Asymptomatic Bacteriuria in Noncatheterized Adults

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KEYWORDS

• Asymptomatic bacteriuria • IDSA • Urinary tract infection • Translational barriers
• Antimicrobial overtreatment • Live biotherapeutics

KEY POINTS

- Asymptomatic bacteriuria (ASB) is defined by the presence of bacteria in an uncontaminated urine specimen collected from a patient without signs or symptoms referable to the urinary tract.
- ASB is highly prevalent among women over the age of 60, hospitalized and institutionalized patients, ambulatory elderly patients, and patients with diabetes mellitus.
- The Infectious Diseases Society of America (IDSA) has recommended against screening for and treating ASB with antimicrobials unless patients are undergoing invasive genitourinary procedures or are pregnant. Despite these clear guidelines, there remains significant overtreatment of ASB with antimicrobials, particularly in patients who are hospitalized or live in a nursing home setting, leading to deleterious consequences in this vulnerable patient population.
- Microbiologic evidence exists to support not treating ASB secondary to reduced virulence factors associated with ASB strains and may suggest that ASB may be beneficial in reducing symptomatic lower urinary tract infections (UTIs) in certain patient populations.
- Translational barriers to the implementation of IDSA recommendations for the management of ASB have been identified and addressed to some degree. In an era in which clinicians' face pay for performance concerns with current practice patterns not reflecting evidence-based recommendations, attention needs to be focused on eliminating these translational barriers on a global scale.

INTRODUCTION

Definition of Asymptomatic Bacteriuria and Infectious Diseases Society of America Recommendations

ASB is defined as the presence of bacteria in a noncontaminated urine specimen obtained from a patient without signs and symptoms of UTI.[1] In asymptomatic women, the diagnosis of ASB requires the isolation of the same organism in 2 consecutive voided urine specimens isolated in quantitative count greater than or equal to 100,000 colony-forming units (CFUs). In asymptomatic men, a single voided urine specimen with 1 bacterial species isolated in quantitative count greater than or equal to 100,000 CFUs/mL or a single catheterized specimen with 1 bacterial species isolated in quantitative count greater than or equal to 100 CFUs/mL in asymptomatic male or female patients constitutes the diagnosis of ASB (**Box 1**).[2] The significance of ASB and the effects of antimicrobial treatment on this condition are well established in some populations but remain unproved or uncertain in others.[3] In 2005, the IDSA published clear, evidence-based guidelines on the diagnosis and treatment of ASB in adults.[2] The only populations the IDSA

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Urol Clin N Am 42 (2015) 537–545
http://dx.doi.org/10.1016/j.ucl.2015.07.003

Box 1
Diagnosis of asymptomatic bacteriuria

Lack of signs and symptoms of UTI

Diagnosis based on urine specimen collected in manner that minimizes contamination

For asymptomatic men – single voided urine specimen with 1 bacterial species isolated in quantitative count ≥100,000 CFUs/mL

For asymptomatic women – 2 consecutive voided urine specimens with isolation of same bacterial strain in quantitative counts ≥100,000 CFUs/mL

For men or women – single catheterized urine specimen with one bacterial species isolated in quantitative count ≥100 CFUs/mL

Based on ISDA guidelines.
Data from Nicolle LE, Bradley S, Colgan R, et al. Infectious Disease Society of America Guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. Clin Infect Dis 2005;40:643–54.

recommended for screening and treatment included pregnant patients to reduce the incidence of pyelonephritis and premature delivery and patients undergoing invasive genitourinary surgery to reduce the incidence of bacteremia and sepsis.[4] The IDSA strongly recommended against screening for ASB in premenopausal nonpregnant women, women with diabetes mellitus, hospitalized patients without UTI symptoms, ambulatory elderly adults, elderly institutionalized residents in long-term care facilities, patients with spinal cord injuries, or individuals with indwelling urethral catheters.[2,3] Despite these available clear guidelines from the IDSA, clinicians continue to misdiagnose and inappropriately manage ASB.[5–10] This article reviews the following:

- A review of the epidemiology and risk factors for ASB
- A review of the literature encompassing the management of ASB in patients with diabetes mellitus
- The basic science of ASB
- A discussion of translational barriers to the application of the IDSA recommendations and approaches to reducing these barriers

EPIDEMIOLOGY OF ASYMPTOMATIC BACTERIURIA

ASB is common among elderly patients in the community, patients in long-term care facilities, and patients in the hospital setting.[11] The prevalence of ASB increases with age, ranging from 0% in men aged 68 to 79 up to 5.4% in men aged 90 to 103.[12] The prevalence of ASB among women is even more pronounced, increasing from 13.6% among women aged 68 to 79 to 22.4% in among women aged 90 to 103.[13] ASB is more common in institutionalized patients, with greater functional impairment compared with community dwellers (25%–50% of women and 15%–35% of men in institutionalized care).[11,14] In healthy young premenopausal nonpregnant women, the prevalence of ASB is 1% to 5%.[15] In hospitalized elderly patients, the prevalence of ASB is 32% to 50% among women and 30% to 34% among men.[12] Among community-dwelling older women, the predominant etiologic pathogens of ASB include *Escherichia coli* (51.4%), *Klebsiella pneumonia* (4.1%), *Proteus mirabilis* (3.3%), and *Enterococcus faecalis* (2.5%) (**Fig. 1**).[16] Among institutionalized patients and patients with long-term indwelling urinary catheters, polymicrobial bacteriuria is common, often including *Pseudomonas aeruginosa*, *Morganella morganii*, and *Providencia stuartii*.[2,17] Risk factors for ASB include older age, female gender, higher postvoid residuals in men, and genetic factors in certain women (**Table 1**).[15] Whether diabetes itself creates a predisposition to ASB is not entirely clear. A single-center study in 511

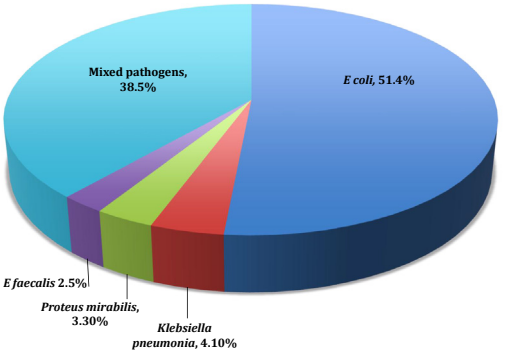

Fig. 1. Prevalence rates of bacterial pathogens among community-dwelling women with ASB.

Table 1
Factors associated with the presence asymptomatic bacteriuria

Physiologic	Pathologic
Age	Neurologic disease (eg, Alzheimer disease, Parkinson disease, stroke)
Gender (female more than male)	Diabetes mellitus Reduced mobility Urinary tract abnormality (eg, calculi, prostate enlargement, high post-void residual volume)
—	Indwelling urinary catheter

Data from Colgan R, Nicolle LE, McGlone A, et al. Asymptomatic bacteriuria in adults. Am Fam Physician 2006; 74:985–90.

diabetic and 97 nondiabetic subjects found a similar incidence of ASB in both groups.[18] The prevalence of ASB was higher in both women (14.2 vs 5.1%) and men (2.3 vs 0.8%) with diabetes than in healthy controls.[19] Taken together these data have confounded decision making regarding the management of ASB in this specific patient population; thus, the literature regarding this patient population is explored in depth.

ASYMPTOMATIC BACTERIURIA IN DIABETIC PATIENTS

UTIs occur more often in patients with diabetes mellitus than in nondiabetics and are associated with more severe infectious complications, such as emphysematous pyelonephritis and cystitis, and concurrent fungal infections.[20] ASB has also been found to have a 4-times higher incidence in diabetic women than nondiabetic women, with an overall prevalence of 26% compared with 6%.[21] Long-term carriage of bacteriuria in diabetics has revealed that up to 25% of diabetic women carry the same strain of *E coli* for up to 6 months compared with their nondiabetic female counterparts, in whom only 1% continue to carry the same bacterial strain beyond 2 months.[22] These differences have not been found to be bacterial strain specific, because the exact same virulence factor expression has been shown in *E coli* isolates in both diabetic and nondiabetic patients.[23] Thus, host factors contributing to bacterial growth as well as an impaired immune response for eradication of bacteria seem the primary drivers of these findings. Accelerated bacterial growth has been shown in vitro after the addition of glucose, mimicking concentrations found in the urine of poorly controlled diabetics, leading to speculation that glycosuria provides an additional substrate for bacterial proliferation.[24] Adherence of *E coli* type 1 fimbriae, a glycoprotein involved in bacterial cell attachment to urothelial cells, has also been demonstrated in vitro to be much greater in diabetic patients with poor glycemic control versus more optimal control.[25] In vivo studies, however, have not proved these factors to contribute to established higher rates of ASB colonization. In a large patient cohort of 636 diabetic women, poor glycemic control was not found a specific risk factor for either the development of ASB or symptomatic UTI.[26]

Concerning the host immune response, early speculation hypothesized that increased glucose in the urine would lead to glycosylation of a variety of immune cells in the urine and impede their bactericidal function. Granulocyte function testing, however, between diabetic and nondiabetic women with ASB has shown no differences in chemotaxis, opsonization, oxidation, phagocytosis, and killing, leading to the conclusion that impaired granulocyte dysfunction is not a factor in persistent bacteriuria.[27] Two proinflammatory cytokines, IL-6 and IL-8, have been found to have a significantly lower concentration in the urine of diabetic women with ASB compared with nondiabetic women with ASB and were correlated to an overall lower leukocyte count in diabetic patients.[28] Thus, the impaired immune response contributing to higher rates of ASB in diabetics seems not due to the qualitative function of leukocytes but rather a blunted quantitative immune cascade.

Untreated ASB in diabetic patients has not been shown to have any increased rates of complications compared with diabetic women without ASB. A long-term follow-up study of 6 years showed no difference in renal function deterioration, as measured by change in creatinine clearance over time, between diabetic woman with and without ASB.[29] Aimed at determining if ASB warranted treatment in diabetic patients to prevent conversion to symptomatic UTI as well as other complications, a prospective trial randomized women with both diabetes and ASB to continual antimicrobial agents to sterilize the urine and placebo. After 4 weeks, only 20% of patients receiving antimicrobials had continued bacteriuria, compared with 78% in the placebo group. At a mean follow-up of 27 months, however, there were no differences in the rate of symptomatic infection (40% vs 42%), or time to first symptomatic infection, pyelonephritis, and hospitalization due to infection.[30] This led the investigators to conclude that the treatment of ASB in diabetic

women does not seem to increase complications and for this reason routine screening and treatment in this population is not recommended.

THE BASIC SCIENCE OF ASYMPTOMATIC BACTERIURIA

Two main factors distinguish acute symptomatic UTI from ASB colonization: (1) the virulence factors of the bacteria itself (fimbriae, lipopolysaccharides [LPSs], and toxins) and (2) the host factors implicated in disease susceptibility (urothelial receptor proteins and adequate immune system activation). These microbiologic factors are discussed in further detail.

Fimbriae

Perhaps the most studied factor in differentiating uropathogenic bacteria from ASB is the presence of specific fimbriae on the bacterial surface. Fimbriae are complex structures that mediate adherence to host epithelium through protein receptors.[31] Uropathogenic *E coli* has been found to express a markedly different fimbriae profile than ASB, including type 1, P, F1C, Dr, Auf, S, and M fimbriae.[32,33] Of all of these, P fimbriae expression has shown the strongest correlation to acute disease severity, found on the surface of more than 90% of *E coli*-causing pyelonephritis but on less than 20% of ASB strains.[34,35]

P fimbriae bind to Galα1-4Galβ epitopes of glycolipids on the urothelium, leading to the activation of the innate immune system promoting the release of cytokines and recruitment of neutrophils.[36,37] The expression of type 1 fimbriae, which bind to the mannosylated epitopes of bladder urolotheial integrin molecules, is also intimately involved in bacterial adherence and immune activation.[38] Although type 1 fimbriae are expressed by more than 90% of ASB strains, a cluster deletion has been identified in its coding gene, *fimH*, which may negate its ability to facilitate adherence and immune activation.[39] A recent study confirmed 26% of *fimH*-positive ASB strains were unable to express functional type 1 fimbriae.[40] This supports the hypothesis that many ASB strains may carry virulence genes but fail to express the associated phenotype for functional virulence.[41] Recently, the detection of 2 previously uncharacterized fimbriae, Yad and Ygi, were found more than twice as prevalent in uropathogenic *E coli* than ASB strains and associated with virulence-related activities including motility, biofilm formation, and cell adherence.[42] Although the expression of other fimbriae, such as F1C and Dr, have also been studied, their contribution to virulence is much less clear but likely contributable to the overall pathogenetic profile.

Lipopolysaccharides

LPS is an endotoxin of gram-negative bacteria, containing the lipid type A anchored in the outer membrane, which activates Toll-like receptor (TLR) 4 on the urothelium and induces immune system activation.[43] This mechanism has proved responsible for significant fever and acute systemic illness associated with septicemia and is undoubtedly a contributor to the virulence of uropathogenic bacteria. Capsular polysaccharides surround bacteria and protect the organism from host defenses in blood and tissues.[43] Mutant bacteria with genetically altered capsular polysaccharide expression have shown significantly reduced virulence in experimental UTI animal models.[44] LPS from ASB *E coli* has biotherapeutic activity.[45]

Toxins

Two major toxins produced by uropathogenic *E coli* are hemolysin and cytotoxic necrotizing factor 1 (CNF1).[31] Hemolysin is a secreted protein found more commonly in uropathogenic strains than fecal strains, which inserts into host cell membranes leading to epithelial damage and hemorrhage.[46] Hemolysin activity has been shown to correlate to the severity of clinical infection, found in only 14% of ASB strains and in 47% and 31% of *E coli*-causing cystitis and pyelonephritis, respectively.[41] Although the actual expression of the hly A gene encoding for hemolysin was found in 58% of ASB, only 14% were functionally hemolytic compared with 100% functional hemolysis when found in *E coli* causing pyelonephritis.[41] Thus, genetic mutation leading to dysfunction of the toxin itself may significantly contribute to the benign nature of ASB strains. CNF1 is a cytokine released by uropathogenic *E coli* that leads to activation of the Rho family of GTP-binding proteins on the host urothelium and has been implicated in inducing bladder cell apoptosis.[47,48] CNF1-positive *E coli* strains have been shown to cause more inflammation than strains lacking production of this toxin.[49]

Host Factors

Fimbriae-mediated adhesion to the host urothelium activates TLR4 signaling, which triggers cytokine production and neutrophil recruitment for bacterial destruction and also determines the severity of signs and symptoms related to acute infection.[50] The loss of functional TLR4 signaling and activation promotes long-term bacterial

colonization and can lead to ASB. Mutations in the TLR4 promotor, which significantly reduce the efficiency of TLR4 expression, have been shown in children with ASB compared with age-matched controls and those with acute pyelonephritis.[51] Thus, these mutations may be protective against recurrent acute UTIs and disease severity.

Growth Factors

The ASB strain *E coli* 83,972, initially isolated from a young Swedish girl who carried it asymptomatically for 3 years, is the most widely studied strain of nonvirulent *E coli*.[52] Despite the loss of functional fimbriae and inability to activate host innate immune response, this nonvirulent strain grows well in human urine and can outcompete uropathogenic *E coli* strains.[53] This property has led to its instillation as a prophylactic treatment method in patients with recurrent UTIs, refractory to traditional medical therapy.[54,55] The survival fitness of *E coli* 83,972 compared with uropathogenic bacteria was initially assumed related to unique biosynthetic pathways, enabling the nonvirulent strain to more efficiently utilize metabolic compounds, such as iron and amino acids for more rapid growth.[56] Genetic sequencing studies, however, have shown surprisingly little divergence of ASB strains from uropathogenic *E coli* in gene expression concerning metabolic pathways.[56] It is, therefore, speculated that the superior growth of *E coli* 83,972 may be due to overall energy conservation, because the production of virulent-factors, such as fimbriae, are costly to produce, but the exact fitness advantage mechanisms remain largely unknown.

Use as Biotherapeutics

The ability of ASB strains to outcompete uropathogenic *E coli* has led to the clinical study of its use a live biotherapeutic in patients with recurrent, symptomatic UTIs. Sundén and colleagues[57] in 2010 randomized 20 patients with incomplete bladder emptying and history of recurrent UTIs to intravesical inoculation with *E coli* 83,972 or saline. Patients who showed elimination of the bacterial strain by sterile urine culture underwent repeat inoculations. They showed a significantly longer time to first infection (11.3 vs 5.7 months) and fewer total numbers of symptomatic infections (13 vs 35 episodes) in patients who received ASB inoculation versus saline controls. Thus, a model for deliberate ASB as a protective mechanism for patients at high risk of recurrent UTI was established. Darouiche and colleagues[58] in 2011 performed a similar study on spinal cord injury patients with a history of recurrent UTIs, inoculating 17 patients with the ASB strain *E coli* HU2117 and comparing results to 10 patients receiving saline placebo. They showed a significant decrease in the average number of UTIs over 1-year follow-up (0.50 episodes in the treatment group vs 1.68 in the placebo group). In a murine model, Rudick and colleagues[59] in 2014 compared the use of ASB inoculation with *E coli* 83,972 to ciprofloxacin to treat acute UTI. Although both treatments showed equal clearance of uropathogenic bacteria, the ASB strain provided superior reduction in pain than ciprofloxacin, comparable to that of intravesical lidocaine. In addition to its analgesic benefit, ASB inoculation was also proved effective at clearance of a wide variety of bacterial pathogens, including *Proteus mirabilis, Enterococcus faecalis*, and *Klebsiella pneumonia*. Although promising, the complexity of administration and monitoring as well as the associated expense of ASB strain inoculation may continue to limit its clinical application.

TRANSLATIONAL BARRIERS TO THE APPLICATION OF THE INFECTIOUS DISEASES SOCIETY OF AMERICA RECOMMENDATIONS

Despite the clear recommendations per the IDSA regarding diagnosing and screening of ASB, many physicians still believe that bacteriuria should be treated with antimicrobials irrespective of the lacking presence of symptoms.[60] It is uncertain whether this belief indicates clinicians' lack of awareness of the IDSA recommendations or simply their disagreement with the evidence. It has been well established that treatment of ASB with antimicrobials has been associated with higher rates of resistance, reinfection, and significant collateral damage, including *Clostridium difficile*–associated disease, bacterial vaginosis, and vaginal candidiasis.[7,8,61–64] The decision to order a urine culture should be guided by the presence or suspicion of symptoms related to UTI.[2] Several studies evaluating physicians attitudes toward practice recommendations indicate that up to two-thirds of clinicians are unaware of practice guidelines, perceive adopting the practice guidelines as a challenge to autonomy, have diminished confidence in the professional organization, are confused regarding the guidelines, and in some instances have a greater concern with the adverse outcomes associated with not prescribing an antimicrobial more than with the risk of downstream complications of inappropriate prescribing.[65–70] Some investigators have suggested a multifaceted approach coupled with appropriate process outcome measures to address the issue of translational barriers to the acceptance of the IDSA ASB

recommendations. The foundation of this multifaceted approach is the support by administrators and medical staff leadership. Second it has been suggested that intensive education be provided, including a review of clinical practice guidelines, identification of symptoms suggestive of UTI, use of diagnostic and therapeutic algorithms for providing feedback, documentation of reasons for obtaining urine specimens, improved collection techniques, and avoiding the pitfalls of pyuria as a marker of symptomatic UTI.[3] Although sound in concept, this multifaceted approach is daunting because it is resource (time and cost) intensive. Leis and colleagues[71] reported their results of a proof-of-concept study whereby a much more simplistic approach was used. All positive noncatheterized urine culture results from hospitalized patients in their study were not reported unless the primary managing clinician made a telephone call request. Through this simple intervention, the investigators were able to demonstrate a significant reduction in antimicrobial therapy for ASB from 48% at baseline to 12% postintervention (P = .002). Although promising, this study can only be extrapolated to medical and surgical inpatients. Larger studies are needed to confirm its generalizability, safety, and sustainability of this model of care.

SUMMARY

ASB is a common finding and is frequently detected in premenopausal nonpregnant women, institutionalized patients, patients with diabetes mellitus, and the ambulatory elderly population. Despite clear recommendations regarding the diagnosis and management of ASB in these populations from the IDSA, there remains an alarming rate of antimicrobial overuse, which has led to issues of increasing antimicrobial resistance of bacterial pathogens and significant deleterious consequences in the form of collateral damage among this already vulnerable patient population. Despite an increased prevalence of ASB among patients with diabetes mellitus and the concern for increased risk of symptomatic UTI, pyelonephritis, and sepsis, the literature does not support screening for or treating ASB in this patient population. To date there exist microbiological evidence to support not treating ASB secondary to reduced virulence factors associated with ASB strains. Some ASB strains have been shown beneficial in reducing symptomatic lower UTIs in certain patient populations.

Despite the existence of translational barriers to the implementation of IDSA recommendations for the management of ASB among a vast array of clinicians, there have been promising data to support the implementation of simplistic strategies to address these barriers. In an era in which clinicians' face pay for performance concerns with current practice patterns not reflecting evidence based recommendations, attention needs to be focused on eliminating these translational barriers in a safe, feasible, and sustainable manner.

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