

Do women treated with ceftriaxone and doxycycline for PID benefit from added metronidazole to broaden anaerobic coverage?

Yes, results from a randomized trial noted a therapeutic benefit in women with pelvic inflammatory disease (PID) who were treated with the addition of metronidazole as they were less likely to have pelvic organ tenderness a month after enrollment than those who received placebo (9% vs 20%, respectively). Their concurrent disorders of bacterial vaginosis and trichomonas vaginitis were more effectively treated, and they had fewer follow-up endometrial cultures that were positive for anaerobic bacteria than the placebo group (8% vs 21%, respectively). Moreover, the combination regimen was no more likely to cause gastrointestinal adverse effects than doxycycline alone.

FAST TRACK

While anaerobes are more commonly isolated from the upper genital tract of patients with acute PID than N gonorrhoeae or C trachomatis, recommended treatments do not necessarily include antibiotics with an antianaerobic spectrum

Wiesenfeld HC, Meyn LA, Darville T, et al. A randomized controlled trial of ceftriaxone and doxycycline, with or without metronidazole, for the treatment of acute pelvic inflammatory disease. *Clin Infect Dis*. February 13, 2020. doi:10.1093/cid/ciaa101.

EXPERT COMMENTARY

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Pelvic inflammatory disease remains prevalent among young women and is commonly diagnosed in emergency departments and sexually transmitted disease (STD) clinics. This tubal infection

is associated with significant reproductive sequelae, including tubal factor infertility, ectopic pregnancy, and chronic pelvic pain. In addition, these women remain at risk for recurrent PID.

Bacterial vaginosis is present in more than half of women with PID. Not surprisingly, anaerobic microorganisms are more commonly isolated from the upper genital tract of patients with acute PID than either *Neisseria gonorrhoeae* or *Chlamydia trachomatis*, yet recommended antimicrobial regimens do not necessarily include antibiotics with an excellent antianaerobic spectrum.

Details of the study

In a randomized, double-blind, placebo-controlled trial, Wiesenfeld and colleagues enrolled women from hospital emergency departments or an STD clinic with symptoms

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of lower abdominal or pelvic pain associated with pelvic organ tenderness. The 233 study participants were randomly assigned to 2 treatment arms: ceftriaxone, doxycycline, and placebo (n = 117) or ceftriaxone, doxycycline, and metronidazole (n = 116).

Findings. Women treated with metronidazole were less likely to have pelvic organ tenderness a month after enrollment compared with the placebo group (9% vs 20%, respectively). Although the clinical cure rates at 30 days were statistically similar in both arms of the study, those receiving metronidazole had a 97% clinical cure rate while those not treated with metronidazole had a 90% clinical cure rate ($P = .38$).

Moreover, the concurrent disorders of bacterial vaginosis and trichomonas vaginitis were more effectively treated in the metronidazole group, and fewer women had positive follow-up endometrial cultures for anaerobic bacteria compared with the placebo group (8% vs 21%, respectively).

The anticipated gastrointestinal adverse effects of a combination doxycycline-and-metronidazole regimen was a significant concern; however, combination therapy was no more likely to cause gastrointestinal adverse effects than doxycycline alone.

Study strengths and limitations

This well-designed randomized, double-blinded clinical trial was performed by clinical investigators experienced in the clinical diagnosis of PID. The demography of the population and their history of

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Metronidazole should be added routinely to the standard antibiotic regimen of ceftriaxone and doxycycline for the treatment of women with PID.

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C trachomatis, *N gonorrhoeae*, plus the concurrent diagnosis of bacterial vaginosis make the diagnosis believable and real world, and these factors contribute to the generalizability of the study results.

However, PID is an imprecise clinical diagnosis (specificity averages 65%) when held to the gold standard of diagnostic laparoscopy to confirm the presence of acute salpingitis. Given the reticence of investigators and clinicians to embark on such an invasive procedure to confirm this diagnosis, endometrial biopsy showing evidence of histologic acute endometritis has been offered as an alternative gold standard. Confirmation of acute endometritis in the trial participants would have enhanced the validity of this study.

This study challenges a long held, but never proven, belief that the combination of doxycycline and metronidazole would be poorly tolerated as a combination antimicrobial regimen. It also further solidifies the role of anaerobic bacteria as major players in the microbial etiology of acute PID. In addition, it appears that treating bacterial vaginosis concurrently may lessen the likelihood of endometrial recolonization with anaerobic bacteria. ●