

Bacteruria and Urinary Tract Infections in the Elderly



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KEYWORDS

• Asymptomatic bacteriuria • Bacteriuria • Urinary tract infection • Cystitis • Pyuria

KEY POINTS

- Despite several consensus guidelines proposed by various interest groups in recent years, a concise definition of urinary tract infection and associated symptoms does not exist.
- Results of urinalysis are often misinterpreted and mishandled.
- Treatment of elderly patients with bacteriuria necessitates skilled history taking, examination, and complete diagnostic urine testing.
- It is now being suggested that the healthy urinary tract is not a sterile environment, but in fact is populated by a dynamic set of microorganisms that change throughout time based on environmental and behavioral factors.
- Multiple studies have shown no morbidity or mortality benefit to antibiotic therapy in either community-dwelling elderly or long-term care facility residents with asymptomatic bacteriuria.

INTRODUCTION

Both urinary tract infection (UTI) and asymptomatic bacteriuria (ASB) are common among elderly adults and represent a significant health care burden. UTIs are responsible for 15.5% of infectious disease hospitalizations in adults aged 65 or older, second only to pneumonia, and they are responsible for 6.2% of infectious disease-related deaths.¹ Despite their frequency, differentiating between ASB and true UTI remains controversial among health care providers. In light of emerging antibiotic-resistant pathogens, this distinction has become increasingly important, because although symptomatic UTI requires appropriate antibiotic therapy, ASB does not.

PURPOSE OF THIS REVIEW

This article will review proposed definitions of ASB and UTI, highlight emerging research in causes and prevention of bacteriuria and UTI in the elderly, and examine improvements in patient outcomes over the past 20 years with improved practice guidelines. The authors' search criteria for the literature review utilized the PubMed database with the following key words: urinary tract infection, asymptomatic bacteriuria, bacteriuria, urinary tract microflora, urinary tract infection treatment, urinary tract infection risk factors, and combinations thereof. For inclusion, papers must have been published after 1980 and written in English. Exclusion criteria included foreign journal articles not translated to English.

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DEFINITIONS OF ASYMPTOMATIC BACTERIURIA

As defined by the Infectious Disease Society of America (IDSA), ASB is the presence of 10⁵ colony-forming units per milliliter (CFU/mL) or more of 1 bacterial species in 2 consecutive urine specimens in women, or a single urine specimen in men, in the absence of clinical signs and symptoms of UTI. A single specimen containing greater than or equal to 10⁵ CFU/mL of a bacteria species is sufficient when obtained by catheterization in both men and women.²

DEFINITIONS OF URINARY TRACT INFECTION

For the purpose of this article, UTI means infection localized anywhere along the urinary tract, manifesting as cystitis, pyelonephritis, or prostatitis. Despite several consensus guidelines proposed by various interest groups in recent years, a concise definition of UTI and associated symptoms does not exist. Conserved criteria typically include pyuria as evidenced by presence of leukocyte esterase or white blood cells on urinalysis, symptoms attributable to the urinary tract, and a urine culture confirming a pathogenic source.²⁻⁴ Of these components, what constitutes urinary tract symptoms is most variable. Typical symptoms include fever greater than 38 C or chills, dysuria, frequency, urgency, new-onset or worsening incontinence, and suprapubic or flank pain. Clinicians often include lethargy, confusion, or a change in baseline function, but this can be particularly difficult to assess in complicated patients with baseline impaired cognition or extensive comorbidities.

CHALLENGES AND CONTROVERSY IN DIAGNOSIS

Several challenges exist in the evaluation of urinary symptoms in the elderly patient. Symptoms of UTI are highly variable, often nonspecific to infection, and can be difficult to assess in patients with limited communication abilities or poor baseline function. Additionally, problems are frequently encountered in the collection, testing, and interpretation of urine specimens. Urine specimens should be obtained midstream by clean catch, or by in-and-out catheter when controlled voiding or cooperation is problematic. Chronic indwelling catheters should be removed and a new catheter inserted prior to obtaining samples, as biofilm is ubiquitous to long-term catheters. However, explanation and adherence to these collection standards are lacking. A prospective observational study by Pallin and colleagues⁵ examined

emergency department cases at a major academic hospital that included urinalysis as part of their evaluation. By postencounter interview, it was found that 57% of the 137 participants received no instruction on urine collection, and that only 6% of participants had in fact used proper midstream clean-catch technique. Improper collection leads to specimen contamination by normal genitourinary flora, increasing the likelihood of false-positive urinalysis or misinterpretation of normal flora as pathogenic infection.

Results of urinalysis are often misinterpreted and mishandled. Pyuria, for example, can be a useful laboratory component in making the diagnosis of UTI but can also lead clinicians astray. Although absence of pyuria has strong negative predictive value for ASB or UTI, presence of pyuria is poorly specific for clinically significant infection.² Pyuria may be present in up to 45% of chronically disabled or incontinent adults, and in up to 90% of institutionalized adults, regardless of colonization or infection status.^{4,6} A retrospective review of 339 cases from 2 academic centers found that pyuria was present in 70% of cases of UTI and 42.3% of cases of ASB, but was associated with inappropriate antimicrobial treatment by an odds ratio of 3.27 (95% confidence interval [CI], 1.49–7.18).⁷ Specimens that do demonstrate pyuria should reflexively be sent for urine culture for confirm presence of a pathogen, but this step remains a common struggle in many health care institutions. In the observation study by Pallin and colleagues,⁵ only 59% of samples with positive urinalysis were sent for urine culture, but again positive urinalysis regardless of symptoms was associated with antibiotic treatment by an odds ratio of 4.9 (95% CI, 1.7–14). These findings highlight the necessity of skilled history taking, examination, and complete diagnostic urine testing for the appropriate treatment of elderly patients.

EPIDEMIOLOGY

Asymptomatic Bacteriuria

Prevalence of asymptomatic bacteriuria increases in both men and women with age. Although ASB is uncommon in young men and found in only 1% to 2% of young women, prevalence increases to 6% to 16% in women and 5% to 21% in men ages 65 to 90 years. The prevalence increases further with increasing comorbidities, and may be as high as 25% to 50% in institutionalized women and 15% to 35% of institutionalized men, although a significant number of these patients have been observed to spontaneously develop negative urine cultures within 3- to 6-month time frames.⁸ In elderly patients with chronic indwelling catheters,

ASB is universal. Multivariate analyses have emphasized that the duration of catheterization is the most important risk factor in development of catheter-associated bacteriuria,^{9–11} while other studies have estimated colonization rate after catheter placement is 3% to 7% per day.⁸ However, one-third to one-half of cases of bacteriuria will clear with removal of the catheter.^{12,13}

Urinary Tract Infection

Because definitions of UTI vary, it should be noted that reported incidence and prevalence across the literature can be difficult to assess. In both community-dwelling and institutionalized adults, the prevalence of UTIs varies with gender and generally increases with age. Incidence of infection in men increases from 0.05 in men ages 65 to 74 years, to 0.08 in men over 85 years.¹⁴ Infection is more common in postmenopausal women, with an incidence of 0.07 per person-year, increasing to 0.13 per person-year after age 85.¹⁵ UTIs are quite common in institutionalized adults, accounting for 30% to 40% of health care-associated infections,^{16,17} and substantially more prevalent in patients with chronic indwelling catheters. Mean incidence of catheter-related UTI was 3.2 cases per 1000 catheter days in 1 long-term care facility, compared with only 0.57 cases per 1000 days for all residents. Bacteremia from a urinary source is anywhere from 3 to 39 times more common in patients with chronic indwelling catheters.^{18–20}

MICROBIOLOGY

Although some differences in common urinary tract pathogen prevalence are noted, *Escherichia coli* remains the most commonly cultured organism in both community-dwelling and institutionalized adults. Studies examining community-dwelling women report *E coli* isolates in 75% to 82% of positive urine culture, with the majority of remaining cultures attributed to *Klebsiella*, *Proteus mirabilis* and enterococcus.²⁰ Similar organisms are responsible for both ASB and UTI in institutionalized adults. Two large cohort studies of long-term care residents found *E coli* to be the most common urinary isolate, accounting for 54.6% to 69% of positive cultures. One study found enterobacteriaceae species to account for 34.8% of remaining cultures, while the second distributed these between *Klebsiella* (12%) and *Enterococcus faecalis* (8%).^{21,22} Other common hospital-associated pathogens like *Pseudomonas aeruginosa*, vancomycin-resistant enterococci, and *Candida* spp have been identified in this population as well.²³

Patients with indwelling catheters are uniquely at higher risk for biofilm-associated organisms, polymicrobial infections, and yeast colonization and infection. Large epidemiologic studies in both Europe and North America show that *E coli* remains the most common cause of both ASB, accounting for 21.4% of positive cultures, and UTI, accounting for 31% to 35.3% of positive cultures in this population.²⁴ Indwelling catheters are uniquely associated with biofilm organisms, making colonization and infection by *P mirabilis*, *P stuarti*, and *P aeruginosa* significantly more common.²³ *Candida* spp are also particularly common in these patients, accounting for 12.9% of catheter-associated UTI by some estimates.²⁴

RISK FACTORS

Many genetic, behavioral, and comorbid host factors have been speculated as risk factors for both ASB and UTI. Some of these represent modifiable behavioral factors, while others are more inherent to the patients overall health. Multiple studies support a history of UTI as a primary risk factor for future infection, conveying as high as a fourfold to sevenfold risk compared with patients who have never had a symptomatic UTI.^{20,25,26} This, combined with the growing understanding of uropathogen virulence and patient genetic variations, seems to imply that a certain percent of the population is inherently more susceptible to UTIs. Comorbid conditions including diabetes, dementia, incontinence, and iron deficiency anemia have all been described as independent risk factors for ASB and UTI.^{27–30}

In premenopausal women, lactobacilli predominate the vaginal flora and are responsible for the relatively acidic pH of the vagina. This acidic environment is lost in postmenopausal women, and is implicated in the increased colonization and infection by *E coli* and enterococcus species.²⁷ Sexual activity has been associated with UTI in postmenopausal women, particularly within a 2 week period after activity, although this association is less robust than in premenopausal counterparts.²⁷

In men, benign prostatic hypertrophy has been established as a risk factor for UTI. Although it is reasonable to presume this association is a product of urinary stasis, the relationship may in fact be more complicated. Interestingly, a cross-sectional study by Truzzi and colleagues³¹ of 196 healthy participants found an association between bacteriuria and postvoid residuals greater than 180 mL in men, but this association has not been reproducible in ambulatory postmenopausal women.^{27,29,30}

PATHOPHYSIOLOGY

Our understanding of urinary tract colonization and infection has greatly expanded over the past decade, and substantial new evidence has highlighted the complicated interplay between protective host factors and pathogen virulence factors that determine the likelihood of infection. In the disease-free state, the urinary mucosa acts as a protective barrier from infectious attacks. Certain bacteria can evade this protective function by binding specific mucosal receptors, which in turn may initiate a rapid inflammatory response by the host. For example, P-fimbriated *E coli*, responsible for the majority of symptomatic UTIs, bind a glycosphingolipid receptor on the mucosal surface, triggering various inflammatory cascades, engaging submucosal tissue, and in some cases, leading to direct invasion of deeper tissues and the blood stream.³²

It is now being suggested that what differentiates ASB from symptomatic infection is not necessarily the virulence factors of the invading bacteria, but a combination of virulence factors and the inherent genetic makeup and immune response of the host. Multiple mouse studies have correlated various genetic variations with decreased initial inflammatory responses, and therefore increased likelihood of ASB.^{33,34} Similar findings have been mirrored in human studies. Specific TLR4 mutations have been associated with ASB in children, while other polymorphisms of the same receptor seem to protect from recurrent cystitis in adults.^{35–38} On the other hand, genes that exaggerate host inflammatory responses or blunt antimicrobial efforts are associated with decreased bacterial clearance, and more severe bladder and kidney infection.³⁵ In both mice and human studies, polymorphisms of IRF3, a component of interferon signaling, have been associated with a majority of subjects.^{34,36} This concept was further highlighted by Marschall and colleagues,³⁰ in a prospective cohort study demonstrating that while patient comorbidities could be correlated to presence of ASB, none of 12 *E. coli* virulence genes tested could be associated with likelihood of ASB.

The human microbiota and its complicated, symbiotic role in maintaining health have gained substantial attention throughout many disciplines over recent years. It is now being suggested that the healthy urinary tract is not a sterile environment, but in fact is populated by a dynamic set of microorganisms that change throughout time based on environmental and behavioral factors. Routine culture media are designed to produce common uropathogens but do not support the

growth of many slow-growing, fastidious, or anaerobic organisms. However, advanced detection technologies have shown many other microbiota in the urinary tract of healthy adults, bringing to question the role of bacteria outside the context of disease. A recent review by Whiteside and colleagues³⁹ reports multiple genera including *Jonquetella*, *Parvimonas*, *Proteiniphilum*, and *saccharofermentas* in the urinary tract of healthy patients over age 70, through polymerase chain reaction (PCR) and detection of 16s rRNA subunits. A study by Santiago-Rodriguez and colleagues⁴⁰ also demonstrated viral communities in 20 individuals, including bacteriophages and low-risk or novel strains of human papilloma virus, but flora components were unassociated with history of urinary tract health. Although the exact role of these symbiotic organisms is still poorly understood, it is postulated that their metabolic byproducts may convey antimicrobial advantages and contribute to urinary health.

TREATMENT

Asymptomatic Bacteriuria

Although antibiotic treatment is indeed necessary in the case of UTI, the current consensus among urology and infectious disease groups is that they are not for ASB. Multiple studies have shown no morbidity or mortality benefit to antibiotic therapy in either community-dwelling or long-term care facility residents with ASB. However, such treatment does expose patients unnecessarily to potential medication adverse effects.^{41–45}

Community-dwelling Adults

Several studies have suggested that for community-dwelling women with nonspecific symptoms, hydration and full diagnostic work up for urinary infection may be preferable to antibiotic treatment.^{46,47} For example, a 2010 study found no superior outcomes to ciprofloxacin over ibuprofen for treatment of uncomplicated UTI.⁴⁶ A separate prospective cohort study of 51 women with symptoms of an uncomplicated UTI in the Netherlands found that delaying antibiotic treatment up to 1 week resulted in spontaneous resolution of symptoms in the majority of participants, with no complications of pyelonephritis or bacteremia.⁴⁸

In elderly adults with unambiguously symptomatic UTI, antibiotic therapy should be chosen to best target suspected causative pathogens while minimizing unwanted adverse effects or interactions in the context of a patient's other comorbidities. Urinary pathogens should be evaluated for antibiotic sensitivity, and therapy should be

tailored to a sensitive antibiotic with the most narrow spectrum. If symptoms are mild, treatment may even be delayed until culture results are available. When available, previous urinary cultures and sensitivities should be reviewed for likely pathogens and possible antibiotic resistance patterns. Where applicable, local antibiograms should also be consulted for consideration of geographic resistance patterns.

For stable patients with cystitis, oral therapy with nitrofurantoin or trimethoprim-sulfamethoxazole (TMP/SMX) is often effective. In women, 3 to 5 days is typically sufficient. Therapy is typically extended to a 7- to 14-day course for men, although a recent retrospective study of male veterans suggests this may not relay any benefit in terms of early or late recurrence of infections.⁴⁹ The IDSA also deems single-dose fosfomycin to be appropriate first-line therapy, since many organisms remain susceptible, although this regimen has been associated with inferior efficacy. Fluoroquinolones like ciprofloxacin and levofloxacin are acceptable second-line therapies for patients with allergies or intolerance to first-line agents, but susceptibility should be followed given increasing resistance of common uropathogens to this class. Amoxicillin-clavulanate may be considered with close follow-up, but amoxicillin alone and ampicillin are no longer recommended due to poor efficacy and high resistance patterns.

In cases of suspected pyelonephritis not requiring hospitalization, a 14 day course of oral TMP/SMX or a 5- to 7-day course of oral fluoroquinolone can be considered. In regions where fluoroquinolone resistance is high, an initial parenteral dose of ceftriaxone or 24-hour dose of aminoglycoside prior to oral therapy is recommended. In cases of known organism resistance to oral medications, pyelonephritis requiring hospitalization, or hemodynamically unstable patients, parenteral therapy is preferred to oral. Aminoglycosides (gentamicin, tobramycin), with or without ampicillin or a cephalosporin, are useful empiric regimens, as most common pathogens remain susceptible. Response should be re-evaluated after the initial 48 to 72 hours and modified according to culture and susceptibility results. Aminoglycoside toxicity is rare within the first 48 to 72 hours of use, but renal function and drug levels should be monitored with use extended past 7 days.^{23,27}

Institutionalized Adults

Both nitrofurantoin and TMP/SMX are good empiric choices for patients residing in long-term care facilities. Nitrofurantoin may in fact have lower resistance rates, but is often avoided in older

adults, because it is contraindicated in renal insufficiency. In patients with a history of enterobacteriaceae or nitrofurantoin-resistant *E coli* infections, TMP/SMX is a reasonable alternative therapy.²¹ For institutionalized women with uncomplicated cystitis, a 3-to 5-day course of TMP/SMX is likely sufficient, although a 2001 publication from the Society for Healthcare Epidemiology of America recommends 7 days.⁵⁰

Chronic Catheterization

Indwelling catheters should be removed and replaced with a new catheter prior to collection of urine specimen and the initiation of treatment. Nitrofurantoin should be avoided in this population, as *Proteus mirabilis* and *Pseudomonas* are widely resistant. In patients who are not severely ill, empiric treatment with levofloxacin is appropriate until culture results are available. Antibiotic therapy tailored to sensitivities is especially important in this population, as frequent antibiotic exposure makes resistance particularly likely. If the patient responds rapidly to therapy, a 7-day course of antibiotic may be appropriate. For those with delayed response, treatment should be expanded to 10 to 14 days.

PREVENTION

Preventive options are of great interest for patients at high risk of infection or who suffer from frequent infection. Speculated options range from behavioral modifications to prescribed medications, but have varied bodies of evidence to support their use.

Community-Dwelling and Long-Term Care Facility Residents

Women with frequent UTIs are often told to increase fluid intake as a means of treatment. However, a 1999 study found that excessive water intake leads to dilute urine, which may actually dilute host-produced antimicrobial factors in urine that serve to prevent and fight infection. Urine from subjects with higher water intake was noted to increase deposition rates of *E coli* and *E fecalis* on silicone rubber.⁵¹

Cranberry supplements in a variety of forms have been long investigated in the prevention of UTI. In vitro studies have demonstrated that proanthocyanidin, a component of the fruit, inhibits P-fimbriated *E coli* from adhering to the bladder epithelium.^{52,53} Interestingly, a randomized control study by Stapleton and colleagues⁵⁴ of 176 women with history of UTI found a reduction in colonization by P-fimbriated *E coli* in women

taking 4 to 8 ounces daily of a well characterized, commercially available cranberry juice, but did not demonstrate statistically significant difference in infection rates. To the authors' knowledge, this is the first study to show potential *in vivo* evidence of the *in vitro* proposed mechanism of proanthocyanidins. A Cochrane review in 2013 found a small trend toward fewer UTIs in people taking cranberry products, but no statistically significant benefit.⁵⁵ However, it should be noted that this review pertained to studies using cranberry juices, but cranberry concentrates or extract. D-mannose, a compound naturally found in pineapple, has been implicated in infection prevention by similar mechanism of interrupting bacterial adherence to the uroepithelium. Its efficacy, however, has not been demonstrated in the scientific literature.

Community-dwelling women who experience frequent UTIs (often defined as than 2 infections within a 6-month period) may be candidates for low-dose prophylactic antibiotic therapy. First-line therapy is typically nitrofurantoin 50 or 100 mg or half-strength TMP/SMX taken daily or every other day. An alternative is to supply short-term, self-administered courses of TMP/SMX or a fluoroquinolone to women who are familiar with their common symptoms and presentation of UTI.⁴⁷

Although multiple studies have shown no association between oral estrogen therapy and UTI frequency, several trials have shown improvements topical vaginal estrogen, possibly through the restoration of normal vaginal flora and re-establishment of an acidic environment.^{56,57}

Indwelling Catheters

There has been no evidence to support the use of antimicrobial impregnated catheters, but hydrophilic-coated catheters for clean intermittent catheterization and chlorhexidine-coated indwelling catheters have shown promising evidence of infection reduction.^{12,13} In general, catheters should be placed only when absolutely indicated, and they should be removed as soon as they are no longer needed. When possible, alternatives to indwelling catheterization should be considered. Both intermittent clean catheterization and condom catheters may be associated both with increased comfort and fewer adverse outcomes.⁵⁸⁻⁶¹

SUMMARY

Both UTI and ASB are common problems among elderly adults and represent a significant health care burden. Despite their frequency, differentiating between ASB and true UTI remains controversial among health care providers. Several challenges exist in the evaluation of urinary

symptoms in the elderly patient. Symptoms of UTI are variable; problems are encountered in the collection, testing, and interpretation of urine specimens; and results of urinalysis are often misinterpreted and mishandled. Multiple studies have shown no morbidity or mortality benefit to antibiotic therapy in either community-dwelling or long-term care facility residents with ASB. The field is in need of research on the use of molecular tools to identify individuals at risk. Furthermore, the elucidation of host genetic factors, and how to incorporate them into clinical practice, could make a huge impact in the treatment of elderly patients.

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