Azithromycin for PID beats doxycycline on all counts

**Practice changer**
Outpatient treatment of patients with mild pelvic inflammatory disease, using 1 g of azithromycin weekly for 2 weeks, combined with 250 mg of ceftriaxone intramuscularly on the first day, is superior to the current recommended treatment with doxycycline plus ceftriaxone.¹

**BACKGROUND**

2 doses or 28 doses?
In the real world, we know that adherence is better when patients have to take 2 pills than when they have to take 28 pills. For most women with mild, uncomplicated PID, outpatient treatment is appropriate² and a shorter treatment course is related to better adherence.³ Azithromycin can be given in 2 single doses a week apart, with few side effects, and its spectrum of activity is similar to that of doxycycline,⁴ which requires a 14-day regimen of 2 pills daily. Earlier studies of azithromycin for PID, however, were not designed specifically for outpatient treatment, or had methodologic bias.⁵ Thus, the evidence has been insufficient to recommend it.

PID affects about 1 million women in the US each year, and can cause pain, scarring of the fallopian tubes, and infertility.

**Current recommendations.** The Centers for Disease Control and Prevention (CDC) recommends oral doxycycline 100 mg twice daily for 14 days, along with a second- or third-generation cephalosporin administered parenterally, for mild PID in ambulatory patients.⁶ Metronizadole can be added at the provider’s discretion. The CDC no longer routinely recommends fluoroquinolones for PID because of gonococcal resistance.⁷ Dynamed, PEPID PCP, and UpToDate all cite CDC guidelines. Dynamed also notes results of the article reviewed here, though treatment recommendations were not changed.⁸⁻¹⁰

**ILLUSTRATIVE CASE**
An otherwise healthy, sexually active 21-year-old woman complains of pelvic pain for a week and yellow vaginal discharge. The history and physical exam are consistent with mild, uncomplicated pelvic inflammatory disease (PID).

You believe outpatient therapy is appropriate in this case and wonder if there is a better alternative to doxycycline, particularly given the challenges of adherence to the recommended 14-day course of treatment.
This RCT shows that azithromycin is superior to doxycycline even when compliance in taking doxycycline is excellent (which is not the reality in clinical practice)

A simpler approach to pelvic inflammatory disease

Patients will likely find it easier to take 1 azithromycin pill initially and 1 pill a week later, than to take a doxycycline pill twice daily for 14 days. If so, then the advantage of azithromycin could be greater than reported in this study.

CLINICAL CONTEXT

First comparison study, first outpatient study

The study by Savaris and colleagues is the first comparison study of azithromycin and doxycycline for PID, and the first study of outpatient treatment of PID with azithromycin.

An earlier study reported that women with PID who were prescribed doxycycline took an average of 70% of the total doses, and fewer than half took it twice daily as directed. An earlier study reported that women with PID who were prescribed doxycycline took an average of 70% of the total doses, and fewer than half took it twice daily as directed.3

Azithromycin is known to be effective for treatment of Chlamydia trachomatis cervical infections,4 and single-dose azithromycin has been also been shown to have better compliance than multidose therapy for Chlamydia infection.10

We identified only 1 prior randomized controlled trial of azithromycin for treatment of PID. That trial reported that intravenous azithromycin followed by oral azithromycin with or without metronidazole is effective in the treatment of PID.11

STUDY SUMMARY

Azithromycin cure rate 90%, doxycycline 72%

This randomized, double-blind, controlled study evaluated the effectiveness of azithromycin plus ceftriaxone in the treatment of mild, uncomplicated PID compared to doxycycline plus ceftriaxone, in outpatients.

Patients

The study enrolled 133 women who presented to an emergency department with PID diagnosed by the following clinical criteria:

• pelvic pain for less than 30 days
• pelvic organ (adnexal or cervical) tenderness on physical examination
• cervical leukorrhea or mucopurulent cervicitis.

Method

The women were randomized into 2 groups, and both groups received 250 mg of ceftriaxone intramuscularly.

• The control group received 100 mg of doxycycline twice daily for 2 weeks.
The study group received 1 g of azithromycin by mouth weekly for 2 weeks and a placebo twice daily for 2 weeks to maintain blinding.

Outcomes
The primary outcome was clinical cure after 2 weeks of treatment. Clinical cure was defined as an improvement in pain scale ratings by 70%. Failure was defined as worsening of pain, lack of improvement of pain, or need for additional antibiotic therapy, hospitalization, or surgery.

Of the 133 women randomized, 13 (9 from the azithromycin group and 4 from the doxycycline group) were found to have diagnoses other than PID after randomization.

Intention-to-treat analysis was performed for the remaining 120 participants. In the azithromycin group, 56/62 (90.3%; 95% confidence interval [CI], 0.80–0.96) women were classified as clinically cured, versus 42/58 (72.4%; 95% CI, 0.58–0.82) in the doxycycline group.

Adverse events. Except for oral intolerance to the first dose of medication, which was similar in both groups, adverse events were not reported.

Adherence similar in both groups
Adherence to the study protocol was similar in both groups. The study authors concluded that azithromycin was superior to doxycycline even though the adherence in the doxycycline group was good.

CAVEATS
Apply these findings in similar cases only
This study addresses ambulatory treatment of mild, uncomplicated PID, and results should only be extrapolated to similar cases.

Azithromycin should not be prescribed to patients with an allergy to macrolide antibiotics.

One of the study authors received azithromycin donated by Pfizer for other research; however, Pfizer did not sponsor this study.

CHALLENGES TO IMPLEMENTATION
Cost of the prescription
Prescription cost may be a consideration for patients without insurance, although azithromycin has been shown to be cost-effective in treatment of Chlamydia.12

Reminding patients to take the second dose
Some patients may have difficulty remembering to take the second dose a week after the first dose.

A follow-up visit, reminder phone call, or suggestion to “mark this on your calendar” may help enhance adherence.

WHAT’S NEW?
Better adherence is the probable bonus
This RCT shows that azithromycin treatment of PID in an ambulatory population is superior to doxycycline even when there is excellent compliance with taking doxycycline (unlike the reality of clinical practice). The patients in this RCT adhered well to the protocol, so it does not provide a realistic head-to-head comparison of treatment completion.

Real-world adherence
In actual practice, we speculate that taking 2 pills 1 week apart will be much easier for patients than taking 2 pills every day for 14 days. The literature on compliance would predict that to be the case. If true, then the advantage of azithromycin over doxycycline would be even greater than reported in this study.

Real-world adherence

Wha T’s new?
PURLs methodology
This study was selected and evaluated using the Family Physician Inquiries Network’s Priority Updates from the Research Literature Surveillance System (PURLs) methodology. The criteria and findings leading to the selection of this study as a PURL can be accessed at www.jfponline.com/purls.

References

Where research gets a reality check

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