Asymptomatic bacteriuria in pregnancy

Fiona Smaill* MB, ChB, MSc
Chair, Department of Pathology and Molecular Medicine
Department of Pathology and Molecular Medicine, Faculty of Health Sciences, McMaster University, Room 2N16, McMaster University Medical Centre, 1200 Main Street West, Hamilton, Ontario, Canada L8N 3Z5

Screening for asymptomatic bacteriuria is a standard of obstetrical care and is included in most antenatal guidelines. There is good evidence that treatment of asymptomatic bacteriuria will decrease the incidence of pyelonephritis. All pregnant women should be screened for asymptomatic bacteriuria, and there are no new data that would indicate otherwise. Antibiotic treatment of asymptomatic bacteriuria is associated with a decrease in the incidence of preterm delivery or low birth weight, but the methodological quality of the studies means any conclusion about the strength of this association needs to be drawn cautiously. A better understanding of the mechanism by which treatment of asymptomatic bacteriuria could prevent preterm delivery is needed. While several rapid screening tests have been evaluated, none perform adequately to replace urine culture for detecting asymptomatic bacteriuria. Until there are data from well-designed trials that establish the optimal duration of therapy for asymptomatic bacteriuria, standard treatment courses are recommended.

Key words: asymptomatic; bacteriuria; preterm; urine; screening; antibiotic; pregnancy.

The relationship between asymptomatic bacteriuria in pregnancy with symptomatic urinary-tract infections and adverse pregnancy outcomes was first suggested by Kass in 1959, with the publication of his original randomized placebo-controlled trial showing that treatment of bacteriuric pregnant women prevented pyelonephritis and avoided up to 20% of preterm deliveries.1 Other studies quickly followed, and it became generally accepted that detecting asymptomatic bacteriuria in pregnancy was important and that symptomatic urinary-tract infections could be prevented with treatment. Screening for asymptomatic bacteriuria became standard obstetric care, and most antenatal guidelines today include routine screening for asymptomatic bacteriuria. The United States Preventive Services Task Force strongly recommends screening and treatment, and similar recommendations are included in guidelines from the
Infectious Diseases Society of America, the National Institute for Clinical Excellence, the European Association of Urology, the Canadian Task Force on Preventive Care, and most recently from the Scottish Intercollegiate Guidelines Network.2–7

There is, however, an ongoing and vigorous debate on the role of asymptomatic bacteriuria in perinatal outcomes, but very little new evidence has accumulated since the mid-1970s to address this issue. Questions also continue to be raised about the value of routine screening for bacteriuria in populations where the prevalence of asymptomatic bacteriuria is low, given effective management of symptomatic urinary-tract infections and improvements in perinatal care, and the recognition that other subclinical infections that were not considered in the original studies from the 1960s and 1970s may have been responsible for the increased rate of prematurity seen.8,9 Although there is a plausible biological explanation for a mechanism by which asymptomatic bacteriuria might cause preterm labour, the experimental data to suggest causation are only weak. It is timely to critically review the evidence that informs our current management of asymptomatic bacteriuria in pregnancy and to discuss areas where further good-quality research is needed. The reader is also referred to recent comprehensive reviews of urinary-tract infections in pregnancy for additional information.10–12

**SIGNIFICANCE OF BACTERIURIA IN PREGNANCY**

There is good evidence that screening for and treatment of asymptomatic bacteriuria will decrease the incidence of pyelonephritis. Combining data from more than 20 of the early descriptive studies from the 1960s, Whalley showed that symptomatic urinary-tract infections occurred in 30% of patients if asymptomatic bacteriuria was untreated, compared with 1.8% of non-bacteriuric controls.13 Cohort studies have confirmed that the incidence of pyelonephritis is low with routine prenatal screening for asymptomatic bacteriuria compared to historical control groups.14–17 In the most recent prospective longitudinal study over a 2-year period from 2000 to 2001, the incidence of hospitalization for acute pyelonephritis was 1.4%, less than the 3–4% rate reported in the early 1970s before screening for asymptomatic bacteriuria became routine.17

A meta-analysis of 13 randomized or quasi-randomized controlled trials of antibiotic treatment versus no treatment for pregnant women with asymptomatic bacteriuria found that treatment substantially decreased the risk of the development of pyelonephritis (odds ratio (OR) 0.24, 95% confidence interval (CI) 0.19, 0.32).18 The methodological quality of the studies included was, however, weak, and no study adequately addressed selection bias. In less than half of the studies was the control group given a placebo, and performance and detection biases were not satisfactorily handled. The results, however, were highly consistent among studies, and the reduction in the incidence of pyelonephritis was dramatic. It was estimated that the number of women needed to treat to prevent one episode of pyelonephritis was seven (CI 6, 9) and treatment of asymptomatic bacteriuria would lead to approximately a 75% reduction in pyelonephritis.

Although an association between asymptomatic bacteriuria and preterm delivery has been consistently shown, the interpretation of this finding remains controversial compared with the widely accepted relationship between asymptomatic bacteriuria and pyelonephritis. Findings from the Cardiff Birth Survey, which prospectively studied 25,844 births, reported that asymptomatic bacteriuria, adjusted for demographic and social factors, was not associated with preterm delivery (OR 1.2, 95%CI 0.9, 1.5).19
However, when preterm births were categorized into medically indicated or spontaneous preterm births, there was a significant association between bacteriuria and medically indicated preterm births (OR 2.03; 95%CI 1.5, 2.8) but not for spontaneous preterm births (OR 1.07; 95%CI 0.78, 1.46)\textsuperscript{20}, and the authors concluded that if asymptomatic bacteriuria does not progress to pyelonephritis it is not associated with preterm birth.

In a meta-analysis of 17 cohort studies that reported on the incidence of low birth weight in pregnant women with or without bacteriuria, and four cohort studies where the outcomes included preterm delivery, Romero et al concluded that there was a strong association between untreated asymptomatic bacteriuria and low birth weight/preterm delivery, and that antibiotic treatment was effective in reducing the occurrence of low-birth-weight infants.\textsuperscript{21} The cohort studies estimated that the risk of low birth weight was reduced by about two thirds (typical relative risk 0.65; 95%CI 0.57, 0.74), corresponding to a 3.4 % (95%CI 1.8, 5.0) reduction in low-birth-weight infants. The estimate was a little lower for the randomized trials (typical relative risk 0.56; 95%CI 0.43, 0.73), but a reduction of 6.4% (CI 3.3, 9.5) in the rate of low birth weight was seen.

In the Cochrane Review of antibiotic treatment for asymptomatic bacteriuria in pregnancy that included ten randomized or quasi-randomized controlled clinical trials where the outcome of preterm delivery or low birth-weight was reported, antibiotic treatment was shown to be associated with a reduction in this outcome (OR 0.60, 95%CI 0.45, 0.80).\textsuperscript{18} There is, however, disquiet over these results because of the poor methodological quality of the studies included in this review, as previously described for the outcome of pyelonephritis, as well as the inclusion of both a birth weight of $<2.5$ kg and delivery with a gestational age of $<37$ weeks in the outcome of prematurity. For this reason, conclusions about the strength of the association between preterm delivery and asymptomatic bacteriuria need to be drawn cautiously.

The mechanism for an association between preterm labour and asymptomatic bacteriuria has not been established, but a theoretical argument is made for a causative role for the production of phospholipase A2 by microorganisms, which then can initiate labour through the activation of prostaglandin.\textsuperscript{22,23} While this mechanism has been well defined for intra-amniotic infection and symptomatic pyelonephritis, there has been no recent research to explore the mechanisms through which asymptomatic bacteriuria exerts adverse pregnancy outcomes.

Using a decision analysis, screening for and treatment of asymptomatic bacteriuria to prevent pyelonephritis in pregnancy was shown to be cost-beneficial over a wide range of estimates.\textsuperscript{24,25} The cost-benefit is diminished, however, if the rate of asymptomatic bacteriuria is $<2$% and, depending on the cost of screening, it may not be cost-saving.\textsuperscript{24} Screening for asymptomatic bacteriuria is, however, included as one of the most cost-effective strategies for maternal and neonatal health in developing countries in a detailed analysis of interventions to achieve the millennium development goals for health.\textsuperscript{26}

Despite almost uniform national guidelines, there is little evidence of adherence to screening recommendations. Screening for asymptomatic bacteriuria is a quality measure listed by the Physician Consortium for Performance Improvement\textsuperscript{22},\textsuperscript{27} but there are no recent reports available on outcomes. In Australia, poor adherence with screening for asymptomatic bacteriuria in indigenous communities has been proposed as one explanation for worse pregnancy outcomes in this population; structural problems related to provision of care in remote communities were identified as contributing factors.\textsuperscript{28} A pilot survey of quality indicators of antenatal care in the United
Kingdom concluded that there was a range of practices, with very few units continuing to screen all patients for asymptomatic bacteriuria, and in this paper the authors questioned the value of screening.29

PATHOPHYSIOLOGY AND MICROBIOLOGY

The rates of asymptomatic bacteriuria in pregnant and non-pregnant women are similar, but while asymptomatic bacteriuria in non-pregnant women is generally benign, obstruction to the flow of urine in pregnancy leads to stasis and increases the likelihood that pyelonephritis will complicate asymptomatic bacteriuria. Pregnancy-induced physiological changes in the urinary system that facilitate the progression of asymptomatic bacteriuria to acute pyelonephritis include progesterone-induced dilatation of the ureters and renal pelvis, displacement of the urinary bladder from the pelvis into the abdomen, and urinary stasis due to decreased ureteral and bladder tone.30,31

In all studies of asymptomatic bacteriuria, Escherichia coli is the most common organism associated with bacteriuria, representing at least 80% of isolates, with other gram-negative rods and certain gram-positive organisms — including Staphylococcus saprophyticus and enterococci — occasionally being isolated.30,31 Specific virulence determinants in uropathogenic strains of E. coli — including toxins and adhesins, pili or fimbriae that allow adherence to uroepithelial cells and prevent bacteria from urinary lavage, allowing for multiplication and tissue invasion — are associated with invasive infection and pyelonephritis in pregnancy. However, the frequency of virulence associated determinants are lower in E. coli associated with asymptomatic bacteriuria compared to pyelonephritis.32 Only 22% of strains of E. coli isolated from women with asymptomatic bacteriuria had the capacity to adhere to uroepithelial cells compared with 75% in the group of women who developed acute pyelonephritis. It has not been prospectively studied whether those women colonized with a more virulent strain are at an increased risk of progression to symptomatic disease or other adverse perinatal outcomes compared with women colonized with a strain that does not demonstrate these virulence determinants. Adherence is the single marker most frequently associated with progression to pyelonephritis. Although proposed as a means to identify a group of women at increased risk of invasive infection, screening for these virulent strains is still only a theoretical possibility.

While group B streptococci (Streptococcus agalactiae) is uncommonly a cause of true urinary-tract infection, its isolation from the urine in pregnancy does reflect heavy vaginal colonization. There is an association between group B streptococcal bacteriuria and preterm rupture of membranes, premature delivery, and early-onset neonatal sepsis. Urine colony counts lower than the typical values reported for asymptomatic bacteriuria (10^5 colony-forming units (cfu)/mL) are probably important, and in the one randomized trial that compared treatment with penicillin with no treatment for any colony count of group B streptococci isolated from the urine, there was a reduction in preterm rupture of membranes and preterm delivery with treatment.33 Guidelines for the prevention of perinatal group B streptococcal disease recommend that women with group B streptococcal bacteriuria receive intrapartum antibiotic prophylaxis.34

Staphylococcus saprophyticus with a low colony count is a recognized cause of symptomatic urine infection in non-pregnant women; however, the importance of this organism in asymptomatic pregnant women has not been established, and it is infrequently reported in studies of bacteriuria in pregnant women. Staphylococcus aureus is not considered a typical uropathogen, and the interpretation of its isolation
from the urine of up to a third of pregnant women in a low-income population from Nigeria requires further evaluation.\textsuperscript{35} Specialized culture techniques have identified anaerobic organisms and other fastidious microorganisms in a large percentage of pregnant women, but the significance of these organisms from the urine and perinatal outcomes has not been systematically studied.\textsuperscript{36} Up to 15% of pregnant women will have \textit{Ureaplasma urealyticum} and \textit{Gardnerella vaginalis} isolated from the bladder urine. At present, there is no evidence to routinely examine the urine for these organisms.

**EPIDEMIOLOGY OF BACTERIURIA**

The prevalence of asymptomatic bacteriuria during pregnancy ranges from about 2 to 10%. While rates from most recent observational studies done in developing countries fall within this range\textsuperscript{37–39}, the prevalence of asymptomatic bacteriuria was reported to be as high as 86.6% in a study from Nigeria, although \textit{S. aureus}, which is not typically recognized as a uropathogen, made up over a third of the isolates.\textsuperscript{35} Prevalence is related to socioeconomic status for reasons that have not been fully understood, but may be related to early treatment of minor symptoms. Most of the early studies of asymptomatic bacteriuria described higher rates in women attending public clinics for indigent women compared with private obstetric patients.\textsuperscript{13}

Other contributing factors recognized as associated with an increased risk for bacteriuria include a history of recurrent urinary-tract infections, diabetes, and anatomical abnormalities of the urinary tract.\textsuperscript{40} Using logistic regression to identify maternal demographic, behavioural and medical history factors in women receiving prenatal care at a university clinic in North Carolina from 1990 to 1993, an antepartum urinary-tract infection prior to any antenatal care (for whites, adjusted prevalence odds ratio (POR) 2.5, 95%CI 0.6, 9.8; for blacks, POR 8.8, 95%CI 3.8, 20.3) and a pre-pregnancy history of urinary-tract infection (POR 2.1, 95%CI 1.4, 3.2) were the two strongest predictors of bacteriuria.\textsuperscript{41} Women with diabetes mellitus, HIV infection, or structural urinary tract abnormalities were excluded from this analysis. For white women only, education beyond high school and age $\geq$ 30 years were inversely associated with bacteriuria (POR $\leq$ 0.6). In this study, sickle-cell disease nearly doubled the prevalence odds for bacteriuria among African Americans (POR 1.9, 96% CI 1.0, 3.5), a finding consistent with other reports\textsuperscript{42}, but in a recent retrospective cohort study from South Carolina there was no increase in the prevalence of asymptomatic bacteriuria in sickle-cell trait carriers compared with control patients.\textsuperscript{43}

It has been suggested, although not prospectively validated, that screening and testing algorithms should be designed incorporating identified risk factors, including a history of previous urinary-tract infection, and that these protocols could lower overall costs while improving maternal and infant outcomes.\textsuperscript{41,44}

**DIAGNOSIS**

Asymptomatic bacteriuria is generally defined as true bacteriuria in the absence of symptoms of acute urinary-tract infection, although many women found to have asymptomatic bacteriuria may report experiencing occasional episodes of dysuria, urgency and frequency retrospectively.\textsuperscript{13} A semi-quantitative urine culture increases the probability of differentiating contamination from true bacteriuria.
The original criterion for diagnosing asymptomatic bacteriuria was \( >10^5 \) cfu/mL of a single uropathogen on two consecutive clean-catch urine samples, with a sensitivity reported to be 96%. The detection of \( >10^5 \) cfu/mL in a single voided midstream urine is generally accepted as an adequate and more practical alternative. However, Kass reported that the positive predictive value of a single specimen for true bacteriuria was only 80%. Although lower colony counts are associated with infection in women with symptoms of acute dysuria, there is no evidence to support the use of this criterion to confirm asymptomatic bacteriuria in pregnancy.

In a prospective study of 3254 pregnant women, 71% of whom were screened at three different time points, if only a single time point was chosen, the 16th week was the optimal time to screen, based on the greatest number of bacteriuria-free gestational weeks gained from treatment. In this study, a single urine specimen obtained at between 12 and 16 weeks' gestation identified 80% of women who ultimately had asymptomatic bacteriuria.

Most guidelines recommend a single urine culture at the first prenatal visit. Based on the results of their prospective studies, however, some authors have suggested that urine should be cultured in each trimester of pregnancy to improve the detection of asymptomatic bacteriuria, as up to half of the cases may be missed with just a single culture.

There is no consistent recommendation for specimen collection, although a clean voided specimen, with cleansing of the perineum and urethra, is standard. Bacteriological contamination rates from a clean catch and non-clean catch are probably similar; however, and there is in fact little evidence to support the additional cost of collecting a clean-catch urine specimen for screening.

Urine cultures are expensive, they require laboratory expertise, and it takes 24–48 hours for results to become available. While several rapid screening tests have been evaluated, the general conclusion is that none performs adequately to replace the semi-quantitative culture for the detection of asymptomatic bacteriuria in pregnancy.

Direct examination of urine is rapid and inexpensive and requires little technical expertise; however, the sensitivity is generally low. For urine microscopy and pyuria, the sensitivity to detect bacteriuria is in the range 8.3–25%, although the specificities are 89–99%, depending on the cut-offs used. The sensitivity of a urine dipstick for leukocyte esterase or nitrites to detect bacteriuria is also consistently low, even when both tests are used, although specificity is again generally high. The positive predictive values reported from these studies are extremely variable.

A recently reported meta-analysis of the accuracy of the urine dipstick to rule out a urine infection also included studies of pregnant women. For this subgroup, the pooled sensitivity from ten studies for the urine dipstick was 0.46 (95%CI 0.38, 0.56) and specificity 0.98 (95%CI 0.79, 1.00). The authors concluded that in pregnant women the accuracy of nitrites was high (diagnostic odds ratio 165), and that a negative test for both leukocyte esterase and nitrites could rule out infection in pregnant women. However, women with both asymptomatic bacteriuria and clinical symptoms were included in the analysis.

In a study comparing various tests, gram-staining of uncentrifuged urine showed the best performance of any of the rapid tests studied (sensitivity 91.7%, specificity 89.2%), but in this study population with a prevalence of bacteriuria of 2.3%, the positive predictive value was only 16%. In a prospective observational study undertaken from 1998 to 1999 of women at their first prenatal visit, the sensitivity of a gram-stained smear of a centrifuged urine remained excellent (100%); however, its very low specificity (7.7%) and positive predictive value of 7.3% make it unacceptable for screening.
There is no evidence to recommend that laboratories provide a gram stain of either a centrifuged or uncentrifuged urine as a simple test to screen for asymptomatic bacteriuria in pregnancy.

A semi-automated screen (Bac-T screen) showed high sensitivity and negative predictive value but low specificity and positive predictive values, and often technical problems interfered with the interpretation of the results. Authors of prospective studies evaluating a rapid enzymatic urine screening test have concluded that its low sensitivity also makes it inadequate for rapid screening in pregnancy, and neither of these tests can be recommended for routine use.

A systematic review of diagnostic tests for asymptomatic bacteriuria in pregnancy that included eight prospective studies where any one or a combination of rapid urine tests was compared with urine culture, and that reported on the methodological quality of the studies, did not support the use of any test other than urine culture for the diagnosis of asymptomatic bacteriuria. There has been no prospective evaluation of a diagnostic strategy that rules out infection with a negative dipstick for nitrates and leukocyte esterase and performs culture on the urines that screen positive for nitrates or leukocyte esterase to confirm bacteriuria.

**TREATMENT**

In practice, the choice of antibiotic to treat asymptomatic bacteriuria is more likely to be guided by national patterns of practice and local resistance patterns than by evidence from clinical trials. In the systematic review that compared antibiotic treatment with no treatment for asymptomatic bacteriuria, several very different antibiotic regimens were used for treatment, and the duration of treatment included 3–7 days (n = 5), 3 weeks (n = 1), was continued to term (n = 5) or for up to 6 weeks post delivery. In a subanalysis, both treatment to term and short-course therapy were associated with a significant reduction in the incidence of pyelonephritis: for continuous antibiotic therapy versus no treatment, OR 0.21 (95%CI 0.15, 0.31); for short-course therapy (3–7 days) versus no therapy, OR 0.35 (95%CI 0.21, 0.58). One study that compared intermittent therapy with continuous therapy concluded that both strategies were equally effective.

The Cochrane Review by Villar et al assessed the effects of different durations of treatment for asymptomatic bacteriuria and concluded that there was insufficient evidence to evaluate whether a single dose or longer-duration doses were equivalent in treating asymptomatic bacteriuria. Ten studies were included that compared single-dose treatment with 4–7-day treatment. The risk of failing to cure asymptomatic bacteriuria was higher for 1-day treatment than for 7 days of treatment (relative risk 1.25, 95%CI 0.93, 1.67), although the difference was not statistically significant. Single-dose therapy was, however, associated with a decrease in side-effects (RR 0.52, 95%CI 0.32, 0.85). It is currently recommended that standard treatment regimens are used for asymptomatic bacteriuria in pregnant women.

There has been no systematic review of which antibiotic is best for the treatment of asymptomatic bacteriuria. An optimal drug should have favourable pharmacokinetics in pregnancy and be safe for the fetus. A Cochrane Review of treatments for symptomatic urinary-tract infections during pregnancy concluded that although antibiotic treatment is effective for the cure of urinary-tract infections, there are insufficient data to recommend any specific regimen. It is likely that there would be a similar conclusion from any similar review of treatment for asymptomatic bacteriuria.
Nitrofurantoin in pregnancy appears safe, with one study reporting a non-significant pooled odds ratio of any fetal malformation with nitrofurantoin of 1.29 (95%CI 0.25, 6.57). Recent review articles list suggested antibiotic regimens for asymptomatic bacteriuria and discuss treatment, but increasing antibiotic resistance complicates empirical regimens. There have been few recent surveys of antibiotic resistance in urinary isolates from women with asymptomatic bacteriuria, but results from surveys of antibiotic susceptibility in pathogens causing community-acquired uncomplicated urinary-tract infections suggest considerable regional variability. Resistance to ampicillin in *E. coli* in a survey of European countries and Canada averaged 29.8%, but was as high as 53.9% in Spain. Overall rates of resistance of *E. coli* to trimethoprim–sulfamethoxazole among urinary tract isolates across the US was 16.8%, but was as high as 33.3% in some states. Two studies in pregnant women from Malaysia and Tanzania reported rates of resistance of *E. coli* to ampicillin of 48% and 17% respectively. In other developing countries, a wide range of antibiotic susceptibilities is reported.

There are differences in national prescribing guidelines in pregnancy that cannot always be explained by resistance profiles. In Canada, the recommended first-line treatment in pregnancy includes trimethoprim and nitrofurantoin, while in the United Kingdom penicillins and cephalosporins are advocated. A survey of physicians in the Nordic countries confirmed that most practitioners adhered to recommended guidelines and reported prescribing pivmecillinam and nitrofurantoin.

**SUMMARY**

Asymptomatic bacteriuria was one of the first subclinical infections where an association with an adverse perinatal outcome was identified. While it was relatively easy to recommend that all pregnant women were screened for asymptomatic bacteriuria and treated to reduce the risk of pyelonephritis in pregnancy, the importance of the association between preterm delivery and asymptomatic bacteriuria remains unknown. A better understanding of the basic mechanism by which treatment of asymptomatic bacteriuria could prevent preterm delivery is needed. Because of the strength of the association between antibiotic treatment and the prevention of pyelonephritis, additional large-scale randomized trials that include a no-treatment arm where the participants are similar to those included in the original treatment studies cannot be advocated, despite the methodological shortcomings of these studies. Any study of the relationship between other subclinical infections in pregnancy and perinatal outcomes, however, needs to control for asymptomatic bacteriuria and its treatment, but it is unlikely that the particular contribution of asymptomatic bacteriuria to preterm delivery will ever be conclusively determined.

There are no new data to indicate that women should not be screened for asymptomatic bacteriuria, but a critical review of the evidence on which the recommendations for screening are based suggest a need for up-to-date information on the prevalence of asymptomatic bacteriuria in different populations and a prospective evaluation of cost-effective diagnostic algorithms in these populations. It is regrettable that there are no adequately powered clinical trials to establish the optimal duration of therapy for asymptomatic bacteriuria, nor recent studies comparing currently recommended antibiotics that include relevant maternal and infant outcomes. Furthermore, there is also a paucity of data from low- and middle-income countries. It is important that the research agenda does not ignore these important deficiencies in our knowledge of the management of asymptomatic bacteriuria in pregnancy.
Practice points

- Pregnant women should be screened for asymptomatic bacteriuria; there are no new data to indicate that this should not be the standard of obstetric care.
- Treatment of asymptomatic bacteriuria decreases the incidence of antenatal pyelonephritis.
- There is an association between antibiotic treatment of asymptomatic bacteriuria and a reduced rate of low birth weight, but this should be interpreted with caution.
- A semi-quantitative urine culture remains the best test for detecting bacteriuria; rapid tests perform poorly.
- Standard antibiotic treatment courses of 3–7 days’ duration are recommended.

Research agenda

- The mechanism by which treatment of asymptomatic bacteriuria may prevent preterm delivery.
- The contribution of asymptomatic bacteriuria along with other subclinical infections to perinatal outcomes.
- Cost-effectiveness of different diagnostic screening algorithms in varied populations.
- Well-designed treatment studies for women in low- and middle-income countries.
- Screening for asymptomatic bacteriuria as a measure of quality of care.

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