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ANTIMICROBIAL THERAPY FOR BACTERIAL AND NONBACTERIAL PROSTATITIS

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ABSTRACT

Antimicrobial therapy is the standard of care for the unusual man with true chronic bacterial prostatitis but does not have much of a role in the treatment of men with nonbacterial prostatitis. The fluoroquinolone antibiotics given for 2 to 4 weeks will cure about 70% of chronic bacterial infections of the prostate. If this treatment fails, the symptomatic manifestations of the infections can almost always be eliminated with suppressive antimicrobial therapy using trimethoprim-sulfamethoxazole, a fluoroquinolone antibiotic, or nitrofurantoin. UROLOGY **60** (Suppl 6A): 24–26, 2002. © 2002, Elsevier Science Inc.

Antimicrobial therapy that is based upon the results of bacteriologic investigation of the urine and/or expressed prostatic secretions (EPS) is the standard of care for men with chronic bacterial prostatitis. Conversely, antimicrobial therapy has no proven impact on the symptoms or natural history of nonbacterial prostatitis, a disorder that is not believed to be caused by bacterial infection.

BASIC PRINCIPLES OF ANTIMICROBIAL THERAPY

Potentially Curative Therapy. Eradication of localized bacterial infections with antimicrobial therapy requires sufficient levels of an appropriate drug at the site of infection. Because infecting bacteria are isolated from the prostatic fluid of men with chronic bacterial prostatitis, it follows that the antimicrobial agent must achieve bactericidal levels in this fluid. Although therapeutic levels of drug also must be achieved in the urine, this consideration has limited clinical relevance because all agents used for the treatment of chronic bacterial prostatitis are concentrated in the urine.

A variety of pharmacologic properties determine whether a drug will diffuse into the prostatic fluid.[1] To penetrate the prostatic epithelium, the agent must be lipid soluble and have minimal binding to serum protein. In addition, ionized molecules do not cross epithelial membranes. Most antimicrobial agents are either weak acids or weak bases and are ionized to varying degrees in biologic fluids. The degree of ionization is determined by both the dissociation constant (pKa) of the drug and the pH of the fluid. Agents with a pKa that approaches 7.4 (the pH of serum) are only partially charged in the serum, whereas those with a pKa that differs substantially from 7.4 are highly charged in the serum.

Trimethoprim and the fluoroquinolones are the only antimicrobial agents that have good activity against gram-negative bacilli and that possess the pharmacologic characteristics that predict a capacity for diffusion into the prostatic fluid. Clinical experiences have demonstrated that these agents are also the most effective for treatment of chronic bacterial prostatitis. The optimal drug doses for potentially curative therapy or for suppressive therapy are not well established, and the recommendations that follow constitute the author's approach rather than those recommended by the manufacturer or cited in the *Physicians Desk Reference*.[2] Trimethoprim-sulfamethoxazole (160 and 800 mg twice daily) over a 12-week period will cure about 40% of patients.[3] It is probable that the sulfamethoxazole component of this combination agent has little therapeutic value, and that the efficacy of trimethoprim alone is similar to that of trimethoprim-sulfamethoxazole. The fluoroquinolone antibiotics, such as ciprofloxacin (500 mg twice daily), given for 2 to 4 weeks cure about 70% of men with chronic bacterial prostatitis and will often cure men with persistent infection after treatment with trimethoprim-sulfamethoxazole.[4–7]

Suppressive Therapy. Unlike conventional antimicrobial therapy, which is designed to eradicate the focus of infection in the prostate gland, and by

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definition, eliminate the cause of persistent bacteriuria, the goal of suppressive therapy is to reduce or eliminate bacterial growth in the urine only. This usually results in complete symptomatic relief and little risk of serious morbidity from infection within the prostate gland.

Considerations important to drug selection for suppressive therapy differ substantially from those of conventional antimicrobial therapy. Agents used for suppressive therapy must be well tolerated during prolonged periods of administration and must be active against the infecting organism at concentrations achievable in the urine. Most antibiotics are physiologically concentrated in the urine, achieving levels 50 to 100 times greater than in serum. Because the susceptibility of most gram-negative bacteria to an antimicrobial agent is directly related to the concentration of the drug, it follows that a variety of agents that are inappropriate for the treatment of invasive infections may be effective for suppressive therapy, and that antimicrobial susceptibility testing may be critical for appropriate drug selection.

Reported experiences with chronic bacterial prostatitis indicate that low-dose trimethoprim (50 or 100 mg once daily), trimethoprim-sulfamethoxazole (40 and 200 mg once daily), and nitrofurantoin (50 or 100 mg once daily) are remarkably effective.[1,8] A large experience with these agents for prophylaxis against frequent urinary tract reinfection in women suggest that indefinite treatment is generally well tolerated.[1] Chronic low-dose fluoroquinolone antibiotic therapy, such as ciprofloxacin (125 or 250 mg once daily), is also well tolerated and may be more effective than the treatment regimens described above. However, the cost of the fluoroquinolones is substantially greater than that of generic trimethoprim-sulfamethoxazole or nitrofurantoin. This issue may warrant careful consideration in an era of cost containment in the healthcare system.

AN APPROACH TO THE DIAGNOSIS AND TREATMENT OF CHRONIC BACTERIAL PROSTATITIS

The symptoms of chronic bacterial prostatitis and of nonbacterial prostatitis are similar. However, the relative incidence of nonbacterial prostatitis is about 20 times greater than chronic bacterial prostatitis, and bacteriologic investigations should be limited to patients with a high likelihood of bacterial infection. A history of culture-documented bacteriuria, or of prompt symptomatic responses to prior antimicrobial therapy, or a urinalysis suggesting bacteriuria, should raise concern about an infectious process. Conversely, the likelihood of chronic bacterial prostatitis is remote if past urine cultures have been sterile during symptomatic episodes or if antimicrobial therapy did not lead to prompt symptomatic relief.

During the initial evaluation of men with symptoms of chronic prostatitis, a second midstream bladder specimen (VB_2) is obtained before or after a careful history and is examined microscopically before physical examination. If the history does not suggest bacterial infection and there is no pyuria, bacteriologic investigations of the urine or EPS are not warranted. Regardless of history, if there is pyuria, the VB_2 specimen is cultured. Finally, if the history is suggestive of bacterial infection and there is no pyuria, EPS is procured during examination of the prostate and cultured.

Nitrofurantoin macrocrystals, 100 mg twice daily for 7 days is recommended for the initial treatment of suspected chronic bacterial prostatitis, and the patient is reevaluated 1 week after the first visit. Nitrofurantoin macrocrystals will not eradicate bacteria in the prostate and will facilitate the interpretation of subsequent lower tract bacterial localization studies.[9] When pathogenic organisms are not isolated from the VB_2 or EPS specimen, further antimicrobial therapy is not pursued and the patient is considered to have nonbacterial prostatitis. When gram-negative bacilli are isolated from the VB_2 or EPS specimen, the clinician may perform a lower tract bacterial localization study or simply treat the patient with a fluoroquinolone antibiotic (such as ciprofloxacin, 500 mg, twice daily) for 3 weeks. *Enterococcus* infections should be treated with ampicillin, 250 mg 4 times daily, for 2 weeks. In the rare event that pathogenic organisms isolated from the VB_2 or EPS specimen appear resistant to a fluoroquinolone antibiotic, an alternative agent that exhibits activity should be given at full oral dosage. If the isolate appears resistant to all oral agents, it is reasonable to proceed with fluoroquinolone antibiotic therapy.

Surveillance cultures of the VB_2 specimen at 4 and 12 weeks after treatment should be done to document therapeutic efficacy. Men with persistent bacteriuria should be retreated with a fluoroquinolone antibiotic for 3 more weeks.

Chronic prostatic infections caused by organisms that are susceptible to the fluoroquinolone antibiotics but that cannot be eradicated with 3 to 6 weeks of treatment will rarely be cured with other antimicrobial agents. Moreover, there is no convincing evidence that treatment with a fluoroquinolone for longer than 6 weeks will increase the likelihood of cure. For these reasons, the most logical approach to subsequent treatment is suppressive antimicrobial therapy. Because this therapy is associated with greater cost and potential morbidity than conventional drug therapy, it is prudent to clearly document prostatic infection with a lower tract localization study.

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DISCUSSION FOLLOWING DR. FOWLER'S PRESENTATION

Anthony J. Schaeffer, MD (Chicago, Illinois): The recommendations we make for urinalysis and culture also serve to rule out other conditions that the pelvic pain could be masking or mimicking. Dr. Shoskes mentioned carcinoma in situ. You should do a urinalysis to rule out other conditions, and you ought to do a culture. If you have positive cultures, as Dr. Fowler suggested, then you investigate localization, and if you have a positive urinalysis, you can start talking about other things.

Daniel A. Shoskes, MD (Weston, Florida): This is based on the supposition that you do not get symptoms from bacteria unless you have a urinary tract infection.

Dr. Schaeffer: Yes. That is true. Have you ever seen a person with documented bacterial prostatitis, but without a urinary tract infection, who has symptoms?

Dr. Shoskes: Because we are just commenting on particular case reports, I can think of several patients without a urinary tract infection who were found to have *Escherichia coli*; antibiotic treatment eradicated the *E. coli* and eradicated the symptoms. This is a personal observation. Unless I have missed some of the published data, I do not think that it is proved.

J. Curtis Nickel, MD (Kingston, Ontario, Canada): We had 102 patients in our study; approximately 50% of them had a significant clinical improvement on fluoroquinolones without bacteria. So quinolones may do more than just treat bacterial infections. Or alternatively, we are not culturing the responsible pathogen. At the very least you should do a urine culture. Is it mandatory to do a localization culture? That is the question.

Dr. Schaeffer: Do we want to mandate a urine localization culture versus a urine culture?

Michel Pontari, MD (Philadelphia, Pennsylvania): In terms of what we want to say about antibiotics, I know the European Commission said in 1998 that all patients should have a course of antibiotics.[1] Localization cultures or not, I think everybody deserves one 4- to 6-week course of antibiotics. Is that what we all do?

Dr. Schaeffer: We never see anybody like that. Approximately 90% of our patients have already been treated.

Dr. Nickel: The study I did was with primary care urologists, and those men treated with the quinolone are patients that this group does not usually see. I do not think we can make too many recommendations until we know the National Institutes of Health (NIH) RCT1 results. Right now, I still recommend that every patient probably should have 1 trial of antibiotic. If it does not relieve symptoms, then it should not be tried again.

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