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Treatment of Acute Pelvic Inflammatory Disease in the Ambulatory Setting: Trial of Cefoxitin and Doxycycline versus Ampicillin-Sulbactam

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Ampicillin-sulbactam (750 mg) given orally twice daily for 10 days was evaluated for the treatment of acute pelvic inflammatory disease (PID) in an ambulatory setting in Nairobi, Kenya. The first 26 women received ampicillin-sulbactam in an open-label fashion, and the remaining 75 women were randomly selected to receive either ampicillin-sulbactam (n = 38) or cefoxitin (2 g) intramuscularly and probenecid (1 g) orally, followed by doxycycline (100 mg) orally twice daily for 10 days (n = 37). Women were enrolled in a sexually transmitted disease clinic and were followed for clinical and microbiologic responses at 1 to 2 weeks and 4 to 6 weeks posttreatment. Women had a later follow-up visit to note interim pregnancy or underwent hysterosalpingography for fertility outcome assessment. The short-term clinical response rates were 70% for ampicillin-sulbactam and 72% for cefoxitin-doxycycline (P = 0.47). Among *Chlamydia trachomatis*-infected women treated with ampicillin-sulbactam, three had microbiologic relapse. The post-PID tubal obstruction rates were similar in the two groups: 18% for ampicillin-sulbactam and 33% for cefoxitin-doxycycline (P = 0.31). Neither regimen was highly effective as a therapy for acute PID. These data strongly argue that primary prevention must be the goal for a reduction of PID morbidity and show that improved therapy for the treatment of PID in the ambulatory setting is needed.

Acute pelvic inflammatory disease (PID) is a frequent infection of women of reproductive age. In 1982 in the United States, 14% of women of reproductive age reported that they had been treated at least once for PID (1). In developing countries, acute PID appears to be even more common, although accurate statistics are unavailable. Despite the fact that most women with acute PID are treated as outpatients, nearly all data regarding the treatment of acute PID is based on the treatment of hospitalized patients (19). The 1989 United States Public Health Services guidelines for the treatment of acute PID in outpatients recommend giving cefoxitin (2 g) intramuscularly and probenecid (1 g) orally, followed by the administration of doxycycline orally twice daily for 10 to 14 days, or an identical regimen except that ceftriaxone (250 mg given intramuscularly) is substituted for cefoxitin (19). A recent trial of the cefoxitin-probenecid-doxycycline combination reported that 22 of 24 women (92%) treated as outpatients responded clinically (27). This regimen is also recommended by the World Health Organization Expert Committee for the treatment of outpatient PID in developing countries (25). Since no studies with this regimen have been performed in developing countries, there is concern that a single dose of cefoxitin followed by an extended course of doxycycline may not be sufficient for the treatment of gonococcal or polymicrobial tubal infection in geographic regions where tetracycline-resistant pathogens are frequent. This may be the case for many areas of the developing world (16). Alternate regimens using drugs given orally which are well absorbed and can be prescribed for extended periods may more reliably treat the broad range of pathogens that cause acute PID. β-Lactamase inhibitors such as clavulanic acid or sulbactam combined with amoxicillin or ampicillin have yielded excellent clinical cure rates among patients with PID in several trials performed in industrialized countries (19). In one trial, 95% of 100 hospitalized women with laparoscopically confirmed PID were clinically cured with parenterally administered amoxicillin-clavulanate (17). Five trials with ampicillin-sulbactam regimens comprising over 118 patients with acute PID yielded cure rates between 86 and 95% (5, 10, 13, 14, 17). These regimens appear to be particularly effective for women with pyosalpinx or tubal abscess, a group known to have a slow response to antimicrobial therapy and a poor reproductive outcome (7, 14). Bruhat et al. (4) reported a small clinical trial that compared the efficacies of parenterally administered ampicillin-sulbactam and cefoxitin in the treatment of 40 women with laparoscopically confirmed acute salpingitis. Twenty-two women (55%) had chlamydial infection (and received supplemental doxycycline) and 8 women (20%) had pyosalpinx or tubal abscess. The trial was useful because it included posttreatment laparoscopy to evaluate pelvic inflammation and tubal patency. Women treated with ampicillin-sulbactam had significantly less severe peritoneal adhesions. One of 20 women treated with ampicillin-sulbactam, versus 6 of 20 women treated with cefoxitin, had severe peritoneal adhesions as determined by a second laparoscopy (P = 0.09).

We were interested in comparing an oral form of ampicillin-sulbactam with cefoxitin-probenecid-doxycycline in the treatment of women with acute PID diagnosed in a sexually transmitted disease clinic in Nairobi, Kenya. We evaluated clinical and microbiologic responses to therapy at days 14 to 21 and days 35 to 42 posttherapy. Women also had later (6 to 12 weeks) posttreatment evaluation of reproductive outcome. Reproductive outcome measurement consisted of

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noting interim pregnancy or tubal patency as assessed by hysterosalpingography. We chose to use hysterosalpingography on the basis of the results reported by Falk (12) that an abnormal hysterosalpingogram with bilateral tubal obstruction was highly predictive of post-PID tubal infertility.

MATERIALS AND METHODS

Recruitment and evaluation of patients. Between February 1987 and March 1988, women attending a sexually transmitted disease clinic in Nairobi, Kenya were screened for inclusion in the study. Nonpregnant women complaining of the acute onset of lower abdominal pain who were not being treated with antibiotics and denied having allergies to the study drugs were evaluated. The study was reviewed and approved by the Institutional Review Board, and women were enrolled after giving informed consent. Acute PID was determined to be the most likely clinical diagnosis if pelvic examination revealed mild to moderate tenderness elicited by movement of the cervix and by bimanual palpation of the uterus and adnexa by the examining gynecologist (M.K.). The severity of pelvic organ tenderness was graded as follows: 0, no pain when examined; 1+, no reaction when examined, but the patient admitted to pain when questioned; 2+, grimaced with pain when examined; 3+, vocalized pain when examined; and 4+, bent over with pain prior to examination (17). Patients were enrolled if the findings of pelvic tenderness were graded at 2+ or greater at the initial examination. Women with signs of pelvic peritonitis or with a tender, indurated, fixed adnexal mass of greater than 6 cm were not enrolled and were referred to a hospital for inpatient care. At enrollment, demographic data, gynecologic, obstetric, surgical, contraceptive, and sexual histories and physical findings were recorded on a standard form. Two endocervical swabs were collected for the culture of *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Serum was collected for the determination of human immunodeficiency virus (HIV) type 1 antibody.

Patients were assigned to one of two treatment regimens: (i) ampicillin-sulbactam (750 mg) given orally twice daily for 10 days or (ii) cefoxitin (2 g) given intramuscularly and probenecid (1 g) given orally, followed by the administration of doxycycline (100 mg) twice daily for 10 days. The first 26 subjects received ampicillin-sulbactam in an open-label fashion, and the remaining 75 women were selected by using a predetermined random number table to receive ampicillin-sulbactam or cefoxitin-doxycycline. Both the patient and the clinician knew which study drug was allocated. Women were instructed to return at any time in the course of treatment or follow-up if symptoms recurred. Otherwise, they were seen approximately 1 and 4 weeks following the completion of treatment. Subjects were asked to abstain from sexual intercourse until the completion of the evaluation. Women were encouraged to have their sex partner(s) attend the clinic for investigation and epidemiologic treatment. At the follow-up visits, women were questioned about symptoms; adverse effects such as rash, diarrhea, nausea, and vomiting; sexual reexposure; and therapeutic compliance. Physical examination was repeated, and endocervical swabs were obtained for *N. gonorrhoeae* and *C. trachomatis* cultures.

Clinical response to treatment was determined as follows. At the first follow-up, women were classified as clinically well, clinically improved, or unimproved. They were classified as clinically well if pelvic tenderness had completely resolved (i.e., grade 0 at examination), as clinically improved if findings were reduced to grade 1+ at examination and they did not require additional antimicrobial therapy, and as clinically unimproved if the severity of the signs persisted at grade 2+ or greater and they required additional antimicrobial treatment. All women with findings of grade 2+ or greater were treated with antimicrobial agents. At the second follow-up visit, women were classified in the same manner.

Women were assessed for fertility outcome after the 6-week follow-up visit. The date of last normal menses was determined, and a pregnancy test was done if pregnancy was suspected. If women were nonpregnant, hysterosalpingography was performed in order to evaluate tubal anatomy and patency after obtaining informed consent. Doxycycline prophylaxis was given during hysterosalpingography as recommended (20). Women who had bilaterally dilated ($\geq$11 mm) fallopian tubes which failed to spill dye into the peritoneal cavity were considered to have tubal occlusion.

Microbiologic procedures. Specimens to be tested for *N. gonorrhoeae* were inoculated directly onto modified Thayer-Martin medium. *N. gonorrhoeae* was identified by colony appearance, Gram stain, and oxidase reaction. Specimens to be tested for *C. trachomatis* were stored in sucrose-phosphate transport medium at −70°C until they were cultured on cycloheximide-treated McCoy cells. Inclusions were identified by staining with fluorescein-conjugated monoclonal antibodies (21). HIV antibody testing was performed with a commercially available enzyme immunoassay (HTLV-III enzyme-linked immunosorbent assay (ELISA); Dupont DeNemours, Geneva, Switzerland). Positive ELISAs were repeated and confirmed by immunoblotting (HTLV-III Western blot; Dupont DeNemours) (9).

Statistical analysis. The chi-square or Fisher's exact test was used for the statistical analysis of nominal, discrete variables. Statistical comparisons of the means were made by using Student's *t* test.

RESULTS

Study population. A total of 101 women were enrolled in the study; 26 received ampicillin-sulbactam in an open-label fashion, and 75 received randomized therapy (38 received ampicillin-sulbactam and 37 received cefoxitin-doxycycline). The treatment groups were similar in baseline characteristics, including age, parity, contraception practices, prior history of PID, duration of symptoms prior to presentation, and the finding of an adnexal mass at bimanual examination (Table 1). Overall, 83 of the enrolled women (82%) were seen at the follow-up visit 2 to 3 weeks after treatment, and 63 (62%) were seen at the follow-up visit 5 to 6 weeks after treatment (Table 1).

Results of open-label study. Twenty-six consecutive women were treated with ampicillin-sulbactam, including 7 women with *N. gonorrhoeae*, 2 with *C. trachomatis*, 2 with both *N. gonorrhoeae* and *C. trachomatis*, and 15 with neither pathogen. Two women had palpable adnexal masses. Three women (12%) were seropositive for HIV. Sixteen of 18 women (89%) seen at early follow-up were clinically cured. One persistent and one recurrent gonococcal infection and two late relapsed chlamydial infections were observed. None of eight evaluable women had an adverse reproductive outcome. On the basis of these data, a randomized comparative trial of ampicillin-sulbactam versus cefoxitin-doxycycline was initiated.

Randomized clinical trial. Thirty-eight women were randomly selected to receive ampicillin-sulbactam, and 37 women were randomly selected to receive cefoxitin-doxycy-

TABLE 1. Selected characteristics in the treatment groups

Characteristic	Value for group		
	Nonrandom, ampicillin-sulbactam (n = 26)	Randomized	
		Ampicillin-sulbactam (n = 38)	Cefoxitin-doxycycline (n = 37)
Mean age (yr) ± SD	22.7 ± 3.7	23.3 ± 4.0	23.8 ± 5.1
Mean no. of lifetime sexual partners ± SD	10.8 ± 10.3	11.6 ± 31.6	15.2 ± 29.6
Mean gravidity ± SD	2.4 ± 1.8	2.4 ± 2.3	2.5 ± 2.0
Mean parity ± SD	1.8 ± 1.5	2.0 ± 1.9	2.0 ± 1.6
No. (%) pregnant in the prior 18 months	10 (38)	10 (32)	13 (35)
No. (%) using no contraception	12 (46)	22 (58)	24 (63)
Current contraception:			
Oral contraception	7	10	6
Intrauterine device	5	4	3
Depo-Provera	1	0	3
Diaphragm, condoms, spermicides	0	2	1
Tubal ligation	1	0	0
No. (%) ever used intrauterine device	6 (23)	6 (17)	6 (16)
Past history of STD[a]	9 (35)	12 (33)	11 (30)
Past history of PID	3 (12)	4 (11)	8 (22)
Mean duration of symptoms prior to presentation (days) ± SD	7.2 ± 5.9	9.2 ± 7.9	13.5 ± 24.5
Palpable adnexal mass	2 (8)	1 (3)	5 (14)
No. (%) seen at 2- to 3-wk follow-up	18 (69)	33 (92)	32 (86)
No. (%) seen at 5- to 6-wk follow-up	10 (38)	25 (69)	28 (76)
No. (%) with fertility assessment	9 (35)	20 (53)	29 (78)

[a] STD, sexually transmitted diseases; these included gonorrhea, syphilis, genital ulcer disease, and PID.

cline. Twenty-seven of the 38 women (71%) treated with ampicillin-sulbactam had *N. gonorrhoeae* and/or *C. trachomatis* infection, compared with 13 of 37 women (35%) treated with cefoxitin-doxycycline (P = 0.004) (Table 2). Four of 38 women (11%) treated with ampicillin-sulbactam and 5 of 37 women (14%) treated with cefoxitin-doxycycline were HIV seropositive.

Clinical and microbiologic responses to therapy: follow-up 3 to 4 weeks after treatment. Sixty-five women returned for at least one visit following the completion of therapy. Thirty-three had received ampicillin-sulbactam and 32 had received cefoxitin-doxycycline (Table 3). Among the women who received ampicillin-sulbactam, 10 (30%) had findings suggestive of persistent PID and required additional therapy. Among women who received cefoxitin-doxycycline, nine (28%) had persistent signs and symptoms necessitating additional antibiotic treatment (P = 0.94). Among the nine women with chlamydial infection who received ampicillin-sulbactam, three clinically failed, four were clinically well or improved, and two did not return, although none were culture positive at the first follow-up. One of 22 women with gonococcal infections who were treated with ampicillin-sulbactam remained culture positive at follow-up, as did 1 of 12 women treated with cefoxitin-doxycycline. Both of these failures to cure gonococcal infection occurred among women who denied having had sexual reexposure.

TABLE 2. Etiologic agents isolated from the cervix at enrollment

Pathogen	No. (%) for group	
	Ampicillin-sulbactam (n = 38)	Cefoxitin-doxycycline (n = 37)
N. gonorrhoeae alone	18 (47)	12 (32)
C. trachomatis alone	5 (13)	1 (3)
N. gonorrhoeae and *C. trachomatis*	4 (11)	0
Neither of above	11 (29)	24 (65)
HIV (seropositivity)	4 (11)	5 (14)

Follow-up 5 to 6 weeks after treatment. Fifty-three patients were seen 5 to 6 weeks after the acute illness, including 25 treated with ampicillin-sulbactam and 28 treated with cefoxitin-doxycycline. This includes eight patients from the ampicillin-sulbactam group and nine from the cefoxitin-doxycycline group who had been retreated because of early clinical failure. The results for 37 patients who previously showed favorable early clinical responses are shown in Table 3. At this visit, 6 of 18 women (33%) who received ampicillin-sulbactam and 4 of 19 women (21%) who received cefoxitin-doxycycline had late clinical relapses and required additional antimicrobial therapy (P = 0.47).

Among women initially infected with *N. gonorrhoeae*, none treated with ampicillin-sulbactam were culture positive at the late follow-up, compared with two of nine women treated with cefoxitin-doxycycline. Both gonococcal treatment failures with cefoxitin-doxycycline occurred among women who denied having had sexual reexposure. Among women initially infected with *C. trachomatis*, three treated with ampicillin-sulbactam were culture positive. Two of the three chlamydial treatment failures occurred in women who denied having had sexual reexposure. The one women with *C. trachomatis* infection randomly selected to receive cefoxitin-doxycycline was culture negative at both follow-up visits.

Fertility outcome. Forty-nine women were evaluated for reproductive outcome, 20 women in the ampicillin-sulbactam group and 29 women in the cefoxitin-doxycycline group. Forty-four women underwent hysterosalpingography, and five had interim pregnancies (Table 4). Among women treated with ampicillin-sulbactam, 3 became pregnant and 11

TABLE 3. Clinical and microbiological results at follow-up visits

Treatment	Value for group				
	Clinically well	Clinically improved	Clinically unimproved or relapsed[a]	*N. gonorrhoeae* culture recurrently or persistently positive[b]	*C. trachomatis* culture recurrently or persistently positive
2- to 3-wk follow-up					
Randomized ampicillin-sulbactam (n = 33)	18	5	10	1	0
Randomized cefoxitin-doxycycline (n = 32)	21	2	9	1	0
5- to 6-wk follow-up[c]					
Randomized ampicillin-sulbactam (n = 18)	10	2	6	0	3
Randomized cefoxitin-doxycycline (n = 19)	14	1	4	2	0

[a] Unimproved at the 2- to 3-week follow-up and relapsed at the 5- to 6-week follow-up.
[b] Persistently positive at the 2- to 3-week follow-up and recurrently positive at the 5- to 6-week follow-up.
[c] Analysis is limited to those women who had favorable responses at the 2- to 3-week follow-up visit.

had hysterosalpingograms which demonstrated at least one clearly patent tube. Three women (18%) showed bilateral distal tubal obstruction and three could not be evaluated because of cornual spasm and absence of filling of the fallopian tubes. Among women treated with cefoxitin-doxycycline, two became pregnant and 14 had hysterosalpingograms which showed at least one normal tubal anatomy; eight women (33%) had bilaterally abnormal tubes with distal obstruction as determined by radiography. Five hysterosalpingograms could not be evaluated because of bilateral tubal spasm at the cornua which prevented tubal filling.

Correlates of post-PID bilateral tubal obstruction. Forty-nine women were evaluated regarding tubal outcome. This included 41 women from the comparative clinical trial and 8 women from the open-label study. Eleven women had bilateral obstruction as determined by hysterosalpingography and 38 had evidence of at least unilateral tubal patency (Table 5). Comparison of these two outcome groups shows that the finding of an adnexal mass at the time of enrollment was significantly associated with bilateral tubal obstruction at follow-up (P = 0.002). Women with bilateral tubal obstruction had marginally lower fertility than did women with tubal patency, since only 1 of 11 women with obstruction (9%) had been pregnant in the prior 18 months compared with 14 of 38 women (37%) with tubal patency (P = 0.08). Women with bilaterally obstructed tubes received ampicillin-sulbactam less often than did women with tubal patency (P = 0.15).

Side effects. Overall, in the ampicillin-sulbactam-treated group, 1 of 51 patients developed a maculopapular, pruritic rash 4 days after the initiation of therapy and 24 patients experienced some gastrointestinal disturbance (diarrhea, nausea, and/or vomiting). These side effects were mild. All side effects were tolerated without therapy being interrupted. In the cefoxitin-doxycycline-treated group, 4 women developed a rash and 16 complained of gastrointestinal symptoms. In three cases, gastrointestinal symptoms were severe enough to cause discontinuation of the antibiotic.

TABLE 4. Fertility outcome

Treatment	No. (%) for group			
	Pregnancy	Hysterosalpingography		
		Normal	Abnormal	Other[a]
Ampicillin-sulbactam (n = 20)	3	11	3 (18)	3
Cefoxitin-doxycycline (n = 29)	2	14	8 (33)	5

[a] Results could not be evaluated.

DISCUSSION

Although most women with acute PID are treated in an ambulatory setting, few studies are available to guide the choice of therapy. The determination of optimal therapy in this situation is an urgent priority and this is especially

TABLE 5. Correlates of post-PID tubal obstruction

Characteristic	Value (%) for group		P
	Bilateral tubal obstruction (n = 11)	Tubal patency (n = 38)	
Age (yr)	22.45 ± 4.6	22.7 ± 3.6	
Contraception:			
Current use of IUD	1	4	
Ever used IUD	1	7	
Current oral contraceptive	2	4	
Palpable mass	4	0	0.002
Past history of PID	2	7	
Nulliparity	4	7	
Mean gravidity	1.64 ± 1.7	2.08 ± 1.8	
Mean parity	1.36 ± 1.4	1.61 ± 1.4	
No. with parity of ≥1	7	30	
Mean time since past pregnancy (months)	27 ± 10.9	25.5 ± 22.0	
No. pregnant within last 18 months	1	14	0.018
Treatment with:			
Ampicillin-sulbactam	3 (27)	22 (58)	0.15
Cefoxitin-doxycycline	8 (73)	16 (42)	
Clinical treatment failure	6	22	
Initial cervical isolation of:			
N. gonorrhoeae	5 (45)	10 (26)	
C. trachomatis	1 (9)	2 (5)	
Neither	5 (45)	24 (63)	
HIV seropositivity	0	5 (13)	

relevant for developing countries. The ideal treatment trial should involve laparoscopic verification, although this is not feasible in most outpatient settings. Both short-term clinical and microbiologic outcome measurements and longer-term reproductive outcome measurement should be determined, since the major shortcoming of most antimicrobial regimens is their effect on late PID sequela (6).

We compared a β-lactamase inhibitor (sulbactam) combined with ampicillin to a widely recommended regimen, cefoxitin-probenecid-doxycycline, in the treatment of 75 women with clinically diagnosed acute PID in a sexually transmitted disease clinic in Nairobi, Kenya. Ampicillin-sulbactam was used alone because of its excellent in vitro activity against *N. gonorrhoeae*, members of the family *Enterobacteriaceae*, and genital anaerobes. Furthermore, clinical evidence suggested that it was useful among women with PID-associated pyosalpinx (14). While β-lactam antibiotics are normally thought not to be useful for the treatment of *C. trachomatis* infection, Crombleholme et al. (11) reported that amoxicillin was highly effective in treating *C. trachomatis* infection among pregnant women. Other smaller trials also suggested that ampicillin-amoxicillin was effective in vivo in eradicating *C. trachomatis* (2, 15, 19–21). We therefore evaluated ampicillin-sulbactam alone.

The short-term clinical cure rates and relapse rates were similar for both regimens. None of the differences were statistically significant. These clinical response rates are less than has been observed in other studies conducted in developed countries. Although we did not document the reason for the lower efficacy, it may relate to the poor performance of ampicillin-sulbactam for *C. trachomatis* infection and the suboptimal performance of cefoxitin-doxycycline for gonococcal and polymicrobial infection. We conclude that neither regimen is optimally effective for the management of outpatient PID in a developing country.

Microbiologic cure rates of gonococcal infection were similar for the two regimens, with ampicillin-sulbactam failing to eradicate 1 of 22 gonococcal infections (5%) and cefoxitin-doxycycline failing to eradicate 1 of 12 gonococcal infections (8%). Two late reinfections or relapses of gonococcal infection occurred among women randomly selected to receive cefoxitin-doxycycline. Both women denied having had sexual reexposure. No late failures occurred among ampicillin-sulbactam-treated women. Ampicillin-sulbactam appeared to suppress rather than eradicate *C. trachomatis* infection, since 3 of 9 infected women who were monitored had late microbiologic relapse. Two of three recurrences occurred among women who denied having had sexual reexposure. Future studies of ampicillin-sulbactam treatment of acute PID should use doxycycline in combination with ampicillin-sulbactam.

A major outcome measurement in the treatment of acute PID is the preservation of tubal function. The best way to determine this is to perform long-term (5 to 10 years) posttreatment follow-up of women, with monitoring of pregnancy rates (23). Such studies are extremely difficult to perform and are of necessity lengthy in duration. We used early posttreatment pregnancy rate or hysterosalpingographic appearance of tubal anatomy to estimate the effect of antimicrobial therapy on tubal function. Forty-nine women had a fertility outcome evaluation. We observed no significant difference in adverse reproductive outcome between the ampicillin-sulbactam-treated group and the cefoxitin-doxycycline-treated group.

Post-PID sequelae include chronic pelvic pain, tubal infertility, and ectopic pregnancy (24). The benchmark studies of Westrom (23) documented that post-PID sequelae occur in approximately 20% of treated women. Risk factors for post-PID sequelae include pyosalpinx and tubal ovarian abscess (7), *C. trachomatis* infection (7), *C. trachomatis* antibodies to a chlamydial hypersensitivity antigen (8), older age (23), prior PID (23), and nonuse of oral contraceptives during the current episode of PID (26). We compared some of these factors for the 11 women with post-PID tubal occlusion and the 38 women with evidence of tubal patency. We observed no difference in age, current use of oral contraceptive, or microbial etiology between the two groups. Women with bilateral tubal obstruction differed from women with tubal patency by more often having palpable adnexal masses at presentation ($P = 0.002$), tending to be subfertile ($P = 0.08$), and more often being treated with cefoxitin-doxycycline ($P = 0.15$). Although HIV seropositivity was relatively frequent (12%) among these women, this finding did not to correlate with post-PID tubal obstruction ($P = 0.57$).

The observation that women with bilateral tubal obstruction may be subfertile suggests that tubal disease detected by hysterosalpingography may have antedated the current episode of PID. This seems possible, since tubal dysfunction is a risk factor both for recurrent PID and for tubal infertility (23). This finding suggests a potential limitation for the use of either hysterosalpingography or a second laparoscopy in the post-PID evaluation of tubal anatomy, since one is unable to determine whether structural damage antedated or followed the episode of acute PID. Restricting analysis to women with an initial episode of PID may reduce but not eliminate this bias because of the occurrence of "silent" PID.

Fifty-one women underwent hysterosalpingography with periprocedural doxycycline prophylaxis. Five women experienced recurrence of pelvic pain following the procedure and required supplemental antibiotics. Symptoms rapidly resolved in four patients; one women became systemically ill, requiring hospital admission because of peritonitis and abscess formation. Following surgical drainage and antibiotic therapy, she eventually recovered. Post-PID women seem to be at a high risk of relapsing infection following hysterosalpingography. The use of radionuclide scanning with technetium-labeled human albumin microspheres (22) and of vaginal ultrasound examination (18) to study tubal function should be evaluated for their abilities to predict post-PID tubal dysfunction, as they may be more acceptable as short-term measurements of tubal anatomy.

The results of this study need to be interpreted within the context of important deficiencies in the study design. The sample size was clearly insufficient to detect any real difference in the response rates between the two regimens. If the anticipated cure rate was 90% (as seems reasonable for the cefoxitin-doxycycline regimen on the basis of the data in reference 16) and a 15% difference in response rates was sought, 146 cases would be required in each arm of the study to achieve a significance of $P < 0.05$ and a power of 0.9 to exclude a β error. Future studies on the outpatient treatment of acute PID should attain sample sizes of this magnitude if important differences between regimens are to be found. In this study as well, randomization did not yield treatment groups comparable in major prognostic factors for post-PID tubal occlusion. For example, 71% of the patients in the ampicillin-sulbactam group had either *N. gonorrhoeae* or *C. trachomatis* infection, compared with only 35% of the cefoxitin-doxycycline group. Also, 5 of 37 cefoxitin-doxycycline-treated women (14%) had a palpable adnexal mass at presentation, compared with 1 of 38 women (3%) treated

with ampicillin-sulbactam ($P = 0.18$); women treated with cefoxitin-doxycycline more frequently had a history of PID than did women treated with ampicillin-sulbactam (22 versus 11%, $P = 0.15$). On the basis of these data, we suggest that future studies using block randomization with stratification according to the presence or absence of adnexal mass and initial or recurrent episode of PID may be of benefit.

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