The Spectrum of Urinary Tract Infections in Family Practice

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Urinary tract infections are among the most frequently encountered health problems in patients of family physicians. The diagnosis requires the demonstration of more than 100,000 bacterial colonies per milliliter in a freshly voided urine specimen. Dysuria, proteinuria, and pyuria are unreliable diagnostic criteria. The pathogenesis is uncertain although vaginal colonization with enteric bacteria, voluntary avoidance of urination, and sexual intercourse are contributing causes. Vesicoureteral reflux is related to recurrent infection but a causal relationship has not been established.

Urinary tract infection in children is related to decreased renal growth and kidney scars, but therapy of the infections does not prevent kidney damage. Infections disappear spontaneously in up to 40 percent of adult women. Bacteriuria in pregnancy, however, is related to low birth weight in infants and increased perinatal mortality.

Asymptomatic bacteriuria need not be diagnosed or treated except in pregnant women. For symptomatic infections, short-term antibiotic therapy is as effective as long-term therapy. Prophylactic antibiotics and therapy by modification of behavior using a multifaceted regimen can reduce the frequency of recurrent infection.

Urinary tract infections (UTIs) encompass a spectrum of clinical entities that include pyelonephritis, cystitis, and asymptomatic bacteriuria. These conditions are among the most frequently encountered health problems in ambulatory patients treated by family physicians and other primary care providers. Nevertheless, the pathogenesis, natural history, and management of urinary tract infections are subjects of controversy. Although urethritis and prostatitis are part of the UTI spectrum, these entities will not be considered in this paper.

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Definition

There is general agreement that a bacterial colony count exceeding 100,000 per milliliter in a freshly voided midstream urine sample collected after washing the genitalia is required for a definitive diagnosis of urinary tract infection. Certainty of diagnosis is enhanced if this degree of bacteriuria is demonstrated in two or more specimens collected on separate days. Urethral catheterization to collect urine specimens is not recommended. In urine obtained by suprapubic bladder puncture (sometimes required in neonates), any number of colonies is significant. The use of symptoms alone for diagnosis is unreliable, because only one half of women who present with symptoms of urinary tract infection have significant bacteriuria.[1] A diagnosis made by the presence of proteinuria or pyuria is equally unreliable.[2,3]

Prevalence and Incidence

The diagnosis of cystitis was made in over 5 million, or 0.8 percent, of all patient visits to office based United States physicians during the period May 1973 to April 1974.[4] It ranked as the 27th most frequently made diagnosis. The precision of these data, however, is questionable because the criteria used for these diagnoses are not given.

The prevalence of bacteriuria as determined by surveys of general populations or of patients in office practices varies with the age and sex distribution of the population studied. In newborns bacteriuria was demonstrated in 2.9 percent of premature and 0.7 percent of full-term infants, most of whom were without other signs of illness.[5] Although a larger percentage of newborn males have bacteriuria than do females,[6] in adults the prevalence of asymptomatic urinary tract infection is six to seven times higher in females than in males.[1] For preschool children, a review of six separate surveys reported a prevalence of bacteriuria that ranges from 0 to 2 percent in boys and 0.8 to 7 percent in girls.[7] Some of the differences noted in the several surveys are due to differences in methods of collection and examination of urine specimens. A study of 200 women at the time of uterine curettage revealed a prevalence of five percent asymptomatic bacteriuria based on catheterized urine specimens obtained at the time of surgery.[8] In a general practice study of children under the age of 13 years, the incidence of bacteriuria was calculated at 1.4 percent per annum for the total group and 4.9 percent per annum for those under age five years.[2] An estimate by Kass[9] that one percent of school girls are bacteriuric in the first decade with a linear rise of one percent in prevalence for each succeeding decade appears to fit survey data reasonably well.

Site of Infection

Based on clinical observations (eg, fever, chills, flank pain), over 90 percent of urinary tract infections involve only the lower tract,[10] but proving the site of infection can be difficult. Although invasive techniques such as ureteral catheterization and bladder washout can differentiate the site of urinary tract infection, recent attention has focused on the demonstration of antibody-coated bacteria in the urine. The presence of coated antibody is believed to correlate closely with upper UTI. The method is attractive because it is noninvasive, but a recent review of several studies demonstrated a sensitivity of only 83.1 percent and a specificity of 76.7 percent for the method. The authors conclude that the assay is not useful for patient management.[11] Moreover, Kunin feels that localization of site of infection has little clinical value because his therapeutic goal is total eradication of bacteria regardless of site.[12]

Pathogenesis

Entry of enteric bacteria into the urinary tract from the vaginal vestibule has been suggested as the mechanism of urinary tract infection in women. Evidence for this hypothesis derives from the demonstration that colonization of the vaginal introitus with Escherichia coli and other enteric

bacteria precedes infection in bacteriuric women.[13] Additional evidence is that the increased prevalence of colonization in postmenopausal women as compared with premenopausal women correlates with increased frequency of infection in older women.[14] The vaginal introitus of non-bacteriuric women, however, can also be colonized with enteric bacteria.[15] Local factors such as bacterial adherence to vaginal cells[16] and production of cervico-vaginal antibodies[17] may explain why some colonized women resist bacteriuria.

The source of infection in boys appears to be the prepuce or the urethra rather than the bowel.[18] Boys also differ from girls in the species of infecting organisms and in the demonstration by urography of a greater percentage of structural abnormalities.[19]

Lapides[20] postulates a different mechanism for the cause of urinary tract infection. He believes that the essential causative factor is over-distention of the bladder, due to either obstruction or voluntary avoidance of voiding. Over-distention presumably decreases vascular circulation to the bladder wall, with a resultant increase in susceptibility to enteric organisms circulating during the episodes of transient bacteriemia that occur periodically in normal persons. Indirect evidence for this hypothesis is provided by Adatto and associates,[21] who found that 61 percent of patients with recurrent urinary tract infection practiced voluntary urinary retention for more than one hour after experiencing the urge to urinate, whereas 11 percent of a healthy control group reported voluntary retention. Two thirds of the patient group habitually deferred urination for more than three hours. The reasons for delay related to embarrassment or desire not to use public toilets, rather than difficulty in micturation.

The role of sexual intercourse is not entirely clear. "Honeymoon cystitis" is an established entity, and transient increases in bacteriuria occur following intercourse.[22] Nuns have a remarkably low prevalence of bacteriuria.[23] Although a single dose of an antibiotic administered after intercourse can reduce the incidence of infection in women with recurrent urinary tract infection,[24] post-coital voiding within one hour has not been shown to have a similar salutary effect.[22] Urethral trauma during intercourse has been proposed as a contributing factor to infection,[24] but the precise mechanism has not yet been determined.

The predominant infecting organism is E coli, accounting for between 80 and 90 percent of outpatient urinary tract infections. Proteus, klebsiella, enterococci, and staphylococci account for most of the remainder of infections, and these bacteria are somewhat more frequent causes of recurrent infection, infections following instrumentation, or infections encountered within the hospital setting. Hemorrhagic cystitis, especially in children, can be caused by adenovirus type II.[25,26] Socioeconomic status, personal hygiene habits, and race are not important determinants of the frequency of infection.[27]

Vesicoureteral reflux demonstrated by cystogram occurs in 34 percent of bacteriuric girls.[28] It appears to be related to infection, but a causal relationship has not been demonstrated. Frequency of reflux decreases with age and disappears spontaneously in over 80 percent of patients.[27] Reflux does not correlate well with decreased renal growth,[28] and indications for surgical correction are unclear. Convincing evidence that surgical correction alters the natural history of reflux in a favorable direction is lacking, and the operation may contribute to the development of hypertension.[29] Furthermore, the investigation with micturating cystography in itself has risk of inducing bacteriuria.[30]

Urethral stenosis has been implicated as a cause of recurrent urinary tract infection. In his recent book, Kunin states "urethral dilatation is probably the most common procedure used by urologists to treat females with recurrent infection."[31] Yet careful measurements of the caliber of the distal urethra do not show a decreased diameter for patients with a tendency toward urinary tract infection, and urethral dilatation has no effect on preventing recurrences.[10]

Family Factors

There is a dearth of information about the risk of urinary tract infection in family members of bacteriuric persons. Using questionnaires and home urine test kits, a greater incidence of systemic hypertension in parents and/or siblings of bacteriuric girls as compared with non-bacteriuric

controls was noted, although none of the bacteriuric children were themselves hypertensive.[32] Using home culture methods, 14 percent of female siblings and 13 percent of mothers of bacteriuric children were found to be bacteriuric, but no control group was studied.[33] An additional paper, also lacking in controls, reports chronic urinary tract infection in 3 families out of 11.[34] Most interesting of the few relevant family studies was the unexpected finding by Gillenwater and associates[35] that 7 children from 65 pregnancies of bacteriuric women had urinary tract infections discovered between eight months to nine years. They have followed 60 bacteriuric females and 38 matched controls for up to 18 years. None of the 24 children of the control group developed urinary tract infection. None of these studies, however, is in itself conclusive, but as a group they suggest an increased risk of urinary tract infection and perhaps hypertension in family members of bacteriuric individuals. Whether the increased risk, if present, relates to genetic or environmental factors is unknown. Further investigation of family factors in urinary tract infection is needed.

Natural History

It is likely that urinary tract infection in children is related to decreased renal growth and the presence of kidney scars, but the risk appears to be small[36] and the damage may occur before the age of five years.[28] A study of 60 bacteriuric school girls followed to adulthood showed that renal scars, reflux, and reduced renal clearance were more common in infected children as compared with matched controls.[35] However, all bacteriuric children received invasive investigative procedures (cystograms and urethral calibrations), and all episodes of bacteriuria were treated with antibiotics. One wonders whether or not therapy and/or investigations may have contributed to the unfavorable outcome. Although a small percentage of asymptomatic bacteriuric children may be at risk for subsequent renal damage, there is currently no simple method of identifying this group, and if identification were possible, no therapeutic interventions have been shown to prevent kidney damage. In adult women, persistent bacteriuria may be more benign than in children. In a longitudinal study of 200 bacteriuric women followed up to 12 years, neither hypertension nor decreased renal function occurred.[37]

During a one-year period bacteriuria disappeared spontaneously in 35.5 percent of 107 nonpregnant adult females.[37] In surveys of populations in Jamaica and Wales repeated at 4-year intervals over a 12-year period, annual spontaneous clearing of bacteriuria is estimated at between 20 and 25 percent.[9] An additional study in a Dutch general practice[38] confirmed spontaneous disappearance of this problem in a significant percentage of female adults.

Pregnancy

The relationship of bacteriuria during pregnancy with low birth weight infants and increased perinatal mortality is fairly well established, although the effects of therapy are less firmly demonstrated. Perinatal mortality was two times greater (42 per 1000 vs 21 per 1000) for pregnancies complicated by urinary tract infection as compared with uninfected women. This excessive mortality was ascribed to non-infectious placental and fetal disorders, in particular to the growth retarded placenta.[39] Other observations indicate that eye infections and impaired motor activity at eight months of age are more commonly observed in children born to infected mothers compared with controls.[40]

Therapy

Modification of behavior by a multifaceted regimen that includes frequent voiding, post-coital voiding, adequate hydration, lubrication during coitus, and avoidance of stool contamination of the vagina can reduce the frequency of recurrent infections,[21] but the effect of each intervention by itself has not been evaluated. Avoidance of over-

distention of the bladder was the focus of therapy by Lapides,[20] who encouraged frequent voiding and on occasion employed self-catheterization for patients with continuing obstruction. He reports good results, but control groups were not studied.

The treatment of the asymptomatic bacteriuric patient is controversial, but there is little evidence that drug therapy is useful. Several studies indicate that treatment has little effect on kidney growth, progression of kidney scars, or clearance of vesicoureteric reflux.[28,37,38,41] In a comparison of treated and untreated adult women after one year, there was no significant difference in the prevalence of bacteriuria, except that treated women were more likely to experience symptoms with a new infection, suggesting that "bacteriuric women may have developed tolerance to the particular organism harbored in their urinary tract and that treatment upset this equilibrium."[37]

For the symptomatic patient with urinary tract infection, drug therapy may be useful, but the ideal length of therapy is a matter of dispute. In cases of cystitis defined by typical symptoms and negative assay of coated bacteria in women with amoxicillin sensitive organisms, both a single dose of 3 gm or an oral dose of 250 mg four times daily for ten days of amoxicillin were 100 percent effective in producing cures. With upper tract infection only, 50 percent of patients were cured with a single dose.[42] The duration of treatment with antibiotics appears to be arbitrary, although in asymptomatic bacteriuria in pregnancy ten days of therapy was superior to five days.[43] A six-week course of drug therapy, however, offers no advantage over ten days of antibiotics.[44,45]

For girls with recurrent urinary tract infection, urethral dilatation or internal urethrotomy offers no advantage over antibiotic therapy alone.[46] Recurrent infections are more apt to be due to reinfection than to relapse, as judged by the emergence of different infecting organisms.[47,48] The reasons for changes in bacterial species are not well understood but may relate to shifts in intestinal flora and the close concordance of urinary bacteria with intestinal bacteria. Nevertheless, for women with recurrent urinary tract infection, long-term prophylaxis with a variety of low-dose antibiotic regimens is effective in reducing bacterial populations in the urinary tract, vaginal vestibule, and feces; and this reduces the number of episodes of symptomatic infection.[49-51] In males with chronic urinary tract infection, continuous therapy with antibiotics can reduce but not eliminate entirely the prevalence of bacteriuria and can reduce the number of symptomatic infections.[52]

Suggested Strategies for Investigation and Management

Given a voluminous literature with conflicting views on the several issues of urinary tract infection, what is a rational approach to the problem? Should bacteriuria be sought out in the asymptomatic patient and additional investigations and therapy applied with vigor? The answers to these questions will, to some extent, be determined by the individual physician's approach to patient care. An aggressive approach includes seeking out all people with bacteriuria and pursuing both investigation and therapy until every last bacterium has been destroyed. The concept of organisms inhabiting the urinary tract without adverse consequences to the host may be difficult for some to accept. For other physicians, concerns with adverse consequences from diagnostic and therapeutic interventions are the dominant determinant of their courses of action.

On some issues there appears to be agreement. The definition of the condition by bacterial colony count is reasonably firm. The benign course of most cases and spontaneous resolution of many cases of bacteriuria are also recognized. There is agreement that bacteriuria in pregnant women can and often does have an adverse effect on the fetus. Other issues are controversial and competent authority can be quoted to substantiate instituting diverse investigations and therapies. Inevitably then, the recommendations that follow are influenced by the individual bias that evolves from this author's philosophical approach to and practical experience with patient care.

Screening and Pregnancy

Screening is not recommended for any patient regardless of age or sex, with the exception of

pregnant women. Urine cultures should be obtained in both the second and third trimesters of pregnancy. Significant bacteriuria with or without the presence of symptoms should be treated with appropriate antibiotics determined by sensitivity testing. Although evidence that treatment can prevent harm to the fetus is less firm than the existence of a relationship between bacteriuria and increased perinatal morbidity and mortality, treatment with appropriate antibiotics appears to be prudent. Follow-up cultures to determine "cures" should be obtained. Antibiotics, such as tetracycline, which are contraindicated in pregnancy should, of course, not be used.

Males and Non-Pregnant Females

The initial symptomatic infection should be documented with the demonstration of more than 100,000 bacteria in a carefully collected urine specimen. Reliable colony counts can be obtained with any of several simple kits designed for office use. Neither identification of the organism nor its sensitivity to antibiotics is required, since most infecting organisms in the ambulatory setting are E coli and any of several drug regimens can be employed. A single large dose of an antibiotic like amoxicillin or ten days of therapy with a sulpha drug are likely to be effective. For patients given a ten-day course of therapy who become asymptomatic, lack of strict compliance by taking all of the medication need not concern the physician. Follow-up culture is not required because the patient with continuing bacteriuria who becomes asymptomatic is now in the group for which benefits of further therapy are uncertain.

For the symptomatic patient who is not infected (so called urethral syndrome), temporizing measures such as increased fluid intake and/or a urinary analgesic agent may be used, although personal experience with urinary analgesics has been disappointing.

For recurrent symptomatic infections, a behavioral approach which includes frequent voiding, adequate fluid intake, and avoidance of fecal contamination of the vaginal introitus may be useful. For infections associated with intercourse a single dose of an antibiotic at the time of intercourse can reduce the incidence of emergence of symptoms. Although each of the recurrent infections can be treated satisfactorily with a short course of antibiotics, there may be a place for low dose, long-term prophylactic antibiotics. Given a knowledge of the risks of continuous therapy as opposed to the benefits of preventing recurrent symptoms, it may be best to have the patient make his/her own decision.

Investigations other than urine examination and culture can be limited to patients with recurrent urinary tract infection. For the most part, an intravenous pyelogram is sufficient to identify structural abnormalities that require surgical intervention. The voiding cystourethrogram is rarely necessary because reflux is a frequent finding, often disappears spontaneously or with antibiotic therapy, and surgical correction is of uncertain value. The cystourethrogram may in itself cause morbidity.

There are many unanswered questions about urinary tract infection which require additional research. Until new information becomes available, this author's evaluation of current literature leads him to suggest a conservative approach to both investigation and therapy.

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