
**BACKGROUND:** There are limited published data describing clinical features and therapeutic response in women meeting the criteria for presumptive treatment of pelvic inflammatory disease associated with Mycoplasma genitalium (MG-PID). The MG-PID has been reported to respond poorly to standard PID treatment regimens and while moxifloxacin is recommended in several treatment guidelines, published data to support its use are scant.

**METHODS:** We conducted a retrospective study of women at Melbourne Sexual Health Centre between 2006 and 2017, who met the Centers for Disease Control and Prevention criteria for presumptive treatment of PID, and had MG detected as the sole pathogen. Clinical and laboratory characteristics of MG-PID were compared to cases of chlamydial PID (CT-PID) by multivariable analysis. Microbiological and clinical cure following moxifloxacin and standard PID treatment was determined for women with MG-PID who returned for test of cure between 14 and 120 days.

**RESULTS:** Ninety-two patients with MG-PID were compared with 92 women with CT-PID. The MG-PID was associated with increased lower abdominal tenderness (adjusted odds ratio, 2.29; 95% confidence interval [CI], 1.14-4.60), but a lesser vaginal polymorphonuclear response compared to CT-PID by multivariable analysis. Of the 92 women with MG-PID, 54/92 (59%) received moxifloxacin (10-14 days) and 37/54 had a test of cure between 14 and 120 days; 27/37 (73%) cases had a median of 7 days of a standard regimen containing doxycycline and metronidazole +/- azithromycin before moxifloxacin. Microbial cure following moxifloxacin was 95% (95% CI, 82-99%) and did not differ from standard therapy (P = 0.948), however clinical cure was significantly higher following moxifloxacin (89%; 95% CI, 75-97%; P = 0.004) although adverse effects were more common. [41% vs 10%]

**CONCLUSIONS:** Women meeting Centers for Disease Control and Prevention criteria for presumptive treatment of MG-PID did not significantly differ to those with CT-PID. Moxifloxacin was associated with higher rates of symptom resolution in women with PID, and although microbial cure was high, it did not differ between regimens.


**Objective:** In the United Kingdom many genitourinary medicine clinics use oral doxycycline and metronidazole to treat pelvic inflammatory disease (PID). A retrospective case note review of PID treatment at our department in 2000 showed that the clinical cure rate (CCR) was only 55% with oral doxycycline and metronidazole for 2 weeks. We therefore added ceftriaxone 250 mg intramuscularly to the doxycycline and metronidazole for treating PID. We have repeated the review and compared the results with those from 2000.

**Methods:** All patients diagnosed as having PID between 1 July 2002 and 31 December 2002 were identified. These episodes were diagnosed on clinical presentations of pelvic pain, vaginal discharge or bleeding, and cervical motion tenderness on physical examination. The CCR was defined as patients who fully resolved their symptoms and signs during 2 week and 4 week follow up. The results were compared with those from 2000.
Results: Women receiving ceftriaxone, doxycycline, and metronidazole had a CCR of 72%. In 2000 the CCR for women receiving only doxycycline and metronidazole was 55%. There were only 8% non-responders in 2002 compared with 18% in 2000. Comparing CCR and non-response rate, in 2002 there was a significant improvement in cure rate, OR 3.01 (95% CI 1.28 to 7.47) p = 0.009. Using an intent to treat analysis and including the defaulters as treatment failures there was still a significant improvement in cure rate, OR 2.03 (95% CI 1.18 to 3.50) p = 0.009.

Conclusions: The treatment of PID with ceftriaxone, doxycycline, and metronidazole gave a significantly higher CCR than doxycycline and metronidazole. Our experience would suggest that doxycycline and metronidazole alone is not a suitable regimen for treatment of PID in the United Kingdom.


The CDC recommended outpatient treatment of pelvic inflammatory disease (PID) is an intramuscular dose of ceftriaxone plus 14 days of doxycycline, with or without metronidazole. European guidelines (2017) include moxifloxacin plus ceftriaxone as a first line regimen, particularly for women with Mycoplasma genitalium-associated PID. However, the susceptibility of bacteria recovered from the endometrium of women with PID to moxifloxacin is unknown. The in vitro antibiotic susceptibility of facultative and anaerobic bacteria recovered from endometrial biopsy samples were evaluated from 105 women having symptomatic PID and/or histologically confirmed endometritis. A total of 342 endometrial isolates from enrollment visits were identified using a combination of biochemical tests and sequencing. Isolates were tested for antimicrobial susceptibility using agar dilution against ceftriaxone, clindamycin, doxycycline, metronidazole and moxifloxacin according to the Clinical and Laboratory Standards Institute (CLSI) guidelines. Neisseria gonorrhoeae was susceptible to ceftriaxone with all isolates having an MIC of 0.03 μg/mL. All the other endometrial isolates were susceptible to ceftriaxone, except for Prevotella species, only half of which were susceptible. The in vitro susceptibility profile for BV-associated bacteria (Gardnerella vaginalis, Atopobium vaginae, Prevotella species, Porphyromonas species and anaerobic gram-positive cocci) revealed greater susceptibility to moxifloxacin compared to doxycycline. Moxifloxacin was superior to metronidazole for G. vaginalis and A. vaginae, and either metronidazole or moxifloxacin was needed to cover Prevotella species. Based on in vitro susceptibility testing, the combination of ceftriaxone plus moxifloxacin provides similar coverage of facultative and anaerobic pathogens compared to the combination of ceftriaxone, metronidazole and doxycycline. Head to head clinical studies of these treatment regimens are needed to evaluate clinical efficacy and eradication of endometrial pathogens following treatment.

Comment:
1) Mgen PID presentation is similar to chlamydia.
2) Mgen causes ~10% PID (BASHH guidelines) and Mgen testing with macrolide antimicrobial resistance testing if positive is recommended.
3) Doxycycline in the absence of ceftriaxone/azithromycin has poor efficacy in treating both Mgen positive/negative PID
4) Doxycycline 100mg bd 14 days plus metronidazole 400mg bds 14 days +/- azithromycin 1g effective in microbiological cure in women with M gen PID when used in era when Mgen macrolide resistance uncommon.
5) Clinical cure rates Mgen PID higher with moxifloxacin 400mgs bd 14 days 89% vs 53% compared to Doxycycline 100mgs bd 14 days plus metronidazole 400mgs bds 14 days +/- azithromycin 1g. But more side effects 43% vs 10%.

6) Unknown if clinical efficacy of Doxycycline/metronidazole with a prolonged course (higher dose) of azithromycin would have better clinical outcomes in Mgen PID if macrolide sensitive. (see 5)

7) PID is often polymicrobial and unclear if addition of ceftriaxone would improve efficacy of moxifloxacin for all types of PID.

8) Moxifloxacin 400mgs od 2 weeks has similar efficacy to Ofloxacin 400mgs bd plus metronidazole 400mgs bd for 2 weeks. Recommended in BASHH guideline as an alternative to Ofloxacin/metronidazole.
   a. Recent update moved quinolones to second line because of recent MHRA guidance on quinolones (https://www.bashh.org/guidelines)

9) Moxifloxacin good compliance 84% despite 41% experiencing side effects – nausea (50%) and diarrhoea (20%)


**Objective** To assess the effectiveness and safety of antibiotic regimens used to treat pelvic inflammatory disease (PID).

**Design** This is a systematic review and meta-analysis of randomised controlled trials (RCTs). Risk of bias was assessed using the criteria outlined in the Cochrane guidelines. Quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation. Data sources Eight electronic databases were searched from date of inception up to July 2016. Database searches were complemented by screening of reference lists of relevant studies, trial registers, conference proceeding abstracts and grey literature. Eligibility criteria RCTs comparing the use of antibiotics with placebo or other antibiotics for the treatment of PID in women of reproductive age, either as inpatient or outpatient treatment.

**Results** We included 37 RCTs (6348 women). The quality of evidence ranged from very low to high, the main limitations being serious risk of bias (due to poor reporting of study methods and lack of blinding), serious inconsistency and serious imprecision. There was no clear evidence of a difference in the rates of cure for mild-moderate or for severe PID for the comparisons of azithromycin versus doxycycline, quinolone versus cephalosporin, nitroimidazole versus no use of nitroimidazole, clindamycin plus aminoglycoside versus quinolone, or clindamycin plus aminoglycoside versus cephalosporin. No clear evidence of a difference between regimens in antibiotic-related adverse events leading to discontinuation of therapy was observed.

**Conclusions** We found no conclusive evidence that one regimen of antibiotics was safer or more effective than any other for the treatment of PID, and there was no clear evidence for the use of nitroimidazoles (metronidazole) compared with the use of other drugs with activity against anaerobes. More evidence is needed to assess treatments for women with PID, particularly comparing regimens with or without the addition of nitroimidazoles and the efficacy of azithromycin compared with doxycycline.

*Comment:* Antimicrobial resistance has increased over the last 30 yrs for gonorrhoea, M genitalium and at least some BV associated bacteria. This adds an additional level of complexity when interpreting this systematic review and meta-analysis.
Conclusion:
1) Doxycycline and metronidazole should not be used alone to treat PID – this may have implications for community based guidelines
2) Standard Ceftriaxone doxycycline/metronidazole used in level 3 services will have reduced efficacy in treating Mgen PID. Mgen NAAT testing with macrolide AMR testing is likely to improve outcomes enabling change to moxifloxacin. Consideration should be given to adding extended azithromycin 1 g then 500mgs od 2 days if macrolide sensitive
3) PID in the community: Ofloxacin 400mgs bd plus metronidazole 400mgs bd 10-14 days reasonable option for treatment of PID in community if ceftriaxone im not available and gonorrhoea unlikely. Moxifloxacin reasonable alternative if compliance poor
   a. Management improved if NAAT testing undertaken for:
      i. Chlamydia/gonorrhoea
      ii. and probably M genitalium.
   b. Refer if severe symptoms or risk of Gonorrhoea and consider ceftriaxone