Asymptomatic bacteriuria

Lindsay E. Nicolle

Purpose of review
Asymptomatic bacteriuria is a common finding. Inappropriate antimicrobial treatment of asymptomatic bacteriuria has been identified as a major issue for antimicrobial stewardship programs. This review summarizes and evaluates recent studies which extend our knowledge of the occurrence, management, and outcomes of bacteriuria.

Recent findings
The reported prevalence of bacteriuria is higher in some developing countries than generally reported for developed countries, but reasons for this remain unclear. Clinical studies of young women, renal transplant patients, and patients undergoing minor nontraumatic urologic procedures confirm that treatment of asymptomatic bacteriuria for these populations is not beneficial, and may be harmful. There is also no benefit for treatment of asymptomatic bacteriuria prior to orthopedic surgery to decrease postoperative surgical site infection. Studies continue to report substantial inappropriate antimicrobial use for treatment of asymptomatic bacteriuria.

Summary
Recent publications confirm that asymptomatic bacteriuria is benign in most patients. Management strategies for pregnant women with recurrent bacteriuria require further clarification. There is a continuing problem with inappropriate treatment of asymptomatic bacteriuria, and sustainable strategies to optimize antimicrobial use for this problem are needed.

Keywords
asymptomatic urinary infection, bacteriuria, pregnancy, urinary catheter, urinary tract infection

INTRODUCTION

Asymptomatic bacteriuria, also referred to as bacteriuria or asymptomatic urinary infection, is a common finding in healthy women, and in both men and women with abnormalities of the genitourinary tract. Asymptomatic bacteriuria is identified when voided urine specimens have at least 10^5 cfu/ml of a uropathogen isolated in the absence of signs or symptoms of urinary infection [1]. Two consecutive positive voided specimens are generally recommended for women, but a single specimen is sufficient for men. For an in and out catheter specimen, including specimens from patients using clean intermittent catheterization, at least 10^2 cfu/ml is sufficient. Identification of bacteriuria in individuals with chronic indwelling catheters is complicated by contamination by biofilm along the catheter. A quantitative count of at least 10^5 cfu/ml is likely also appropriate for these patients. Asymptomatic bacteriuria is usually benign [1]. Morbidity attributable to bacteriuria is recognized only for pregnant women and persons undergoing invasive urologic interventions accompanied by mucosal trauma. Recent publications further expand knowledge relevant to several aspects of bacteriuria, and refine our understanding of appropriate management of this syndrome for selected populations.

EPIDEMIOLOGY

The prevalence of bacteriuria in developing countries has not previously been well characterized. Three studies from Nigeria describe a high prevalence in pregnant women of 18.1% [2], 40% [3], and 10.7% [4], compared to 2–7% in developed countries [1]. In another Nigerian population of patients with sickle cell anemia, bacteriuria was

Departments of Internal Medicine and Medical Microbiology, University of Manitoba, Health Sciences Centre, Winnipeg, Manitoba, Canada

Correspondence to Lindsay E. Nicolle, MD, Professor, Departments of Internal Medicine and Medical Microbiology, University of Manitoba, Health Sciences Centre, Room GG443, 820 Sherbrook Street, Winnipeg, MB R3A 1R9, Canada. Tel: +1 204 787 7029; fax: +1 204 787 4826; e-mail: lnicolle@hsc.mb.ca

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KEY POINTS

- Asymptomatic bacteriuria may be more common in some populations in developing countries, but the reasons for this require further clarification.
- Asymptomatic bacteriuria in young healthy women is benign. Antibiotics given to treat asymptomatic bacteriuria in this population may be harmful, leading to an increased frequency of symptomatic urinary tract infection.
- Minor urologic procedures performed in bacteriuric individuals not treated with antimicrobials, including cystoscopy and urodynamic studies, are associated with few adverse outcomes. Prophylactic antimicrobial therapy does not lead to beneficial outcomes for these patients.
- Asymptomatic bacteriuria identified prior to hip surgery is not a source for postoperative wound infections. Thus, there is no indication for treatment in this clinical setting.
- Treatment of asymptomatic bacteriuria in renal transplant recipients is not beneficial, although further randomized trials of this intervention are necessary.

identified in 8.3% of 48 men and 20% of 55 women [5]. Patients over 20 years were more often bacteriuric. *Escherichia coli* was the most common organism isolated in most of these studies. However, *Proteus mirabilis* formed 21.6% of isolates in one study of pregnant women [2], and *P. mirabilis* 17.9% and *Enterobacter cloacae* 10.7% in patients with sickle cell anemia [5]. In the study reporting a 40% prevalence in pregnant women, *Staphylococcus aureus* was isolated from 72%, and *Proteus* species from 14% [3]. The high prevalence of *S. aureus* is consistent with specimen contamination but the frequent isolation of *P. mirabilis* suggests an influence of variables not recognized in developed countries, including *Schistosoma* infection as well as sickle cell disease.

The prevalence of bacteriuria in pregnant women in Nepal was only 5% and *E. coli* was isolated from 75%, consistent with studies from developed countries [6]. A screening program for bacteriuria in school children in India reported a prevalence of 16.5% in a population of 140 girls and 60 boys [7]. This compares with less than 1% for boys and 2–5% for girls in developed countries. Organisms isolated were *E. coli* 27%, *Klebsiella pneumoniae* 24%, and *P. mirabilis* 21%. The reasons for the high prevalence in these Indian schoolchildren are not clear. A review of 4290 positive urine samples from pregnant women in India, 75% of whom were asymptomatic, identified extended-spectrum beta-lactamases (ESBLs) in 47% of *E. coli* isolates and 37% of *K. pneumoniae* isolates [8].

PATHOPHYSIOLOGY

The clinical manifestation of asymptomatic bacteriuria is determined by both host and organism factors.

Host variables

The host immune response is less vigorous with asymptomatic bacteriuria than with symptomatic infection. Genetic control of the variable innate immune response was characterized in 23 patients in whom long-term asymptomatic bacteriuria was established following inoculation with the nonvirulent *E. coli* 83972 strain [9]. Several cytokine/chemokines in the urine were increased compared with sterile urine collected from the same group of patients. Bacteriuria in individuals with selected interferon regulatory factor 3 (*IRF3*) and toll-like recptor 4 (*TLR4*) promoter polymorphisms was characterized by low urinary neutrophil numbers, low interleukin (IL)-6, and low mast cell proteinase-1; *TLR4* polymorphisms were also correlated with low interferon-γ induced protein 10 (IP-10) and soluble IL-2 receptor α (sIL-2Rα). The authors suggested that the host-specific immune response to asymptomatic bacteriuria is mainly determined through innate immune mediators, and that host genetic variability directly influences the magnitude of this response.

Organism variables

Virulence characteristics of *E. coli* strains isolated from healthy schoolgirls or hospitalized male and female urology patients with asymptomatic bacteriuria were compared to commensal strains isolated from the intestinal flora of healthy children without urinary infection [10▪]. *E. coli* clonal complex 73 (CC73) isolates dominated among the asymptomatic bacteriuria strains. Bacteriuric isolates from both populations had a similar overall virulence gene repertoire which distinguished them from commensals, but the typical uropathogenic *E. coli* (UPEC) virulence genes were less frequently attenuated in the hospital strains than bacteriuric schoolgirl or commensal strains. The genetic determinants required for growth and fitness in urine of bacteriuric *E. coli* strains were explored using transposon mutagenesis of the prototypic *E. coli* 83972 strain and a second clinical *E. coli* asymptomatic bacteriuric strain VR89 [11]. Site-specific mutants were created for six genes involved in the biosynthesis

of selected amino acids and nucleobases. All mutants exhibited reduced growth rates and reduced final cell densities in human urine *in vitro*. The growth defects could be complemented *in trans* as well as by supplementation with the appropriate amino acid or nucleobase, and the mutants showed a reduced competitive advantage in a mouse co-infection model. The authors concluded these biosynthetic pathways were important fitness factors promoting growth of *E. coli* strains isolated from asymptomatic bacteriuria.

MANAGEMENT

A prospective, nonblinded clinical trial enrolled 673 young, sexually active, Italian women with asymptomatic bacteriuria ($\geq 10^5$ cfu on two consecutive occasions) aged 18–40 years, attending a sexually transmitted diseases clinic [12▪▪]. Patients were randomized to antimicrobial treatment with a standard antibiotic regimen, or no treatment. There were no differences in time to first symptomatic urinary infection (6.3 months untreated, 5.8 months treated) or frequency of symptomatic urinary infection by 3 months (3.5% untreated, 8.8% treated). At 6 months, 7.6% of untreated patients and 29.7% of treated patients had recurrent infection [relative risk (RR) 1.31; 95% confidence interval (CI) 1.21–1.42; $P < 0.001$], and by 12 months, 13.1 and 46.8%, respectively (RR 3.17; 95% CI 2.55–3.90; $P < 0.0001$). Quality-of-life measures were also significantly improved for patients who were not treated. The authors concluded that asymptomatic bacteriuria may be protective and should not be treated in young women. These observations are consistent with previous studies concluding that treatment of asymptomatic bacteriuria, in the short term, increases the frequency of symptomatic infection. However, *E. coli* were isolated from only 38.9% of the patients at enrollment, and *Enterococcus* spp. from 46.6%. The high proportion of women with *Enterococcus* bacteriuria is unusual, as this organism is usually a contaminant. Outcomes specific for *E. coli* bacteriuria were not reported.

Observations from participants enrolled in two clinical trials of prevention of recurrent urinary infection with trimethoprim/sulfamethoxazole compared with either cranberry capsules or *Lactobacillus* spp. probiotic were combined in an analysis of whether asymptomatic *E. coli* bacteriuria identified on monthly urine cultures predicted development of symptomatic urinary infection [13▪]. At 15 months follow-up, symptomatic infection was similar for women with and without asymptomatic bacteriuria at baseline (hazard ratio 1.07; 95% CI 0.8–1.42). However, the authors suggested that susceptibility of strains isolated from bacteriuria in the month prior to symptomatic infection may direct initial empiric therapy when symptomatic infection occurs.

Inappropriate antimicrobial treatment of asymptomatic bacteriuria remains an important clinical problem. A review of urine cultures from asymptomatic patients at two Texas tertiary care hospitals reported 54% of 375 grew *Enterococcus* spp. in any quantitative count [14▪]. Of these, 75% were specimens from outpatients or emergency patients, and one-third of patients had an indwelling catheter. Antimicrobial treatment was given for 33%. A multivariate analysis identified only pyuria to be independently associated with receiving antimicrobial therapy. Thus, there appears to be a lack of appreciation that pyuria is not an indication for treatment in patients with asymptomatic bacteriuria. A Minneapolis survey described approaches to asymptomatic bacteriuria for 280 resident physicians [15]. The mean percentage correct answers for patient vignettes was 48%. Neither physician experience nor demographic variables correlated with overall knowledge, but year of training correlated with a nonsignificant trend to improvement in correct answers. These knowledge deficits of resident physicians likely contribute to unnecessary detection and treatment of asymptomatic bacteriuria. Trautner [16] reviewed current evidence addressing therapeutic approaches for asymptomatic bacteriuria. She concluded that a change in prescribing behavior for asymptomatic bacteriuria can be achieved through high-intensity interventions such as interactive educational sessions for physicians, and audit and feedback, but the duration of improved practice is unknown.

SPECIAL POPULATIONS

There are some populations with unique considerations relevant to asymptomatic bacteriuria.

Pregnant women

Treatment of asymptomatic bacteriuria in pregnant women prevents pyelonephritis in pregnancy and improves fetal outcomes [1]. It is recommended that women be screened for bacteriuria in early pregnancy by urine culture. In developing countries, microbiology resources for urine cultures may be limited, and evaluation of cheaper and more accessible screening tests for bacteriuria would be beneficial. For Nigerian women attending a first antenatal visit, combined positive leukocyte esterase and nitrite dipstick tests of urine had a predictive value of only 45.8% for bacteriuria, and were

concluded not to be sufficiently sensitive for routine pregnancy screening [4]. A Bangladeshi study of urine specimens from 600 healthy pregnant women, 4% with bacteriuria, reported a bacterial count of at least 1 on oil immersion field of urine Gram stain was the most sensitive (91.7%) and specific (97.2%) compared with the gold standard of culture, but the positive predictive value for bacteriuria was only 57.9% [17]. An Indian study reported a prevalence of bacteriuria of 9.6% in 300 pregnant women and concluded the nitrite test, with a positive predictive value of 72%, was the most reliable screening test, but that urine culture remained the gold standard [18].

The Society of Obstetricians and Gynecologists of Canada published a clinical practice guideline addressing management of group B streptococcal bacteriuria in pregnant women [19▪]. Isolation of this organism with count of at least 10^5 cfu/ml identifies asymptomatic bacteriuria and requires antimicrobial treatment. Quantitative counts below 10^5 cfu/ml in specimens from asymptomatic women should be interpreted as contamination and not treated. However, the guidelines note that isolation of any quantitative count identifies a colonized woman, and appropriate prophylaxis during labor to prevent disease in the newborn should be given. No further screening cultures for group B streptococcus colonization are recommended during the pregnancy following isolation of the organism from the urine in any quantitative count.

A Cochrane review of the optimal duration of treatment for asymptomatic bacteriuria during pregnancy evaluated evidence from 13 studies [20]. The authors concluded that single-dose therapy was less effective and women should be treated with a standard duration of the antimicrobial regimen. A second Cochrane review addressed prevention of recurrent symptomatic or asymptomatic urinary tract infection during pregnancy [21▪▪]. Only one relevant trial met search criteria. In this study, it was not clear whether nitrofurantoin and close surveillance or close surveillance alone would be the preferred management. The review concluded that evidence was lacking to support any specific approach as optimal for prevention of recurrent urinary tract infection in pregnant women.

Urology procedures

Recent studies are consistent in concluding that treatment of bacteriuria is not indicated prior to minor urologic interventions where mucosal trauma is unlikely. A prospective case series describes 354 bladder cancer patients undergoing induction with bacillus Calmette-Guérin (BCG) and 663 with cystoscopy alone for low-grade tumors [22]. Urine specimens were collected prior to the procedure, and antibiotic prophylaxis was not given. Bacteriuria was present before the procedure in 25% of the BCG patients and 17% undergoing cystoscopy. For BCG, 2.2% with bacteriuria and 1.1% without ($P = 0.17$) had febrile urinary infection within 3 months after procedure, and for cystoscopy, 3.5 and 1%, respectively ($P = 0.08$). Another study by the same author reports that 25% of 243 patients with BCG induction therapy had initial bacteriuria and were untreated. Febrile urinary infection developed after the procedure in only one (1.6%) patient with and one (0.5%) without bacteriuria [23]. Finally, a prospective observational study reported 58 (66%) of 88 bacteriuric BCG patients who received no antibiotic therapy were bacteriuria-free at 1 year, compared to only 16 (18%) of 89 cystoscopy patients ($P = 0.001$) [24]. The author suggested that BCG therapy was effective for eradication of bacteriuria, but further studies are clearly needed to confirm this observation.

A randomized clinical trial which enrolled men and women compared prophylactic single-dose levofloxacin 500 mg or placebo prior to elective outpatient cystoscopy for any nonurgent indication [25▪]. The preprocedure prevalence of bacteriuria was not determined. At 3 days after procedure, asymptomatic bacteriuria was present in 14.5% of placebo patients and 5.8% who received levofloxacin ($P = 0.01$). The incidence of symptomatic urinary infection was 0.7% of levofloxacin patients and 3% of placebo patients ($P = 0.17$). All symptomatic episodes presented with lower tract irritative symptoms only. In a prospective, noncomparative study of women undergoing urodynamic studies, a urine culture was collected 3–5 days prior to, during, and 5–7 days after the intervention [26▪]. Of the 30 (21.4%) women with bacteriuria prior to the procedure, 11 (36.7%) had persistent bacteriuria at 5–7 days. The remainder resolved spontaneously. Among initially nonbacteriuric women, four (3.6%) acquired bacteriuria following the studies. There were no complications attributed to bacteriuria. Thus, there is limited morbidity with these benign urologic interventions and prophylactic antimicrobial therapy is not appropriate.

A nonrandomized case–control study in bacteriuric Turkish patients compared single-dose or prolonged antimicrobial therapy prior to traumatic urologic procedures and reported no differences in length of stay or hospital costs between the groups [27]. Isolation of resistant organisms was more common following the longer course of antimicrobial therapy. In a prospective multicenter study of 217 patients undergoing transurethral resection of the prostate and 239 patients with transurethral

resection of the bladder, 35 (7.6%) patients had postoperative positive urine cultures on routine screening, 9 of whom were treated [28]. A positive postoperative urinalysis was not a risk factor for an infectious complication within 1 month following the procedure [odds ratio (OR) 1.4; 95% CI 0.4–4.9]. The authors concluded that postoperative urinalysis was indicated only for symptomatic patients.

Orthopedic surgery

The treatment of asymptomatic bacteriuria in patients prior to elective orthopedic surgery to prevent postoperative surgical site infections has been controversial. A prospective, randomized trial evaluated the efficacy of preprocedure antimicrobial treatment of asymptomatic bacteriuria for hip surgery [29▪▪]. None of the 471 patients enrolled had urinary catheters. Intravenous cefazolin was given to all patients immediately prior to the procedure and for 48 h postoperatively. A urine culture was obtained from patients with an abnormal preoperative urinalysis and patients with bacteriuria were randomly assigned to treatment or no treatment. Asymptomatic bacteriuria was identified in 8 of 228 patients undergoing total hip arthroplasty (THA) (mean age 84 years) and 38 of 243 undergoing hemiarthroplasty (mean age 68 years). Arthroplasty site infection by 3 months postprocedure was identified in 1 of 228 patients undergoing THA and 12 of 243 undergoing hemiarthroplasty. This included 0.9% of treated bacteriuric patients and 0% without treatment for arthroplasty, and 5.1 and 4.8%, respectively, for hemiarthroplasty. Bacteria cultured from the infected surgical wounds were uniformly distinct from organisms isolated from the urine prior to surgery. Thus, asymptomatic bacteriuria is not a cause of postoperative orthopedic surgical site infection, and treatment of bacteriuria prior to surgery is not indicated.

Renal transplant recipients

A retrospective cohort study described 89 patients followed for at least 12 months after renal transplantation in 2009 at one center in Poland [30]. There were 1170 urine cultures obtained with routine screening; 151 episodes of asymptomatic bacteriuria occurred in 49 patients (65% of positive cultures), lower urinary tract infection in 19 patients (13%), and upper tract infection, including 5 cases with bacteremia, in 34 (22%). Almost half of all urinary infections were diagnosed during the first month following transplantation. The most frequent uropathogens were *Enterococcus* spp. (33%) and *E. coli* (31%), but after the second month, *E. coli* predominated (65%). Independent risk factors for post-transplant urinary infection were female sex, history of an acute rejection episode, and cytomegalovirus infection. All patients with vesicoureteral reflux or strictures at the uretero-vesicle junction experienced recurrent urinary infections. The evolution of renal graft function did not differ significantly between patients with or without urinary infection. The authors concluded that whereas urinary infection remains frequent following renal transplantation, there was no evidence that asymptomatic or symptomatic infection was harmful in the long term.

A retrospective observational study at one Swiss transplant center reported outcomes of treated or untreated asymptomatic bacteriuria identified in the first year following renal transplantation [31▪▪]. The primary outcome was a composite of hospitalization for symptomatic urinary infection or more than 25% reduction in the estimated glomerular filtration rate 30 days after documentation of asymptomatic bacteriuria. The outcome was similar for 22 treated and 90 untreated patients (18.2 vs. 19.6%; OR 3.78; 95% CI 0.9, 15). The treated group were three times more likely to develop symptomatic urinary infection following therapy, and hospitalization days at 6 months were significantly higher for the treated group. The authors concluded there were no short or long-term benefits with antibiotic treatment of asymptomatic bacteriuria. However, the study design was subject to bias, and a prospective randomized comparative trial is necessary to definitively answer this question.

Diabetes mellitus

The sodium glucose cotransporter 2 (SGLT2) inhibitors are a new class of agents recently introduced for the treatment of diabetes mellitus. The hypoglycemic effect of these agents is mediated through blocking the renal receptor in the proximal tubule which reabsorbs glucose. This results in very high levels of glucosuria, and the impact of this glucosuria on the frequency and severity of urinary tract infection is of interest. An initial study described a 12-week phase 2 study of canagliflozin therapy [32]. There was no increased occurrence of bacteriuria associated with use of this agent, although there was an increase in isolation of low counts of *Candida albicans* from urine specimens.

Elderly

A case–control study enrolled 136 resident, aged 65 years or older, in two long-term care facilities

in Taiwan; 46 (34%) had asymptomatic bacteriuria (20 men and 26 women). Bacteriuria was associated with a slightly lower serum creatinine and higher level of resident functional impairment [33]. Serum IL-8 was elevated in patients with bacteriuria, whereas serum tumor necrosis factor (TNF)-α was significantly lower. Urine IL-6 was decreased and IL-8 was increased. These observations are similar to reports of cytokines in other bacteriuric populations. A pilot study in residents of long-term care facilities in Taiwan [34] described the impact of increased fluid intake compared with no alteration in fluid intake on the prevalence of asymptomatic bacteriuria. The prevalence of bacteriuria in the study population was 29.7% at baseline and 17.6% at 6 weeks following the intervention. Whereas a higher percentage of the 49 individuals in the increased fluid group had resolution of bacteriuria compared with the 30 residents in the maintenance group (15.9 vs. 6.7%), there was no significant difference between the two groups in decline of bacteriuria from baseline.

Spinal cord injury

A prospective randomized trial of patients with C8 to T12 spinal cord injury evaluated the impact and safety of an intervention of aerobic physical training for management of chronic asymptomatic bacteriuria [35]. The intervention group had a reduction of 'chronic asymptomatic bacteriuria', undefined, from 52.3 to 14.2% (95% CI 3, 36.3%; $P < 0.001$). The authors concluded that moderate-intensity physical activity may decrease asymptomatic bacteriuria for patients with spinal cord injury. The mechanism by which this occurs and the clinical importance in reducing symptomatic infection or other outcomes remain undetermined.

CONCLUSION

Recent publications address a wide range of aspects relevant to asymptomatic bacteriuria. Observations describing the prevalence of asymptomatic bacteriuria in some developing countries suggest further studies characterizing bacteriuria prevalence, infecting organisms, and risk factors are needed. Several studies support nontreatment of asymptomatic bacteriuria in young women, renal transplant patients, prior to minor urologic procedures, and prior to orthopedic surgery. Further studies are necessary to refine knowledge of the appropriate management of pregnant women with asymptomatic bacteriuria.

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Conflicts of interest

The author has served as a consultant for J & J Pharmaceuticals, Leo Pharmaceuticals, Boehringer Ingelheim, and Cerexa.

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