31. Screening for Asymptomatic Bacteriuria

RECOMMENDATION

Screening for asymptomatic bacteriuria by urine culture is recommended for all pregnant women (see ***Clinical Intervention***). There is insufficient evidence to recommend for or against routine screening for asymptomatic bacteriuria in diabetic or ambulatory elderly women, but recommendations against such screening may be made on other grounds. Routine screening for asymptomatic bacteriuria in other persons is not recommended.

Burden of Suffering

Asymptomatic bacteriuria is defined as a significant bacterial count (usually $\geq 10^5$ or 10^6 organisms/mL) present in the urine of a person without symptoms. Asymptomatic bacteriuria may precede symptomatic urinary tract infection, characterized by dysuria, frequency, pain, fever, etc., which accounts for over 6 million outpatient visits each year.[1] Urinary tract infection may be associated with renal insufficiency and increased mortality in adults, but these complications rarely occur among those without underlying structural and functional diseases of the urinary tract.[2] In both institutionalized and noninstitutionalized elderly, urinary tract infection is the most common cause of bacteremia, which may be associated with a 10–30% case fatality rate.[3,4] Most such bacteremia occurs in residents with indwelling catheters or urinary tract abnormalities, however. Similarly, most of the 300,000 hospitalizations each year for urinary tract infections[1] involve patients with indwelling urethral catheters.

In children, asymptomatic bacteriuria may be a sign of underlying urinary tract abnormalities. About 10–35% of infants and children with asymptomatic bacteriuria have vesicoureteral reflux and 6–37% have renal scarring or other abnormalities (the lower prevalences generally reflecting more stringent definitions of abnormality),[2,5–8] whereas such abnormalities are uncommon in the general population of children.[2,9] Children with major structural abnormalities, chronic pyelonephritis, or severe vesicoureteral reflux are at increased risk of renal scarring, obstructive renal atrophy, hypertension, and renal insufficiency.[2] Pyelonephritis, reflux nephropathy, and urinary tract malformations may cause as much as one

fifth of cases of renal failure in children.[10] In pregnancy, 13–27% of untreated women with asymptomatic bacteriuria develop pyelonephritis, usually requiring hospitalization for treatment.[11–14] Bacteriuria in pregnant women increases the risk for preterm delivery and low birth weight about 1.5–2-fold, and may also increase the risk of fetal and perinatal mortality.[15–23]

The risk of acquiring bacteriuria varies with age and sex. Asymptomatic bacteriuria in term infants is more common in males (estimated prevalence of 2.0–2.9% vs. 0.0–1.0% in females), but it is considerably more common in girls after age 1 (0.7–2.7% in girls vs. 0.0–0.4% in boys).[2,5–8,24] Approximately 5–6% of girls have at least one episode of bacteriuria between first grade and their graduation from high school, and as many as 80% of these children experience recurrent infections.[2] Asymptomatic bacteriuria in adulthood is more prevalent in women than men (3–5% vs. <1% in those under 60 years), and its prevalence increases with age.[25–27] Asymptomatic bacteriuria is a common finding in older persons, especially those who are very old (20% of women and 10% of men >80 years old living in the community) or institutionalized (30–50% of women and 20–30% of men).[3,4] Bacteriuria occurs in 2–7% of pregnant women; of those who are not bacteriuric at initial screening, 1–2% will develop bacteriuria later in the pregnancy.[28–30] An increased prevalence of asymptomatic bacteriuria (about 10–20%) has been reported in asymptomatic diabetic women, although several studies have found no increase when compared to matched nondiabetic controls or to expected age- and sex-specific population rates.[2,31–34]

Accuracy of Screening Tests

The most accurate test for bacteriuria is urine culture, but laboratory charges make this test expensive for routine screening in populations that have a low prevalence of asymptomatic bacteriuria. The most commonly used tests for detecting bacteriuria in asymptomatic persons are dipstick urinalysis and direct microscopy. The dipstick test is rapid, inexpensive, and requires little technical expertise. The dipstick leukocyte esterase (LE) test, which detects esterases released from degraded white blood cells, is an indirect test for bacteriuria. When compared with culture (at least 100,000 organisms/mL), it has a sensitivity of 72–97% and a specificity of 64–82%.[35–40] The nitrite reduction test, which detects nitrites produced by urinary bacteria (usually limited to Gram-negative bacteria), has variable sensitivity (35–85%) but good specificity (92–100%).[35–39,41–49] In children, dipstick testing for LE and/or nitrites has been found to have sensitivity and specificity of around 80% compared to quantitative culture.[50–57] Among pregnant women, a sensitivity of only 50% for dipstick testing compared to culture has been reported.[30] False-positive and false-

negative urinalysis results are due to a variety of factors, including specimen contamination, certain organisms, and the timing of specimen collection. The sensitivity of this test can be improved by obtaining first-morning specimens, preferably on consecutive days, instead of performing random collection.[41] Many of the studies assessing the accuracy of dipstick testing in children and adults do not describe the patients included. A proportion of these patients were undoubtedly symptomatic, possibly leading to bias in the accuracy estimates. In one study, dipstick sensitivity was significantly lower (56% vs. 92%) and specificity significantly higher (78% vs. 42%) in patients with few symptoms and a low prior probability of bacteriuria, compared to patients with a high prior probability of bacteriuria (i.e., those with dysuria, frequency, etc.).[58]

Examination of the sediment by microscopic urinalysis to detect bacteria and white blood cells has also been evaluated as a screening test for bacteriuria. In children (including symptomatic patients), microscopy performs similarly to dipstick testing for detection of bacteriuria.[50] In pregnant women, microscopic analysis, with either bacteriuria or pyuria indicating a positive test, had a sensitivity of 83% but a specificity of only 59%.[30] In hospitalized adults, only 3% of urine specimens that were macroscopically (including dipstick) negative had clinically significant abnormalities detected by routine microscopic examination.[59,60] Microscopy has limited value as a screening test for asymptomatic persons because of the cost, time, and technique required.[30]

In populations with a low prevalence of urinary tract disorders, most positive screening tests are falsely positive. Thus, in asymptomatic men, and in asymptomatic women under age 60, a dipstick test has a positive predictive value for significant bacteriuria of less than 10% (assuming a sensitivity of 85% and a specificity of 70%).[20,25,43] In children, the likelihood of bacteriuria in the presence of a positive dipstick screening test has been estimated at 0.1% for boys and 4% for girls.[57] In groups at increased risk for urinary tract infection, the positive predictive value of dipstick tests is higher: 13% in pregnant women, 18% in women over age 60, 33% in diabetic women, and 44% in institutionalized older persons.[20,25,29,32,41,43,61–64] The predictive value of bacteriuria found on microscopic urinalysis among pregnant women was 4.2–4.5%.[30]

Urine screening tests are generally performed on a clean-catch specimen. In infants and young children, collection of a "clean" urine specimen is difficult, and as a result few studies of the accuracy of screening tests have included infants. Adhesive polyethylene bag specimens are the most acceptable choice, but these may have a significant contamination rate (false positives). Compared to suprapubic aspiration, positive results on bag specimens indicate true bacteriuria in only 7.5% of specimens.[65] The collection of confirmatory sterile culture specimens by suprapubic aspira-

tion or urethral catheterization is too invasive and costly to be considered in a screening protocol for asymptomatic infants, as is routine screening by urethral catheterization.

Effectiveness of Early Detection

The early detection of asymptomatic bacteriuria may reduce the rate of bacteriuria and prevent symptomatic infection and its complications. Some observational studies suggest that persons with untreated asymptomatic bacteriuria are at increased risk of developing symptomatic urinary tract infection[66,67] and other complications (e.g., structural damage, renal insufficiency, hypertension, or mortality).[41,61–64,68–71] Evidence is not conclusive, however, that these clinical outcomes are caused by bacteriuria (especially in the absence of a structural abnormality), or that early treatment results in important clinical benefits. A randomized placebo-controlled trial of conventional treatment for asymptomatic bacteriuria in both young and middle-aged women (ages 20–65) reported no significant differences in the prevalence of bacteriuria or incidence of symptomatic urinary tract infection at 1-year follow-up.[66] Another randomized controlled trial (available only in abstract form) among women ages 16–69 years with asymptomatic bacteriuria reported significant reductions in bacteriuria at 1 and 3 years with vigorous individualized antimicrobial therapy, but did not report on clinical outcomes.[72] Among a cohort of middle-aged women (38–60 years) screened for asymptomatic bacteriuria, the prevalence of asymptomatic bacteriuria at 6-year follow-up in women identified with asymptomatic bacteriuria and appropriately treated remained significantly higher than in the nonbacteriuric group (23% vs. 5%) and 58% of the treated women had recurrent or persistent infection within 2 years of treatment.[25] Studies evaluating the treatment or natural history of asymptomatic bacteriuria are not available for young or middle-aged men.

Randomized controlled trials in institutionalized elderly women[73] and men[74] found no decreases in genitourinary morbidity with treatment of asymptomatic bacteriuria despite a reduced prevalence of bacteriuria. In both studies, life-table analyses suggested a survival advantage for the untreated group, but the differences were not statistically significant. In women, treatment was associated with an increased incidence of adverse antimicrobial drug effects and increased reinfections.[73]

Among noninstitutionalized ambulatory elderly women, a randomized controlled trial reported that treatment significantly reduced the prevalence of bacteriuria at 6-month follow-up.[67] Symptomatic urinary tract infection and mortality rates were 16.4% and 4.9%, respectively, without treatment, compared to 7.9% and 3.2%, respectively, with treatment, but these differences were not statistically significant; sample size may have

been inadequate to detect a difference, however. In a nonrandomized controlled trial in noninstitutionalized elderly women, treatment of asymptomatic bacteriuria did not significantly reduce mortality (adjusted relative risk 0.92, 95% confidence interval, 0.57 to 1.57), although wide confidence intervals do not exclude the possibility of a substantial benefit.[75] A large cohort study from the same center reported no association between asymptomatic bacteriuria and mortality in ambulatory elderly women after control for confounding, even though the cure rate with treatment was 83% compared to a 16% spontaneous remission rate in untreated patients.[75] It is not clear whether the possible but unproven benefits from treatment of such women justify routine screening or the potential adverse effects of antibiotic therapy, including drug toxicity and the development of resistant organisms while treating recurrent infections. No controlled trials of therapy for asymptomatic bacteriuria in noninstitutionalized elderly men have been reported. In a prospective cohort study of 234 elderly men followed for up to 4.5 years, 29 (12%) had asymptomatic bacteriuria at initial screening, and 20 (8%) became positive in follow-up.[76] Of untreated bacteriuric subjects, 76% spontaneously cleared. Only five bacteriuric subjects were treated for symptomatic infection, with prompt recurrence of asymptomatic bacteriuria in three; no adverse outcomes from symptomatic infection were reported. Cohort and cross-sectional studies that have included elderly ambulatory men have reported no differences in mortality, chronic genitourinary symptoms, or systemic symptoms such as anorexia, fatigue, or malaise between those with and without asymptomatic bacteriuria, after adequate adjustment for confounding variables.[77–79]

Although some trials of elderly patients may have included persons with diabetes, we found no controlled clinical trials specifically evaluating the effectiveness of early detection of asymptomatic bacteriuria in diabetics for improving clinical outcome. Case series suggest treatment of asymptomatic bacteriuria usually clears bacteriuria and may reduce clinical symptoms, but bacteriuria recurs in more than two thirds of treated patients.[80–83] Continuous suppressive antibiotic therapy in diabetic patients can prevent re-infection but provides no posttreatment benefit.[80,81] The long-term consequences of asymptomatic bacteriuria in this population are undefined, although in one series persistent bacteriuria did not appear to contribute to renal damage.[83]

The early detection of asymptomatic bacteriuria is of greater potential value for pregnant women, in whom bacteriuria is an established risk factor for serious complications, including acute pyelonephritis, preterm delivery, and low birth weight. Randomized controlled trials, cohort studies, and a meta-analysis of 8 randomized clinical trials have shown that treatment of asymptomatic bacteriuria during pregnancy can significantly re-

duce the incidence of symptomatic urinary tract infection, low birth weight, and preterm delivery.[12–14,18,20,28,84] There is little evidence regarding the optimal periodicity of screening in pregnancy. A urine culture obtained at 12–16 weeks of pregnancy will identify 80% of women who will ultimately have asymptomatic bacteriuria in pregnancy,[85] with an additional 1–2% identified by repeated monthly screening.

In children, detection of bacteriuria might lead to the identification of correctable abnormalities of the urinary tract and the prevention of renal scarring, obstructive atrophy, hypertension, and renal insufficiency. However, in three randomized controlled trials in girls aged 5–15 years, treatment of asymptomatic bacteriuria did not significantly reduce emergence of symptoms, pyelonephritis, renal scarring, or persistence of vesicoureteral reflux.[86–88] In two of these trials,[86,87] sample sizes may have been too small to detect important differences, but adverse outcomes were rare in both groups. Treated and control subjects had similar growth, blood pressure, renal growth, and concentrating capacity at the end of follow-up, ranging from 12 to 48 months. In longitudinal studies from the Oxford-Cardiff Cohort screening program, girls with asymptomatic bacteriuria in childhood had an increased prevalence of asymptomatic bacteriuria in pregnancy, and among those with asymptomatic bacteriuria and renal scarring, increased preeclampsia, hypertension, and obstetric interventions.[89,90] On the other hand, in pregnant women with a history of symptomatic urinary tract infection in childhood, there were no differences in preeclampsia or operative delivery, although asymptomatic bacteriuria was again more common.[91] All pregnancies in these studies had satisfactory maternal and fetal outcomes.

Most of the complications from urinary tract abnormalities are thought to occur before children reach school age,[2] and therefore screening might be more effective in younger children. There have been no studies, however, proving that preschool urinalyses result in lower morbidity from recurrent infection or in less renal damage.[2,92] Several studies have evaluated the natural history of asymptomatic bacteriuria detected in infancy and followed through the preschool years. In a Swedish cohort of 3,581 screened newborns, 50 infants were identified with asymptomatic bacteriuria, of whom 3 (<0.1%) were treated for underlying renal or urologic abnormalities and 2 were treated for pyelonephritis that occurred within 2 weeks of testing.[8,93] All 45 infants with untreated asymptomatic bacteriuria followed for up to 7 years cleared either spontaneously (80%) or after antibiotic treatment for other conditions (20%). Three subsequently developed cystitis and 20% had recurrences of asymptomatic bacteriuria, but none had major renal or urologic abnormalities as measured by concentrating capacity and urography at a median follow-up of 32 months. Forty infants developed symptomatic urinary tract infection in the

first year of age, but only 2 (5%) had evidence of bacteriuria on previous screening. In another cohort of 1,617 healthy infants followed for 5 years, screening for asymptomatic bacteriuria detected 5 cases (0.3%) with high-risk lesions (such as obstructive uropathy, vesicoureteral junction ectopia, etc).[94] Whether early detection of bacteriuria improved prognosis was not established by this study. In 113 infants less than 1 year old undergoing urologic evaluation, the proportion of abnormal kidneys on dimercapto-succinic acid (DMSA) scan did not differ between those with and without urinary tract infection (33% vs. 28%), suggesting that renal scarring from reflux may occur independently of bacteriuria.[95] Renal abnormalities detectable by ultrasound are found in 1.4% of infants who are considered normal,[2,96] compared to 6% of infants with asymptomatic bacteriuria.[8] However, these infants might have been detected outside the screening program as their symptoms developed.

The effectiveness of detecting asymptomatic bacteriuria in patients with indwelling or intermittent urethral catheterization, of periodic screening in patients with known urologic structural abnormalities, or of follow-up of symptomatic urinary tract infection with repeat cultures, is not discussed in this report. These forms of testing are considered within the domain of diagnostic studies for patients with existing medical or surgical conditions, rather than a part of routine screening tests for asymptomatic persons.

Recommendations of Other Groups

The American Academy of Family Physicians (AAFP) recommends periodic screening by dipstick combining leukocyte esterase and nitrite tests to detect bacteriuria in preschool children, those who are morbidly obese, persons with diabetes or a history of gestational diabetes, and persons aged 65 years and older.[97] The recommendations of the AAFP are currently under review. The American College of Physicians recommends against routine screening of adults for asymptomatic bacteriuria with urinalysis or urine culture.[98] The Canadian Task Force on the Periodic Health Examination recommends against routinely screening asymptomatic infants, children, elderly men, or institutionalized elderly women for bacteriuria, and found insufficient evidence to recommend for or against screening noninstitutionalized elderly women.[99] Bright Futures does not recommend routine urinalyses in infants, children, or adolescents.[100] The American Academy of Pediatrics (AAP) recommends routine urinalysis at age 5, and dipstick urinalysis for leukocytes for all adolescents, preferably at age 15 years.[102]

The American College of Obstetricians and Gynecologists and the AAP recommend a urinalysis, including microscopic examination and infection screen, at the first prenatal visit, with the need for additional laboratory

evaluations including urine culture determined by findings obtained from the history and physical examination.[101] The Canadian Task Force recommends a urine culture at 12–16 weeks of pregnancy.[99]

Discussion

Screening for asymptomatic bacteriuria is important during pregnancy, where there is strong evidence that treatment is efficacious in improving outcome. Given the benefits of detecting asymptomatic bacteriuria in pregnancy, prenatal testing should be carried out by urine culture (rather than by urinalysis) to reduce the risk of false negatives. A specimen obtained at 12–16 weeks will detect most cases of asymptomatic bacteriuria. There are, however, inadequate data to determine the optimal frequency of subsequent urine testing during pregnancy.

Screening for asymptomatic bacteriuria in school-age girls has been shown to produce little clinical benefit in controlled trials. The effectiveness of screening school-age boys for asymptomatic bacteriuria has not been evaluated, but because the prevalence is extremely low in this population and the specificity of screening tests is only about 80% in children, most positive tests will be false positives (estimated at 99.9% in one overview[57]), with the potential for consequent adverse effects including unnecessary antibiotic therapy and invasive testing. Screening in infants, toddlers, and preschool children might be beneficial in preventing renal damage, but its effectiveness has not been established and cohort studies suggest little risk from untreated asymptomatic bacteriuria. In addition, no accurate and noninvasive screening test is available for infants or toddlers in diapers. Given an 80% sensitivity and specificity of current screening methods, and a 1% prevalence of asymptomatic bacteriuria in girls and 0.03% in boys, screening 100,000 children is estimated to result in 19,897 false-positive tests, or nearly 1 in 5 children screened.[57]

Trials of routine screening have shown no benefit for institutionalized elderly persons and suggest the occurrence of adverse consequences such as unintended drug effects and increased reinfection rates. Screening is therefore not justified in this population. Screening urinalysis might be appropriate in certain high-risk groups, such as diabetic and noninstitutionalized elderly women, but firm evidence of benefit is not available. Several trials in ambulatory elderly women have found no clinical benefit from screening for asymptomatic bacteriuria, but sample sizes were small and do not exclude the possibility of important benefits. Potential benefits must be balanced against the high likelihood of reinfection after treatment in these groups and the adverse effects associated with antibiotic use. Screening is not justified in the general adolescent and adult population, or in ambulatory elderly men, because unrecognized, serious urinary tract

disorders are uncommon, the positive predictive value of screening urinalysis is low, and the effectiveness of early detection and treatment is unproven.

CLINICAL INTERVENTION

Screening for asymptomatic bacteriuria with urine culture is recommended for pregnant women at 12–16 weeks of gestation ("A" recommendation). The optimal frequency for subsequent periodic urine cultures during pregnancy has not been determined and is left to clinical discretion. The urine specimen should be obtained in a manner that minimizes contamination. Routine screening for asymptomatic bacteriuria with leukocyte esterase or nitrite testing in pregnant women is not recommended because of poor test characteristics compared to urine culture ("D" recommendation).

There is currently insufficient evidence to recommend for or against routine screening for asymptomatic bacteriuria with leukocyte esterase or nitrite testing in ambulatory elderly women or in women with diabetes ("C" recommendation), but recommendations against such screening may be made on other grounds, including a high likelihood of recurrence and the potential adverse effects of antibiotic therapy. Routine screening for bacteriuria with leukocyte esterase or nitrite testing is not recommended for other asymptomatic persons, including school-aged girls ("E" recommendation), institutionalized elderly ("E" recommendation), and other children, adolescents, and adults ("D" recommendation). Screening for asymptomatic bacteriuria with microscopy testing is not recommended ("D" recommendation).

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