycin or doxycycline. Clinically severe PID should prompt hospitalization and imaging to rule out a tubo–ovarian abscess. Parenteral broad-spectrum antibiotic therapy with activity against a polymicrobial flora, particularly Gram-negative aerobes and anaerobes, should be implemented.

Keywords: antimicrobial treatment • pelvic inflammatory disease • PID • tubo–ovarian abscess

Pelvic inflammatory disease (PID) presents as a spectrum of infection-induced inflammation of the upper genital tract that includes endometritis, salpingitis, pelvic peritonitis and/or tubo–ovarian abscess (TOA) [1]. Acute PID is caused by the ascending spread of microorganisms from the vagina and/or endocervix to the endometrium, fallopian tubes and/or adjacent structures.

Over 800,000 cases of PID are diagnosed annually in the USA and estimates indicate that the direct costs of treatment exceed US$2 billion [2]. This estimate fails to take into consideration both the recent increase in *Chlamydia trachomatis* and gonococcal infections [3] and the existence of subclinical or atypical PID (also referred to as 'silent salpingitis'), which may go untreated [4].

Etiology of PID

The microbial etiology of PID has been defined by investigators using endometrial biopsy, culdocentesis and laparoscopy to assess the presence of pathogens in upper genital tract sites, the endometrium, fallopian tube and peritoneal cavity (cul-de-sac). *Neisseria gonorrhoeae*, *C. trachomatis* and *Mycoplasma genitalium* have all been recovered from the cervix, endometrium and fallopian tube of women with laparoscopically proven acute salpingitis [5–8]. In addition, a polymicrobial flora was documented in these sites consisting of microorganisms such as *Prevatella* sp. and *Peptostreptococcus* sp. These microorganisms have also been noted to be associated with histologic evidence of inflammation (endometritis) in asymptomatic women harboring the microorganism in their cervix or with evidence of bacterial vaginosis (BV) [9]. The microorganisms isolated from women with TOAs reflect the facultative and aerobic microorganisms and commonly include *Escherichia coli* and anaerobic Gram-negative rods. The choice of an antibiotic regimen should reflect our current knowledge of the microbial etiology of PID and offer broad-spectrum coverage of these microorganisms.

Diagnosis

Clinicians should maintain a low threshold for the diagnosis of PID. The diagnosis should be considered in sexually active women with or

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Box 1. Symptoms in women with clinically suspected pelvic inflammatory disease.

- Abdominal pain
- Abnormal discharge
- Intermenstrual bleeding
- Postcoital bleeding
- Fever
- Urinary frequency
- Lower back pain
- Nausea/vomiting

Data taken from [50,51].

without lower abdominal pain and symptoms noted in **Box 1**. A physical examination should be performed to assess the abdomen for tenderness. Vaginal secretions examination should be performed to assess for the presence of BV. Microscopy of the vaginal secretions (wet mount) should be examined for the presence of leukocytes as well as clue cells and trichomonads. The cervical canal should be examined for the presence of yellow or green mucopus and friability, and testing for *C. trachomatis* and *N. gonorrhoeae* should be performed. A bimanual pelvic examination should be performed to assess for pelvic organ tenderness and for evidence of a pelvic mass, which might suggest a TOA.

Other ancillary tests that can be performed in diagnosing PID include a complete blood count, erythrocyte sedimentation rate or C-reactive protein test. These tests are recommended for patients with clinically severe PID. Imaging studies are most helpful when ruling out competing differential diagnoses such as the use of pelvic ultrasonography to rule out symptomatic ovarian cysts and computed tomography to rule out appendicitis. Pelvic ultrasonography has limited sensitivity for the diagnosis of PID, but the specific finding of thickened fluid-filled tubes by ultrasonography supports the diagnosis of upper genital tract inflammation. Pelvic ultrasonography should be performed in patients requiring hospitalization or those with a pelvic mass noted on bimanual pelvic examination to further characterize what could be a TOA.

Women with evidence of lower genital tract infection (*N. gonorrhoeae*, *C. trachomatis*, *Trichomonas vaginalis* or BV) and cervicovaginal inflammation and no pelvic organ tenderness can be treated for an uncomplicated lower genital tract infection or cervicitis (**Box 2**) [10]. For those with lower genital tract inflammation and pelvic organ tenderness, treatment for the syndromic diagnosis of PID is required. Most women with PID are clinically mild or moderate cases and can be treated as outpatients. Women with severe PID or those meeting the criteria noted in **Box 3** should be considered for hospitalization and inpatient parenteral therapy.

Treatment

Cervicitis

As mentioned previously, women with a clinical diagnosis of cervicitis often test positive for *C. trachomatis*, *N. gonorrhoeae* and *T. vaginalis* or have evidence of BV. It is known that up to 27% of these women will have histologic evidence of endometritis [9], therefore we must be confident that the choice of antibiotic therapy

Box 2. Outpatient antibiotic regimen for cervicitis.

Cefixime 400 mg orally in a single dose
Plus
Azithromycin 1 g orally in a single dose
Plus
Metronidazole 500 mg orally twice daily for 7 days if bacterial vaginosis or *Trichomonas vaginalis* is present

Data taken from [10].

for the treatment of cervicitis also covers endometritis (diagnosed in some women with mucopurulent cervicitis and no pelvic organ tenderness during bimanual exam). The antibiotic regimen should not only treat the potential pathogens noted but also result in a resolution of their endometritis. Fortunately, Eckert *et al.*, showed that a short course of an oral antibiotic regimen consisting of single-dose cefixime 400 mg, single-dose azithromycin 1 g and metronidazole 500 mg twice daily for 7 days was highly effective (89%) in leading to the resolution of histologic endometritis (**Box 2**) [10]. Metronidazole may be withheld if no evidence of BV or *T. vaginalis* is present.

Mild-to-moderate PID

Most cases of PID (diagnosed in women with evidence of lower genital tract inflammation and pelvic organ tenderness but no mass) have mild-to-moderate disease. These patients can safely be treated as outpatients. Treatment of PID should provide high rates of clinical and microbiologic cure for *N. gonorrhoeae* and *C. trachomatis*, even in the presence of negative endocervical screening for these organisms. It should also provide coverage for the polymicrobial flora found associated with BV [8,11–14].

The Pelvic Inflammatory Disease Evaluation and Clinical Health Randomized Trial (PEACH) provides the best guidance regarding the antibiotic therapy of women with mild-to-moderate PID. In this large, multicentered, prospective randomized trial, a single dose of intramuscular cefoxitin administered with probenecid, followed with 14 days of oral doxycycline, resulted in a similar short-term cure rate (both >98%) in outpatients when compared with multiple parenteral doses of cefoxitin and oral doxycycline in inpatients. There was no difference in the long-term outcomes of fertility and ectopic pregnancies between the two groups. Although two-thirds of the PEACH participants had BV, concurrent metronidazole was not administered. This suggests that a single dose of cefoxitin, which has good activity against Gram-negative anaerobes, and multiple doses of doxycycline, despite suboptimal activity against

Box 3. Criteria for hospitalization in women with pelvic inflammatory disease.

- Surgical emergencies (e.g., appendicitis) cannot be excluded
- Patient is pregnant
- Patient does not respond clinically to oral antibiotic therapy
- Patient is unable to follow or tolerate an outpatient oral regimen
- Patient has severe illness, nausea and vomiting or high fever
- Patient has a tubo–ovarian abscess

Data from [52].

Box 4. The April 2007 CDC updated recommended oral regimens.

Ceftriaxone 250 mg intramuscularly in a single dose
Plus
Doxycycline 100 mg orally twice a day for 14 days
With or without
Metronidazole 500 mg orally twice a day for 14 days
Or
Cefoxitin 2 g intramuscularly in a single dose and
Probenecid 1 g orally administered concurrently in a single dose
Plus
Doxycycline 100 mg orally twice a day for 14 days
With or without
Metronidazole 500 mg orally twice a day for 14 days
Or
Other parenteral third-generation cephalosporins (e.g., ceftizoxime or cefotaxime)
Plus
Doxycycline 100 mg orally twice a day for 14 days
With or without
Metronidazole 500 mg orally twice a day for 14 days

Data taken from [18].

anaerobic bacteria, are sufficient for clinical cure and apparently do not adversely affect long-term outcome comparatively [15]. The CDC-recommended regimens allow substitution of cefoxitin with other extended-spectrum cephalosporins such as ceftriaxone, ceftizoxime and cefotaxime. The CDC-recommended regimens also allow the clinician discretion to extend the anaerobic coverage by prescribing oral metronidazole in addition to the aforementioned doxycycline (Box 4).

Severe PID & TOA

Women with clinically severe PID or who meet the criteria noted in Box 3, or both, should be considered for hospitalization and inpatient parenteral therapy. These patients are most likely have nonchlamydial polymicrobial PID or, less commonly, acute gonococcal PID. Imaging should be considered in hospitalized patients to evaluate for other diseases and/or abscess. Women hospitalized with severe PID may have TOA, and imaging with pelvic ultrasonography or computed tomography is recommended [16]. Although 75% of women with TOA will respond to antibiotic therapy alone, some will fail to respond and require surgical intervention [17]. The need for surgical intervention is related to the size of the TOA with 60% of those with abscesses 10 cm or greater in diameter, 30% of those measuring 7–9 cm, and only 15% of those 4–6 cm in diameter needing surgery [17]. Patients who fail to respond to antibiotic treatment within 48–72 h, as characterized by persistent fever and increasing leukocytosis, should be considered for surgical drainage. Drainage of TOA can be effected by laparotomy, laparoscopy or image-guided percutaneous routes.

Proper antimicrobial therapy of pelvic abscesses includes an antibiotic regimen with activity against anaerobic bacteria such as *Bacteroides fragilis* and *Prevatella bivius,* which are β-lactamase producing. In addition, the antimicrobial regimen should have good coverage for *E. coli,* a common and predominant isolate from patients with ruptured TOA and a well-recognized cause of Gram-negative sepsis. Regimens recommended for this clinical scenario include the combination regimens of clindamycin with gentamicin, cefotetan or cefoxitin with doxycycline, and ampicillin/sulbactam with doxycycline (Box 5) [18].

Expert commentary

Treatment of PID should take into account the short-term goals of clinical and microbiological cure and the long-term goals of prevention of infertility, ectopic pregnancy, recurrent infection and chronic pelvic pain. Optimal antimicrobial regimens should be well tolerated with little to no gastrointestinal side effects and tailored for compliance, for example, single- to short-course regimens administered once a day or even less frequently if possible. Oral therapy is preferred over parenteral therapy for reasons of convenience and cost as well as to avoid the pain of needle injection. Cost is an important consideration and relative expense of the antimicrobials under consideration is noted in Table 1.

Several quinolone antimicrobials (e.g., moxifloxacin, ciprofloxacin and ofloxacin) alone or in combination with other agents have been studied and shown to be effective in the treatment of PID [19–22]. However, ciprofloxacin appeared less effective in clearing BV-associated microorganisms from the endometrium despite the patients' clinical cure [20]. This causes some concern that persistent anaerobic infection could lead to a relapse of endometritis and salpingitis. In addition, owing to increasing *N. gonorrhoeae* resistance, quinolone use is no longer recommended for the treatment of *N. gonorrhoeae* in the USA and therefore cannot be considered a primary monotherapy option for the treatment of PID in areas with quinolone-resistant *N. gonorrhoeae* (QRNG) [23,24]. In areas where QRNG is uncommon, moxifloxacin is an antibiotic that should be considered for the treatment of acute PID.

Box 5. The April 2007 CDC updated parenteral regimens.

Recommended regimen A
Cefotetan 2 g intravenously every 12 h
Or
Cefoxitin 2 g intravenously every 6 h
Plus
Doxycycline 100 mg orally or intravenously every 12 h
Recommended regimen B
Clindamycin 900 mg intravenously every 8 h
Plus
Gentamicin loading dose intravenously or intramuscularly (2 mg/kg of bodyweight), followed by a maintenance dose (1.5 mg/kg) every 8 h. Single daily dosing may be substituted
Alternative regimen
Ampicillin/sulbactam 3 g intravenously every 6 h
Plus
Doxycycline 100 mg orally or intravenously every 12 h

Data taken from [18].

Table 1. Cost of frequently used antibiotics in the treatment of pelvic inflammatory disease.

Drug	Regimen dose	Regimen cost
Azithromycin	500 mg p.o. × one dose followed by 250 mg q.d. × 7 days	Tablets: 250 mg (eight tablets) US$26.40†
Amoxicillin/clavulanate	875 mg p.o. q 12 h for 12 days	Tablets: 875–125 mg (24 tablets) US$38.40†
Ampicillin/sulbactam	3 g iv. q 6 h for 48 h	iv. vial: (2 g:1 g) for 48 h US$80‡
Ceftriaxone	1 g iv. q 12 h for 48 h	iv. vial: (250 mg) US$3; iv. vial: (2 g) for 48 h US$18.28‡
Cefixime	400 mg p.o. × one dose	Tablets: 400 mg (one tablet) US$11‡
Cefoxitin	2 g im. × one dose (mild-to-moderate PID) 2 g iv. q 6 h for 48 h in severe PID	iv. vial: (1 g/50 ml) US$11.23‡ US$22.46 for 2 g dose US$179.68 for 48 h
Cefotetan	2 g iv. q 12 h for 48 h	iv. vial: (2 g) US$28.45‡ US$113.8 for 48 h
Clindamycin	900 mg iv. q 8 h	iv. vial: (900 mg) US$13.28‡ US$79.68 for 48 h
Doxycycline	100 mg p.o. q 12 h for 14 days 100 mg iv. q 12 h in severe PID	Capsule: 100 mg (28 capsules) US$12.13†
Gentamicin	Loading dose 2 mg/kg iv. followed by maintenance dose (1.5 mg/kg) q 8 h single q.d. Dosing may be substituted by 4.5 mg/kg iv. q.d.	Solution: 10 mg/ml (25 vials, 2 ml) US$125†
Metronidazole	500 mg p.o. q 12 h for 14 days	Tablets: 500 mg (28 tablets) US$12.12†
Probenecid	1 g p.o. administered concurrently with cefoxitin	Tablets: 500 mg (two tablets) US$1.17‡
Trimethoprim/sulfamethoxazole	160/800 mg p.o. q 12 h for 12 days	Tablets: 160–800 mg (24 tablets) US$16†
Ciprofloxacin	500 mg p.o. q 12 h	Tablets: 500 mg (28 tablets) US$11†
Levofloxacin	500 mg p.o. q.d.	Tablets: 500 mg (14 tablets) US$236.60†
Moxifloxacin	400 mg p.o. or iv. q.d.	Tablets: 400 mg (14 tablets) US$225.60†

†Approximate retail price from [101].
‡Average wholesale price from [102].
im.: Intramuscularly; iv.: Intravenously; PID: Pelvic inflammatory disease; p.o.: Orally; q: Every; q.d.: Daily.

Moxifloxacin has been found in three randomized controlled trials to be an effective and well-tolerated oral treatment in women with acute PID [25]. Ross *et al.* found that moxifloxacin once-daily monotherapy was as clinically and bacteriologically effective as twice-a-day ofloxacin–metronidazole combination [22]. Heysteck *et al.* also demonstrated the efficacy of moxifloxacin monotherapy in a comparative study with a combination of doxycycline, metronidazole and ciprofloxacin [26].

Moxifloxacin rapidly penetrates uterine tissue where it remains in high concentrations and is sufficiently high to eliminate the principal pathogens of PID [27]. In addition, Bradshaw *et al.* reported that moxifloxacin was able to eradicate *M. genitalium* in patients who had failed azithromycin treatment [28,29]. Thus, moxifloxacin represents a useful addition to the treatment armamentarium for acute PID in women.

Owing to persistent concern about the current outpatient antimicrobial regimens lacking comprehensive coverage of anaerobic bacteria, metronidazole has been suggested as an addition to doxycycline, particularly for those women with PID and BV. However, the combination of doxycycline and metronidazole has been associated with low clinical and microbiological cure rates of 75 and 71%, respectively, for PID [24,30]. These observations suggest that the combination of doxycycline and metronidazole is a suboptimal choice for an oral antibiotic regimen used to treat PID [24,31]. The low efficacy rates may be due to the poor coverage of these drugs against *N. gonorrhoeae*, and the addition of an effective anti-gonoccocal antibiotic to the regimen should improve the efficacy rates. Piyadigamage *et al.* demonstrated that by adding ceftriaxone to doxycycline and metronidazole, there was a significant clinical cure rate improvement from 55 to 72% [31].

Azithromycin provides excellent coverage of chlamydia and moderate-to-good coverage for a range of aerobic and anaerobic bacteria, including Gram-negative anaerobes [30,32]. It is also at least 100-fold more active *in vitro* against *M. genitalium* than the quinolones or tetracyclines [33,34]. Although not included in the updated CDC 2007 guidelines for treatment of PID, several studies suggest that azithromycin can be used for the treatment of acute PID [30,32]. In a randomized controlled trial, cure rates of azithromycin for chlamydial infections, concomitant gonorrhea and gonorrhea only were high (95.8, 84.2 and 98.2%, respectively) [35]. Another randomized trial comparing the efficacy and safety of azithromycin as monotherapy or combined with metronidazole showed cure rates of 97.6 and 95.5%, respectively [36]. Malhotra *et al.* reported a clinical cure rate of 93% among those given a one-time dose of fluconazole, azithromycin and secnidazole [37]. In the macaque animal model,

azithromycin was more effective in eradicating chlamydial organisms from the upper and lower reproductive tract tissues than doxycycline, and also exerted a significant anti-inflammatory effect [38]. Azithromycin's advantages over doxycycline include single-dose administration and fewer side effects [30]. However, *N. gonorrhoeae* resistance to azithromycin has been reported and the higher 2 g dose recommended to treat this pathogen is associated with significant gastrointestinal side effects. Despite these concerns, multidose regimens of azithromycin monotherapy reliably eradicated *N. gonorrhoeae* when isolated in women with PID in the studies cited. Savaris *et al.*, in a randomized controlled trial conducted in Brazil, showed that when combined with ceftriaxone, 1 g of azithromycin weekly for 2 weeks was equivalent to ceftriaxone plus a 14-day course of doxycycline for treating mild PID [39]. The discussion on azithromycin would be incomplete without discussing azithromycin failure in the treatment of *M. genitalium* urethritis. A total of 15% of patients experienced treatment failure with azithromycin versus 55% treatment failure with doxycycline [40]. Azithromycin treatment failure of 15–30% has also been reported in patients with *M. genitalium* urethritis in Australia and the use of moxifloxacin in these cases resulted in rapid symptom resolution and eradicated the infection [28,29].

Given the above commentary, it appears that optimal regimens for the treatment of mild-to-moderate PID should include an antibiotic with reliable activity against *N. gonorrhoeae* in addition to an antibiotic with reliable activity against *C. trachomatis* and *M. genitalium*. There is not a single agent with these characteristics so only combination therapy can be recommended for the treatment of PID. Given the increasing concern about *M. genitalium* as an etiologic agent for PID, coverage of this microorganism is desirable [11]. Finally, broad-spectrum coverage of the BV-associated microorganisms appears less important [15,24]. In fact, the combination of doxycycline with metronidazole appears to be inferior and therefore one might consider avoiding it.

The extended-spectrum cephalosporins offer excellent coverage of *N. gonorrhoeae*. For the reasons of convenience, cost and ease of administration, oral cefixime 400 mg in a single dose is our first extended cephalosporin of choice. Ceftriaxone 250 mg intramuscularly in a single dose is our second choice owing to the fact that, unlike cefoxitin, it does not require the addition of oral probenecid. However, it should be pointed out that both of these cephalosporins fail to cover the Gram-negative anaerobes often associated with BV that cefoxitin covers. Cefoxitin is high on our list but given the need to split the intramuscular dose into two 1 g intramuscular injections plus the need to add oral probenecid, this is a less attractive alternative. These choices reliably treat a gonococcal infection. Optimally, one would use cefixime or ceftriaxone in those women with PID and no BV present, but opt for cefoxitin, owing to its superior anaerobic coverage in the presence of PID with concurrent BV (**Box 6**).

The second antibiotic should be either doxycycline or azithromycin owing to their effectiveness against *C. trachomatis* and *M. genitalium*. Doxycycline has been studied in the gold standard of PID studies, the PEACH study, and along with cefoxitin has been shown to be highly efficacious. However, doxycycline requires a twice-a-day dosing regimen for 14 days, making compliance improbable. Azithromycin, on the other hand, can be dosed in either a single daily dose (500 mg followed by 250 mg daily) for 1 week or in two single doses (1 g each) 1 week apart. In addition, azithromycin appears to work more efficiently in eradicating *in vitro* infection and has the added benefit of a significant anti-inflammatory effect [38]. Moreover, there is some concern about persistent *M. genitalium* infection following doxycycline [11,14]. Given these observations, azithromycin appears to be the superior choice.

Finally, we have to ask ourselves, how important is it to cover the anaerobic bacteria associated with BV and isolated from the upper genital tracts of women with PID? The antibiotics discussed above have modest activity against these microorganisms. The antibiotic, cefoxitin, with the best coverage against Gram-negative anaerobes, is administered in a single dose. Antibiotic regimens prospectively studied with little to no activity against anaerobic bacteria have uniformly performed well, while regimens containing metronidazole and doxycycline, which should enhance anaerobic coverage, have performed comparatively poorly. This leads us to suggest that dual therapy with an extended-spectrum cephalosporin and doxycycline or azithromycin is an excellent regimen for the treatment of women with PID who can be treated as outpatients.

Women with clinically severe PID should be considered for imaging to evaluate for TOA. As mentioned earlier, antibiotic regimens recommended for clinically severe disease should cover

Box 6. Outpatient antibiotic regimen for treatment of mild-to-moderate pelvic inflammatory disease.

Recommended oral regimen
Cefixime 400 mg orally in a single dose
Plus
Azithromycin 500 mg orally followed by 250 mg orally daily for a total of 7 days
Or
Doxycycline 100 mg orally twice daily for 14 days
Alternative regimen
Ceftriaxone 250 mg intramuscularly in a single dose
Plus
Azithromycin 500 mg orally followed by 250 mg orally daily for a total of 7 days
Or
Doxycycline 100 mg orally twice daily for 14 days
Preferred regimen if concurrent bacterial vaginosis infection
Cefoxitin 2 g intramuscularly in a single dose and
Probenecid 1 g orally administered concurrently in a single dose
Plus
Azithromycin 500 mg orally followed by 250 mg orally daily for a total of 7 days
Or
Doxycycline 100 mg orally twice daily for 14 days

Gram-negative aerobic and anaerobic bacteria. If a TOA is present, regimens should have the ability to penetrate abscess cavities while remaining stable in an acidic, hypoxic abscess environment.

Although regimens containing an aminoglycoside have been used effectively in women with pelvic abscesses, this class of antibiotic has its activity significantly reduced at low pH, low oxygen tension and in the presence of drug-binding purulent debris [41]. McNeeley *et al.* showed that the combination of clindamycin and gentamicin was associated with a significantly lower cure rate (47%) than the combination of clindamycin/ampicillin/gentamicin (87.5%) when used to treat patients with TOA [42]. For these reasons, an extended-spectrum cephalosporin, for example, ceftriaxone, may be a better choice to combine with either clindamycin or metronidazole in treating women with severe PID with or without a TOA. Not only do extended-spectrum cephalosporins maintain their activity in an abscess environment, but they have a much higher serum level to MIC ratio than the aminoglycosides (**Box 7**).

Clindamycin is actively transported into polymorphonuclear leukocytes and macrophages and is present in relatively high concentrations compared with peak serum levels in experimental abscesses [43]. Clindamycin has long been used in combination therapy for PID because of its activity against anaerobes and continues to be recommended in the treatment of PID on the basis of earlier studies and previously successful experience, but resistance to clindamycin has recently been observed among isolates recovered from the lower genital tract [44]. Among nonpregnant women with BV, 17% of isolates demonstrated clindamycin resistance at baseline, a rate that increased to 53% after clindamycin therapy. Although there are no data indicating that these observations of resistance are associated with PID treatment failures with clindamycin-based regimens, there is concern that resistance to clindamycin may be on the rise [45]. Clinicians should be aware of bacterial resistance when selecting antimicrobial therapy. In this light, renewed interest has been focused on ampicillin/sulbactam or metronidazole which, in contrast to clindamycin, does not appear to have the same problems with selective pressure for microbial resistance [46].

For the reasons noted earlier, we recommend metronidazole or clindamycin in combination with ceftriaxone as our regimen of choice. Other antimicrobials with similar broad-spectrum coverage and activity within the hostile environment of the abscess include β-lactam agents with β-lactamase inhibitors (e.g., ampicillin/sulbactam, ticarcillin/clavulanate and piperacillin/tazobactam) and the carbapenems (e.g., ertapenem, merepenem and imipenem/cilistatin). Of these alternative choices, we recommend ertapenem owing to our ability to dose it once a day. Finally, for those women with an immediate hypersensitivity to penicillin, we would recommend the combination of a quinolone (e.g., ciprofloxacin or levofloxacin) plus metronidazole. It would be important to test for *N. gonorrhoeae* by culture in these patients as susceptibility to quinolones would need to be ascertained (**Box 7**).

Patients admitted with severe PID and/or TOA should be discharged on a broad-spectrum oral antimicrobial regimen to complete a 14-day course. Recommended oral regimens for discharge include amoxicillin/clavulanate (875 mg twice daily) or the combination of trimethoprim/sulfamethoxazole (160/800 mg twice daily) and metronidazole (500 mg twice daily), owing to excellent polymicrobial coverage.

The most severe form of clinical PID-ruptured TOA should be considered in patients with PID presenting with an acute abdomen and signs of septic shock. TOAs in patients undergoing medical management of PID may rupture and require emergent surgical therapy. Surgical exploration with extirpation of the involved adnexa and drainage of purulent loculations is lifesaving. Hysterectomy is usually not necessary [47,48].

Box 7. Inpatient parenteral antibiotic regimens for treatment of severe pelvic inflammatory disease and tubo–ovarian abscess[†].

Recommended regimen[‡]
Ceftriaxone 1 g intravenously every 12 h
Plus
Metronidazole 500 mg intravenously every 6 h
Or
Clindamycin 900 mg intravenously every 8 h

Alternative regimens[‡]
Ertapenem 1 g intravenously daily
Or
Piperacillin/tazobactam 3.375 g intravenously every 6 h
Or
Ticarcillin/clavulanate 300 mg/kg/day intravenously in divided doses every 4 h
Or
Ampicillin/sulbactam 3 g intravenously every 6 h

Alternative regimen for penicillin-allergic patients[§]
Levofloxacin 500 mg orally once daily for 14 days
Or
Ciprofloxacin 400 mg intravenously every 12 h
Plus
Metronidazole 500 mg intravenously every 6 h

[†]Intravenous antibiotics can be switched to oral antibiotics after 48–72 h of therapy or based on clinical judgment.
[‡]If *Chlamydia* positive, add either azithromycin or doxycycline.
[§]Culture for quinolone-resistant *Neisseria gonorrhoeae* is required if the quinolones are used.

Conclusion

Optimal therapy for PID must take into consideration the severity of disease, the polymicrobial etiology of disease, the availability and costs of the antimicrobials, and their ease of administration. For this reason we recommend regimens for use in the treatment of those women who are candidates for outpatient therapy that can be administered as single or infrequent oral doses. Cefixime or a similar oral extended-spectrum cephalosporin can be used to cover the gonococcus, while azithromycin can be recommended to cover chlamydia and *M. genitalium*. Both agents together

Box 8. European guidelines for the management of pelvic inflammatory disease.

Outpatient regimens
Ceftriaxone 250 mg intramuscularly in a single dose
Or
Cefoxitin 2 g intramuscularly 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
Plus
Metronidazole 400 mg orally twice daily for 14 days
Alternative regimen
Moxifloxacin 400 mg orally once daily for 14 days
Or
Ofloxacin 400 mg orally twice daily for 14 days
Plus
Metronidazole 500 mg orally twice daily for 14 days
Inpatient regimens
Cefoxitin 2 g intravenously four times daily
Or
Cefotetan 2 g intravenously twice daily
Or
Ceftriaxone 1 g intravenously or intramuscularly once daily
Plus
Doxycycline 100 mg intravenously twice daily (oral doxycycline may be used if tolerated)
Followed by
Doxycycline 100 mg orally twice daily for a total of 14 days
Plus
Metronidazole 400 mg orally twice daily for a total of 14 days
Or
Clindamycin 900 mg intravenously every 8 h
Plus
Gentamicin intravenously (2 mg/kg loading dose followed by 1.5 mg/kg three times daily†)
Followed by either
Clindamycin 450 mg orally four times daily to complete 14 days; or
Doxycycline 100 mg orally twice daily for 14 days
Plus
Metronidazole 400 mg orally twice daily to complete 14 days
Alternative regimen
Ofloxacin 400 mg intravenously twice daily for 14 days
Plus
Metronidazole 500 mg intravenously three times daily for 14 days
Or
Ciprofloxacin 200 mg intravenously twice daily
Plus
Doxycycline 100 mg intravenously or orally twice daily for 14 days
Plus
Metronidazole 500 mg intravenously three times daily
Antibiotic therapy should be given for 14 days

†A single dose may be substituted.
Adapted from [49].

appear to have satisfactory anaerobic coverage to render women with the clinical diagnosis of mild-to-moderate PID asymptomatic. Moxifloxacin is a good alternative regimen for acute PID but it is costly, and its use should be restricted to areas were gonococcal PID is uncommon. Gonococcal culture and sensitivity testing is required to ensure *N. gonorrhoeae* is sensitive to moxifloxacin. A repeat gonococcal test is also required post-treatment to document eradication of the pathogen.

Women with more severe disease, particularly in the context of an associated TOA, must have the non-sexually transmitted microorganisms covered. This will include anaerobic bacteria and aerobic Gram-negative bacteria, especially *E. coli*. In addition, broad-spectrum therapy should include those microorganisms commonly associated with BV. A combination of parenteral ceftriaxone and metronidazole or clindamycin provides this coverage.

It is unclear how long therapy need continue but most studies (Box 8) and the CDC recommendations suggest 14 days. It is unlikely that most patients will adhere to such a long regimen after their symptoms resolve. It is most likely safe to discontinue antibiotic therapy once the patient's fever has lysed, her white blood cell count has normalized and her pelvic exam is non-tender, or at most reflects mild tenderness.

Five-year view

There are several important areas in which additional investigation could provide important guidance. Despite the revelation of a polymicrobial etiology of acute PID in 1975, we still do not understand the true importance of anaerobic bacteria as etiologic agents of acute PID. Current data suggest that antimicrobial regimens with little to no anaerobic coverage are highly effective in the treatment of mild-to-moderate PID, even in women with concurrent BV. Prospective studies need to be performed that will compare well-tolerated antibiotic regimens with excellent anaerobic coverage with those with little to no such coverage in the treatment of mild-to-moderate PID. In addition, prospective randomized trials are required to study oral cefixime versus other parenteral cephalosporins. We also understand little with respect to the need for duration of treatment and the frequency of dosing. It would be interesting to see if short courses (<1 week) of therapy are as effective as our now recommended longer courses (2 weeks). The reality of prolonged therapy is that compliance is notoriously poor, so shorter therapy may not only turn out to be more cost effective but may have equal efficacy as well. In addition, pulse dosing, for example, 1 g of azithromycin a week apart, appears promising as an alternative dosing schedule and needs further investigation.

Mycoplasma genitalium is an emerging pathogen of importance as an etiologic agent of lower and upper genital tract infection. Evidence suggests that it is associated with persistent endometritis

despite doxycycline therapy and its optimal therapy is unknown. *M. genitalium* could become the next *C. trachomatis* if widespread testing was undertaken, yet commercially available nucleic acid tests are not available. It will be important to define the epidemiology, sequelae and most effective therapy for this emerging sexually transmitted infection.

It would be preferable to use a single agent that covers all the potential microbial pathogens, can be administered once daily and is inexpensive. Currently, moxifloxacin (not available as a generic in the USA) comes closest to being this agent but quinolone-resistant *N. gonorrhoeae* and its cost (US$225.60 for 14 tablets) prevent it from being embraced in this regard. Continued antibiotic development could provide us with this agent in the future.

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Key issues

- Pelvic inflammatory disease (PID) is an infection-induced continuum of the female genital tract capable of causing tubal factor infertility and ectopic pregnancy.
- PID is a polymicrobial infection caused by the sexually transmitted microorganisms *Neisseria gonorrhoeae*, *Chlamydia trachomatis* and *Mycoplasma genitalium*.
- It is clear that anaerobic bacteria play a significant etiologic role in PID complicated by tubo–ovarian abscess, but it is less clear as to whether these microorganisms can infect and cause inflammation in previously undamaged fallopian tubes.
- Outpatient therapy is recommended for patients with mild-to-moderate PID.
- Azithromycin needs further study to confirm its effectiveness in the treatment of mild-to-moderate acute PID.
- Women with clinically severe PID should be admitted to hospital for imaging to rule out tubo–ovarian abscess and be started on parenteral therapy utilizing an antibiotic regimen that will remain active within an abscess environment.
- Aminoglycosides are inactive in an abscess environment and are therefore of limited use in the treatment of women with clinically severe PID and/or tubo–ovarian abscess.
- Fluoroquinolones cannot be recommended to treat PID unless culture for *N. gonorrhoeae* is performed to allow susceptibility studies to be carried out to rule out quinolone-resistant *N. gonorrhoeae*.
- *M. genitalium* needs to be further characterized as a sexually transmitted pathogen.
- Prospective randomized trials are required to study oral cefixime versus other parenteral cephalosporins.

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