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Asymptomatic Bacteriuria is a Complicated Disease in Pregnant Women

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Annotation: Asymptomatic bacteriuria is the presence of bacteria in the properly collected urine of a patient that has no signs or symptoms of a urinary tract infection. Asymptomatic bacteriuria is very common in clinical practice and its incidence increases with age. The incidence is 15 percent or greater in women and men age 65 to 80 years and as high as 40 to 50 percent after age 80. Most patients with asymptomatic bacteriuria will never develop symptomatic urinary tract infections and will have no adverse consequences from asymptomatic bacteriuria. Only patients with asymptomatic bacteriuria that will benefit from treatment should be treated, and most patients will not benefit from treatment.

Asymptomatic bacteriuria is very common, and is usually benign. An individual may have transient bacteriuria of any duration, or bacteriuria may persist for days to years with the same or differing organisms. Resolution of bacteriuria may occur spontaneously or as a consequence of antimicrobial therapy given for any indication. Recurrent bacteriuria is frequent. Bacteriuria has been associated with harmful outcomes in a few well-characterized populations, for whom screening and treatment of bacteriuria prevents adverse outcomes. On the other hand, antimicrobial therapy prescribed inappropriately to the many individuals with asymptomatic bacteriuria who are not at risk for adverse outcomes contributes to antimicrobial pressure, which promotes the development of antimicrobial resistance. In addition, asymptomatic bacteriuria appears to prevent development of symptomatic urinary tract infection for some populations. This observation has stimulated exploration of the potential therapeutic benefit of establishing asymptomatic bacteruria with an avirulent strain to prevent recurrent symptomatic infection, referred to as bacterial interference.

Keywords: Antibiotic stewardship, Asymptomatic bacteriuria, Diagnosis, Screening,Treatment.

The frequency of ABU in different adult populations is as follows [1] :

- Premenopausal women, 1-5%
- Pregnant women, 1.5-9.5%
- Women aged 50-70 years, 2.8-8.6%
- Women aged 70 years or older in the community, 10.8 -16%
- Men aged 70 years or older in the community, 3.6-19%
- Women aged 70 years or older in a long-term care facility, 25-50%
- Men aged 70 years or older in a long-term care facility, 15-50%
- Women with diabetes, 10.8-16%
- Men with diabetes, 0.7-11%
- Individuals with spinal cord injury and intermittent cathetar use, 23-69%
- Individuals with spinal cord injury and sphincterotomy/condom catheter, 57%
- Individuals with long-term catheter use, 100%

Patient characteristics also influence the microbiology of ABU. *Escherichia coli* is the most common organism and is the most likely to occur in healthy persons. A variety of organisms may be found, however, including Enterobacteriaceae, *Pseudomonas aeruginosa*, *Enterococcus* species, and group

B *Streptococcus*. In men, *Enterococcus* species and gram-negative bacilli are common. Catheterized nursing home residents may have polymicrobial ABU. [1]

Voided urine specimens collected from women are invariably contaminated with quantitative counts $\geq 10^2$ cfu/ml of one or more organisms which normally colonize the periurethral area or vagina (7, 8). Rigorous collection methods using repeated periurethral cleaning or midstream collection do not decrease the frequency of contaminated specimens (3, 9–11). In fact, use of the antiseptic chlorhexidine for vulvar cleansing prior to specimen collection resulted in falsely low quantitative counts of the infecting organism in the urine (11). It is now accepted that collection of a clean catch voided urine specimen without perineal cleaning is appropriate for most women.

A second specimen is recommended for women to confirm bacteriuria when $\geq 10^5$ cfu/ml of a potential uropathogen is isolated from an initial specimen. This recommendation was based on the observation of a 20% error rate in a single voided specimen compared with a catheter urine, but 96% accuracy with two consecutive voided specimens compared with the catheter specimen (4, 12). For schoolchildren, an initial specimen with a gram-negative organism isolated at $\geq 10^5$ cfu/ml was confirmed by a second specimen obtained within 2 weeks in only 61% (13). When three voided urine specimens were collected from pregnant women to confirm bacteriuria with the same organism at $\geq 10^5$ cfu/ml, the second urine specimen remained positive for 91% following an initial positive specimen, while 96% of third specimens remained positive following two consecutive positive specimens (9). However, in another study the prevalence of bacteriuria with a gram-negative organism in pregnant women decreased from 7.0% on a first specimen to 4.4% with a second specimen (14), while a Swedish study reported 15% of pregnant women had a negative second culture (15). Only 42% of healthy, sexually active non-pregnant women aged 18–40 years had *E. coli* $\geq 10^5$ cfu/ml confirmed on a second urine specimen obtained one week or one month after the first (16). For these women, isolation of $<10^5$ cfu/ml *E. coli* on a first specimen was followed by $\geq 10^5$ cfu/ml isolated on the next culture in only 3%. In a cohort of 40- to 64-year–old women in Finland, a second specimen obtained within 2 weeks confirmed bacteriuria in 90% (17). Diabetic women of mean age 56 years, had persistence of an organism in 69% of repeat specimens obtained within 2 weeks (18), while 56% of 18- to 75-year–old diabetic women had persistent *E. coli* bacteriuria at 2–4 months (19). Swedish women resident in the community with a mean age of 83 years, had bacteriuria with a single gram-negative organism $\geq 10^5$ cfu/ml confirmed on a second urine specimen obtained within 2 weeks in 85% (20). Female residents of a long-term care facility with a mean age of 83.4 years had bacteriuria confirmed on 90% of second specimens repeated within 2 weeks (21). However, a second specimen at 2 weeks was positive for only 53% of women of mean age 85 years in Swedish nursing homes, although the impact of intercurrent antimicrobials was not described (22).

The variability in persistence of bacteriuria on a second urine specimen obtained from women following an initial positive specimen is likely attributable to differences in patient characteristics, the spectrum of species reported as bacteriuria, time elapsed between specimen collection, and any concurrent antimicrobial therapy. It seems likely, for most women, that a single appropriately collected voided urine specimen with *E. coli* or other gram-negative organism isolated at $\geq 10^5$ cfu/ml represents true bacteriuria, rather than contamination. A second positive specimen then identifies persistent bacteriuria. Many episodes of bacteriuria are likely transient, especially in sexually active young women.

Eligibility criteria Studies were considered eligible if they met the following eligibility criteria (Table 1): - Quantitative studies including RCTs, observational studies, pilot-, case-control-, and cross-sectional studies - Including pregnant women with ASB (≥105 cfu/ml urine of the same bacteria in two consecutive voided cultures without any symptoms) - Including pregnant women with ASB who both received antibiotic treatment and no antibiotic treatment - Including pregnant women with ASB who had one or more of the following pregnancy outcomes: pyelonephritis, chorioamnionitis, and prelabour rupture of membranes (PROM), and one or more of the following birth outcomes with following definitions: o PTB: < 2500 g o Small for gestational age (SGA): Weight

Evaluation of the benefits and risks of detection and treatment of ASB in children poses unique problems. Young children cannot reliably provide a clean-catch urine specimen, and studies using perineal bag collection for urine specimens have found that bacteriuria rates are overstated because of the high likelihood of contamination with this collection method. Important outcomes relevant to children with ASB for whom antimicrobial therapy is being considered include not only symptomatic infection, but also the development of long-term renal scarring. Most of the evidence describing prognosis and treatment of ASB in children was performed in the 1970s and 1980s. Based on current evaluations of the quality of clinical trials, these early studies have substantial methodological limitations, including poor case definitions, small sample size, lack of randomization, no placebo group, inconsistent outcome measures, inconsistent drug choice, and lack of evaluation of risks and adverse events.

ASB is rare in children with a normal urinary tract and does not appear to be associated with important harms. One study from 1987 used suprapubic aspiration to obtain urine cultures at ages 2 weeks, 3 months, and 10 months and reported that ASB was present in 2.5% of boys and 0.9% of girls [49]. Eleven percent of children with ASB had grade 1–2 vesicoureteral reflux (VUR). Of 50 children with ASB, 2 (4% [95% confidence interval {CI}, 0.5%–13.7%]) were subsequently diagnosed with acute pyelonephritis. No cases of renal scarring were observed in any of the children with ASB (95% CI, .7%–7.1%). An observational study of neonates in New Zealand [50] reported that 14 of 1460 urines obtained by bladder puncture had bacteriuria (prevalence, 1% [95% CI, .5%–1.6%]): 5 with nonlocalizing symptoms and 9 asymptomatic. Mild or moderate VUR was detected in 8 infants with bacteriuria (prevalence, 57.1% [95% CI, 28.9%–82.3%]). ASB occurred in 1.8% of female and 0.5% of male infants (aged 3–23 months) evaluated in an office setting in the United States [7] and 0.8% of preschool girls and no boys (aged 2–5 years). Of those with ASB, VUR was present in 46% of infants and 9% of preschool children. One study reported a higher rate of ASB in black compared to white adolescent girls, (2.5% vs 0.8%, respectively), but similar ASB prevalence in younger (5–14 years) white or black girls (0.5%) [51]. ASB was present in 1.8% of 16 800 British schoolgirls aged 5–12 years who were screened for bacteriuria and followed for up to 13 years [9]. In adolescent girls in Boston, 1.6% of females had ASB [10].

A long-term study of the epidemiology and natural history of ASB conducted in Virginia in the 1960s enrolled 8872 school-aged girls followed for a 7-year period [52]. The rate of ASB was 2.9%, and 3% had symptomatic UTI, but the rate of UTI was not compared to girls without ASB. A subset of 60 girls with persistent bacteriuria was followed up in the 1970s and compared to 38 matched controls [53]. Renal scarring or caliectasis were present in 16 cases and none of the controls (risk difference [RD], 32.0% [95% CI, 18.7%–45.3%]). Hospitalization rates for UTI and pyelonephritis were significantly higher in children with ASB (15%) than controls (2.6%; RD, 13.4% [95% CI, 2.0%–24.7%]). The mean serum creatinine was significantly higher in cases than in controls (0.88 vs 0.76 mg/dL) but did not exceed the normal range in any of the participants. There were no differences in mean blood pressure between groups. In a noncomparative study of a cohort of girls with ASB and radiographic evidence of renal scarring, initially aged 4–14 years and followed until 16 years of age, acute pyelonephritis was not observed in girls with persistent bacteriuria or those who spontaneously cleared bacteriuria [54]. The duration of bacteriuria did not influence renal growth or the glomerular filtration rate. It is not clear why the rates of renal sequelae were substantially higher in this study compared with other reports. The long-term consequences of ASB were also reported for a cohort of 116 Swedish schoolgirls followed for 3 years, of whom 12 (10%) had renal scarring, 13 (11%) VUR without scarring, and 91 (78%) no reflux or scarring [55, 56]. Recurrence or persistence of ASB was common; 47% of the girls remained bacteriuric after 3 years. Renal growth and concentrating capacity in these subjects remained normal.

An uncontrolled trial of antimicrobial therapy (sulfonamide, tetracycline, ampicillin, or nitrofurantoin) in school-aged girls with persistent ASB, defined as ≥3 consecutive positive urine cultures, reported a reduction in the rate of recurrent bacteriuria of 25% in white and 40% in black girls; 10% of girls in this study developed clinical episodes of acute pyelonephritis [57]. This study did not address long-

term outcomes such as renal scarring. In a trial of short-term antimicrobial therapy in the Swedish cohort, 30 patients received nitrofurantoin and 31 no treatment [56]. There was 1 case of pyelonephritis and 1 case of cystitis in each group (RD for both, 0.1% [95% CI, –8.8% to 9.1%]). In American schoolgirls (5–7 years old) monitored over a 2-year period with an overall rate of ASB of 1.6% [8], a randomized controlled trial (RCT) of short-term antimicrobials (nitrofurantoin, ampicillin, or trimethoprim-sulfamethoxazole [TMP-SMX]) in 63 subjects reported a lower ASB recurrence rate in the first 6 months in the treatment group, but no differences in ASB between groups at 4 years and no differences in renal scarring in treated subjects compared to untreated controls [58]. In the British schoolgirl cohort [9], a nonrandomized, open-label, controlled trial of antimicrobial treatment (TMP-SMX, nitrofurantoin, nalidixic acid, or pivmecillinam) for 7–14 days in 110 of these girls with ASB reported no differences in subsequent symptoms of UTI, resolution of VUR, kidney growth, or renal scarring in treated or untreated girls.

Conclusion

In asymptomatic bacteriuria, the patient does not show clinical symptoms, and only a pathological condition can be observed in a urinalysis as a result of laboratory tests.

This disease poses a serious threat to the life of a pregnant woman and her fetus. Therefore, every woman planning a pregnancy should not neglect her health, but undergo timely medical examinations, receive treatment if necessary, and then become pregnant. Because only a healthy mother gives birth to a healthy child. Asymptomatic bacteriuria is a pathological process that requires a deeper, more complete study.

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