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INFECTIOUS DISEASE

Acute cystitis ... Treating STD partners ... Simpler therapy for chorioamnionitis ... Varicella immunity testing

New findings I selected for this *Update* affect the management of 4 common and potentially serious clinical problems: acute cystitis, gonorrhea and chlamydia infection, chorioamnionitis, and varicella.

- A comparison of amoxicillin-clavulanic acid vs ciprofloxacin for uncomplicated lower urinary tract infections yielded surprising results, and more evidence on *E coli's* resistance to antibiotics.
- Sexual partners of women with gonorrhea or chlamydia are more likely to receive appropriate treatment if it is offered by the women themselves or by the women's caregivers.
- Short-course therapy for chorioamnionitis had a very high cure rate, equal to the traditional course, and furthers the possibility of shorter hospitalizations and cost savings without compromising outcomes.
- The CDC's 1995 call for universal childhood vaccination for varicella has already sharply reduced varicella-related mortality in adults; still, we must determine immunity in our reproductive-age patients.

IN THIS ARTICLE

Acute cystitis: Ciprofloxacin prevails in *E coli* skirmish

Hooton TM, Scholes D, Gupta K, Stapleton AE, Roberts PL, Stamm WE. Amoxicillin-clavulanate vs ciprofloxacin for the treatment of uncomplicated cystitis in women: a randomized trial. JAMA. 2005;293:949–955.

- Amoxicillin-clavulanate was not as effective as ciprofloxacin even in women who were infected with bacteria sensitive to amoxicillin-clavulanate.

A total of 320 nonpregnant women, aged 18 to 45 years, with uncomplicated acute cystitis were treated for 3 days with either oral amoxicillin-clavulanate (500 mg/125 mg twice daily) or oral ciprofloxacin (250 mg twice daily). Two weeks after treatment, 95% of women treated with ciprofloxacin were clinically cured, compared with only 76% of women treated with amoxicillin-clavulanate ($P<.001$).

Start with ciprofloxacin

The difference in outcome was attributed to a marked difference in vaginal colonization with the single most common pathogen in acute cystitis—*Escherichia coli*—at the 2-

week follow-up (45% in the amoxicillin-clavulanate group vs 10% in the ciprofloxacin group, *P*<.001).

Even though successful treatment of cystitis usually is possible with short courses (3–7 days) of oral antibiotics, persistent and recurrent infections may occur and usually are related to persistent vaginal colonization with *E coli*.

Treatment may require an extended course of oral antibiotics.

Initial selection of an antibiotic for acute cystitis is empiric and should be based on probable susceptibility of the dominant uropathogens. For many years, the typical initial antibiotic has been ampicillin.

***E coli* resistance.** Now, however, more than a third of *E coli* strains, as well as most strains of *K pneumoniae*, are resistant to ampicillin. Therefore, ampicillin no longer should be used for the empiric treatment of cystitis.[1]

Surprising results

In theory, amoxicillin-clavulanate should have enhanced activity against *E coli* and other enteric organisms.

Therefore, these findings are surprising. The outcome with amoxicillin-clavulanate was inferior to that of ciprofloxacin, even in women who seemingly had susceptible uropathogens.

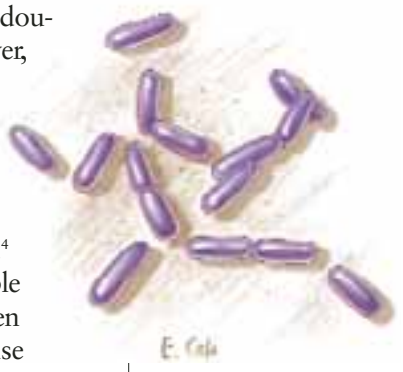
Based on this study, ciprofloxacin clearly is a more effective (and less expensive) empiric treatment in nonpregnant women.

In gravidas, start with nitrofurantoin

Ciprofloxacin is not appropriate for treatment of cystitis or asymptomatic bacteriuria in pregnant women. The quinolone antibiotics may cause injury to the developing cartilage of the fetus and are contraindicated in pregnant and lactating women, and in children younger than 17 years.[1]

What, then, is the most appropriate choice for treatment of uncomplicated cystitis during pregnancy?

One reasonable selection is oral trimethoprim-sulfamethoxazole, double-strength, twice daily. However, increasing resistance of *E coli* to this antibiotic has been documented recently.[2,3]



Therefore, a better choice is nitrofurantoin monohydrate macrocrystals, 100 mg twice daily.[4] One organism that is not susceptible to nitrofurantoin is *Proteus*. When this organism is suspected, use trimethoprim-sulfamethoxazole.

Follow-up is a must

Because persistent and recurrent infections are common, patients should be followed with urine dipstick assessment or urine culture to be certain that the infection is resolved.

Follow-up is particularly important when infected women are pregnant, because of the risk of ascending infection leading to preterm labor, sepsis, or acute respiratory disease syndrome.

FAST TRACK

Ampicillin should not be used empirically for cystitis. More than a third of *E coli* strains are resistant

Treat sex partners, sight-unseen?

Golden MR, Whittington WL, Handsfield HH, et al. Effect of expedited treatment of sex partners on recurrent or persistent gonorrhea or chlamydial infection. N Engl J Med. 2005;352:676–685.

- Providing a separate prescription for the partner(s) resulted in a 24% decrease in the frequency of persistent or recurrent infection.

Almost 2,000 men and women with uncomplicated gonorrhea or chlamydia infection were included in this study of expedited treatment compared with stan-

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dard referral. In the standard referral group, investigators treated 931 patients and referred their sex partners to other physicians or facilities for evaluation and treatment. In the expedited treatment group, 929 patients were treated and also were provided with antibiotics to give to their partners. The partners of patients who were unwilling to do so were contacted and treated by the investigators.

At follow-up 21 to 126 days after treatment), persistent or recurrent infection was found in 13% of standard referral patients and 10% of expedited treatment patients (relative risk, 0.76; 95% confidence interval, 0.59–0.98).

Expedited treatment decreased the rate of persistent or recurrent gonorrhea more than that of persistent or recurrent chlamydia.

Patients in the expedited group were more likely to report that all of their partners were treated, and less likely to report having had sex with an untreated partner.

Advantages of the direct approach

The challenge for the ObGyn is how to arrange treatment for the female patient's sex partner(s). This study indicates that a proactive approach is likely to be more effective than simply asking the patient to encourage her partner to seek medical attention. Direct provision of a separate prescription for the partner(s) resulted in a 24% decrease in the frequency of persistent or recurrent infection.

Failure to treat the patient's sex partner is the principal cause of persistent or recurrent infection, which may lead to pelvic inflammatory disease, Fitz-Hugh-Curtis syndrome, and infertility. Gonorrhea may disseminate and manifest primarily by arthritis and dermatitis. If a pregnant woman is colonized with gonorrhea or chlamydia at the time of delivery, her infant may acquire gonococcal or chlamydial conjunctivitis or chlamydial pneumonia.

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Document rationale in chart if you proactively treat sex partners

6 caveats

Although the results of this investigation are impressive and of great practical importance, these caveats should be noted.

1. The oral drug used to treat gonorrhea in this study, cefixime (400 mg), is not presently available, and although another oral drug such as ciprofloxacin (500 mg) would be highly effective, it should not be used in pregnant or lactating women, or women younger than 17 years.[1]
2. Although ceftriaxone, 125 mg intramuscularly, also is a superb drug for treatment of uncomplicated gonorrhea, the logistical problems of arranging for the partner to receive an intramuscular injection are daunting.
3. Some women in the expedited treatment group were reluctant to provide medication to their partner(s), and study personnel were forced to intervene. Keep in mind that individual private practitioners and even well-organized clinics may not have sufficient support personnel to trace and treat all contacts.
4. There is the important issue of a provider writing a prescription for an individual who is not actually his or her patient and who has not been interviewed and examined. Certainly, many state laws and insurance company regulations may discourage or even prohibit such a practice.
5. Lack of a detailed assessment of the partner(s) means there is no opportunity to evaluate them for other conditions such as syphilis and HIV infection.
6. Finally, taking a proactive approach in treating the sex partner(s) of patients who have gonorrhea or chlamydia (and, by extension, trichomoniasis) requires documentation of complete rationale in the patient's medical record.

In addition, detailed written instructions must be provided for the partner(s) and must include a specific caution about possible reactions to the antibiotic.

Single-dose plus intrapartum therapy effective for chorioamnionitis

Edwards RK, Duff P. Single additional dose postpartum therapy for women with chorioamnionitis. Obstet Gynecol. 2003;102:957–961.

- Short-course therapy is simpler to administer and reduces costs compared with more extended treatment.

Intrapartum therapy plus 1 additional dose of combination antibiotics after delivery produced a very high rate of cure (95.4%)—equivalent to that achieved when a more extended course of treatment was used.

In this randomized study of 292 otherwise healthy women with chorioamnionitis, 151 women were treated intrapartum with intravenous (IV) ampicillin (2 g every 6 hours) plus gentamicin (1.5 mg/kg every 8 hours). They received 1 dose of each drug postpartum. In addition, if they had a cesarean delivery, they received 1 dose of IV clindamycin (900 mg) immediately after the infant's umbilical cord was clamped.

Women in the control group received IV antibiotics (including clindamycin, if indicated) until they had been afebrile and asymptomatic for 24 hours.

In the study group, 4.6% of women had a treatment failure and required an additional course of antibiotics. In the control group, 3.5% of patients required additional antibiotics (P = .639, not significant). When patients were stratified by method of delivery, no significant difference was found in treatment outcome.

Pathogens and regimens

Chorioamnionitis occurs in approximately 1% to 5% of term patients and in as many as 25% of patients having a preterm delivery. The infection is caused by multiple aerobic and anaerobic organisms, notably group B streptococci, *E coli*, and anaerobes. The former 2 pathogens pose the greatest risk to the infant and are the predominant causes of neonatal pneumonia, bacteremia, and meningitis. These organisms also are major causes of maternal bacteremia.

Anaerobes usually do not pose a major threat to the fetus or neonate, but are particularly likely to lead to pelvic abscess in women who require a cesarean delivery in the face of preexisting intrauterine infection.[5]

Accordingly, the initial antibiotic therapy for chorioamnionitis typically targets the 2 organisms most likely to infect the fetus/neonate—group B streptococci and *E coli*. The antibiotic regimen of ampicillin plus gentamicin provides excellent, and inexpensive, coverage of these pathogens. The addition of a drug such as clindamycin or metronidazole provides a reassuring measure of coverage against anaerobes in women who require a cesarean delivery.[1]

Traditionally, patients with chorioamnionitis have been treated with IV antibiotics until they have been afebrile and asymptomatic for 24 hours.

Chapman and Owen,[6] who were among the first to suggest that a shortened course of treatment might be as effective as a more extended course, assessed the effectiveness of a single postpartum dose of cefotetan in women who were treated intrapartum for chorioamnionitis and who delivered vaginally. The rate of treatment failure was 11% in the single-dose group and 3.7% in the women treated with multiple doses of cefotetan until they had been afebrile for 24 hours. This observed difference was not statistically significant (P = .27), but the study lacked sufficient power to firmly establish the safety and effectiveness of short-course therapy.

A trial of "no therapy" vs "extended therapy" in women with chorioamnionitis

FAST TRACK

Anti-anaerobic coverage is critical in cesareans

who delivered by cesarean found the rate of treatment failure was 21.8% in the "no therapy" group and 14.8% in the women who received clindamycin plus gentamicin for at least 24 hours postoperatively.[7]

Again, this observed difference was not statistically significant (P = .32), but the power of the investigation was limited.

This more recent study was sufficiently large and included a reasonable number of women who delivered both vaginally and abdominally.

Anti-anaerobic coverage critically important. Complications related to persistent infection developed in 2 patients in the short-course group who had cesarean deliveries: pelvic abscess and incisional abscess. In both instances, the patients did not receive the dose of clindamycin specified in the protocol, illustrating the critical importance of proper anti-anaerobic coverage in patients who require abdominal delivery.

Short-course therapy offers advantages in terms of ease of administration and cost savings compared with more extended treatment regimens.

Whether short courses of single agents, such as the broad-spectrum cephalosporins, penicillins, and carbapenems, would be as effective as ampicillin plus gentamicin plus clindamycin remains to be determined.

CDC data show "herd" immunity, thanks to varicella vaccination policy

Nguyen HQ, Jumaan AO, Seward JF. Decline in mortality due to varicella after implementation of varicella vaccination in the United States. N Engl J Med. 2005;352:450–458.

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Test women of reproductive age if varicella history is uncertain

- Question all women of reproductive age about varicella. Women who lack a convincing history of natural infection should have a serologic test for varicella-zoster IgG. If immunity is not evident, they should be vaccinated prior to attempting pregnancy.

This study demonstrates that, through the phenomenon of herd immunity, universal vaccination has significantly lowered the overall risk of varicella-related mortality in the general population. Universal childhood varicella vaccination was recommended by the Centers for Disease Control and Prevention in 1995; the rate of death due to varicella, either as the underlying cause or the contributing cause, fluctuated from 1990 through 1998, and then sharply declined.

Data from the National Center for Health Statistics Multiple Cause-of-Death Mortality for 1990 through 2001 reveal reduced varicella-related mortality in all age groups younger than 50 years. The greatest reduction (92%) was in children 1 to 4 years of age. Most deaths due to varicella were among persons who did not have an underlying high-risk condition and who would have been excellent candidates for vaccination.

Life-threatening in adults, especially pregnant women

Varicella usually is a relatively mild, self-limited disease of childhood. However, in immunocompromised persons and even in otherwise healthy adults, varicella can cause life-threatening complications such as severe pneumonia and encephalitis. Pneumonia develops in approximately 20% of adults who contract varicella, and encephalitis in approximately 1%. In the era before acyclovir was available, as many as 20% of persons with these complications died.[8]

Unique set of problems during pregnancy. Although pregnant women are not more likely than nonpregnant women to contract varicella or even to develop pneumonia or encephalitis, they do have a higher mortality if they experience these complications.

When varicella occurs during the first half of pregnancy, anomalies or spontaneous abortions occur in 1% to 2% of fetuses. Moreover, when the mother has varicella near or at the time of delivery, neonatal varicella develops in as many as 20% of infants, manifested as a mucocutaneous exanthema, pneumonia, encephalitis, or disseminated visceral infection. Even with acyclovir treatment, severe morbidity and death can occur in affected neonates.[8]

Test and, when necessary, vaccinate women

The key point for clinicians to recognize is that varicella now can be almost completely prevented through universal vaccination.[9]

Although the principal target group for vaccination is young children, ObGyns should question all women of reproductive age about susceptibility to varicella. Women who do not have a convincing history of natural infection should have a serologic test for varicella-zoster IgG. If immunity is not evident, they should be vaccinated prior to attempting pregnancy.

- The present varicella vaccine (Varivax) is a live-virus vaccine, which should be administered in 2 subcutaneous injections (0.5 mL) 4 to 8 weeks apart.
- The vaccine should not be administered to infants younger than 12 months of age, to pregnant or lactating women, or to patients who have received systemic steroids within the last month.
- The vaccine also should not be given to persons who are immunosuppressed, except as part of a carefully supervised research protocol.

The vaccine is highly immunogenic and produces immunity in approximately 90% of healthy children. The rate of seroconversion is lower in adults and immunosuppressed patients. Vaccinated patients have a significantly lower rate of natural infection after exposure. ■

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Varicella can be almost completely prevented by universal vaccination