Asymptomatic Bacteriuria and Bacterial Interference

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ABSTRACT

Asymptomatic bacteriuria is very common. In healthy women, asymptomatic bacteriuria increases with age, from <1% in newborns to 10% to 20% of women age 80 years, but is uncommon in men until after age 50 years. Individuals with underlying genitourinary abnormalities, including indwelling devices, may also have a high frequency of asymptomatic bacteriuria, irrespective of age or gender. The prevalence is very high in residents of long-term care facilities, from 25% to 50% of women and 15% to 40% of men.

*Escherichia coli* is the most frequent organism isolated, but a wide variety of other organisms may occur. Bacteriuria may be transient or persist for a prolonged period. Pregnant women with asymptomatic bacteriuria identified in early pregnancy and who are untreated have a risk of pyelonephritis later in pregnancy of 20% to 30%. Bacteremia is frequent in bacteriuric subjects following mucosal trauma with bleeding, with 5% to 10% of patients developing severe sepsis or septic shock. These two groups with clear evidence of negative outcomes should be screened for bacteriuria and appropriately treated. Asymptomatic bacteriuria in other populations is benign and screening and treatment are not indicated. Antimicrobial treatment has no benefit but is associated with negative outcomes including reinfection with antimicrobial resistant organisms and a short-term increased frequency of symptomatic infection post-treatment. The observation of increased symptomatic infection post-treatment, however, has led to active investigation of bacterial interference as a strategy to prevent symptomatic episodes in selected high risk patients.

INTRODUCTION

Asymptomatic bacteriuria is the presence of bacteria in the normally sterile urine of the bladder or kidneys, together with the absence of clinical signs or symptoms attributable to urinary tract infection (1). Asymptomatic bacteriuria is also referred to as asymptomatic urinary tract infection and, occasionally, bladder colonization. In this chapter, the terms asymptomatic urinary infection, asymptomatic bacteriuria, and bacteriuria are used interchangeably, and the discussion is also relevant to asymptomatic candiduria. Bacteriuria, when present, may be restricted to the bladder, or may involve one or both kidneys. Bacteriuria in the prostate in men will not be discussed.

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 bacteriuria with an avirulent strain to prevent recurrent symptomatic infection, referred to as bacterial interference.

**DIAGNOSIS**

**Quantitative Urine Culture**

Asymptomatic bacteriuria is diagnosed by isolation of one or more organisms meeting appropriate quantitative counts from a urine specimen collected in a manner that minimizes contamination (Table 1). For most patients, a voided urine specimen is obtained and the relevant quantitative count is ≥10⁵ colony-forming units (cfu/ml). The groundbreaking studies of Kass (2) in the 1950s, confirmed the validity of a quantitative count of ≥10⁵ cfu/ml as the threshold to differentiate urinary infection from contamination and facilitated clinical and epidemiologic studies addressing asymptomatic bacteriuria. Two consecutive urine specimens collected by in and out catheter from asymptomatic outpatients distinguished specimens growing either <10⁵ cfu/ml (usually <10⁴ cfu/ml) of bacteria, which seldom persisted in a second specimen, and ≥10⁵ cfu/ml, where *E. coli* was more likely to be isolated and tended to persist. Only 1% of patients had counts between 10⁴ cfu/ml and 10⁵ cfu/ml. Subsequent studies confirmed that growth of ≥10⁵ cfu/ml from a voided urine specimen correlated with a similar quantitative count in a catheter specimen (3, 4) or suprapubic aspirate (5, 6).

**Voided Urine Specimens**

**Women**

Voided urine specimens collected from women are invariably contaminated with quantitative counts ≥10² 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, 2–11). 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 ≥10⁵ 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 ≥10⁵ 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 ≥10⁵ 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* ≥10⁵ cfu/ml confirmed on a second urine specimen obtained one week or one month after the first (16). For these women, isolation of <10⁵ cfu/ml *E. coli* on a first specimen was followed by ≥10⁵ 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 ≥10⁵ 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

### Table 1: Quantitative urine culture criteria for diagnosis of asymptomatic bacteriuria

<table>
<thead>
<tr>
<th>Population</th>
<th>Quantitative count</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voided urine specimens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy women</td>
<td>≥10⁵ cfu/ml</td>
<td>2, 3</td>
</tr>
<tr>
<td>Ambulatory men</td>
<td>≥10⁵ cfu/ml</td>
<td>2, 3, 204</td>
</tr>
<tr>
<td>Catheter specimens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In and out catheter</td>
<td>≥10³ cfu/ml</td>
<td>7, 29</td>
</tr>
<tr>
<td>Intermittent catheter</td>
<td>≥10² cfu/ml</td>
<td>30</td>
</tr>
<tr>
<td>Indwelling catheter</td>
<td>≥10⁵ cfu/ml</td>
<td>35, 35, 36</td>
</tr>
<tr>
<td>Condom: elderly men</td>
<td>≥10⁵ cfu/ml</td>
<td>24, 25</td>
</tr>
<tr>
<td>Suprapubic aspirate</td>
<td>any number</td>
<td>5, 6</td>
</tr>
</tbody>
</table>

*Two consecutive specimens preferred.*
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 intermittent 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 ≥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.

### Men

Contamination of voided specimens collected from men is less frequent, with only 12.3% of men reported to have <10^4 cfu/ml of bacteria isolated from voided specimens (23). Circumcision and povidone-iodine meatal cleaning did not decrease the frequency of contaminated cultures, but contamination was less frequent with midstream urines, where 8.4% of specimens had low counts isolated compared with 13% of initial void urine specimens. Isolation of bacteria at ≥10^5 cfu/ml was, however, similar for initial voided or midstream urine specimens (7.1% vs 7.8%, respectively). When urine specimens are collected from elderly men using a freshly applied clean condom catheter, isolation of ≥10^5 cfu/ml of one or two organisms has a positive predictive value of 85% to 100% and negative predictive value of 86% to 94% for isolation of the same organism in a concurrent catheter specimen (24, 25). In men with spinal cord injury, most of whom were receiving prophylactic antimicrobials or antiseptics and using external urine-collecting devices, 81% of organisms isolated from a suprapubic aspirate were present in counts ≥10^5 cfu/ml from the voided specimen (26).

Older, ambulatory asymptomatic men with an isolation of single gram-negative organism ≥10^5 cfu/ml from a voided urine specimen had bacteriuria confirmed in 95% when a second voided specimen was obtained within 1 month (27). However, of 22 Japanese men, only 46% had a persistent positive culture when a urine specimen was repeated within 2 months, including 3 of 10 men who had a gram-positive organism initially isolated and 7 of 12 men who had a gram-negative organism (28). Co-operative institutionalized elderly men in Sweden with an initial positive screening culture had bacteriuria confirmed on a repeat culture at 2 weeks in 53%, but interval antimicrobial therapy was not described (22). A single voided urine specimen is generally considered adequate to identify bacteriuria in men, although a repeat specimen may be advisable when a gram-positive organism is isolated.

### Other Urine Specimens

Growth of any organism in any quantitative count from a urine specimen collected by direct puncture of the urinary tract, including suprapubic or renal pelvis aspiration, is diagnostic of bacteriuria (5, 6). When urethral catheterization is used for specimen collection, a small number of periurethral organisms may be introduced into the bladder. Evaluation of paired specimens collected by in and out catheter and suprapublic aspiration identified ≥10^2 cfu/ml as the most reliable quantitative count for identification of bacteriuria in specimens obtained by in and out catheter, including intermittent catheterization (7, 29, 30).

Indwelling urinary devices, including urethral catheters, nephrostomy tubes, and ureteric stents uniformly acquire biofilm on the device surface (31). Some organisms present in the biofilm but not in urine may contaminate a specimen collected through the device. When low counts of bacteria (<10^2 cfu/ml) are isolated from urine specimens collected through short term indwelling catheters, the quantitative count progresses to ≥10^5 cfu/ml by 72 hours in 96% of patients who remain catheterized and do not receive antibiotics (32). Presumably, the low counts reflect initial biofilm formation on the catheter followed by bladder bacteriuria as the biofilm ascends to the bladder. Compared with bladder urine, a higher number of organisms are isolated and at higher quantitative counts when urine specimens are collected through a biofilm-laden chronic indwelling device (33–35). Replacing an in situ indwelling catheter allows urine specimen collection from the freshly inserted catheter where biofilm has not yet formed, so bladder urine rather than urine contaminated by biofilm is sampled. A specimen obtained from a chronic indwelling catheter was 90% sensitive but only 43% specific to identify organisms isolated from urine collected through a freshly placed catheter (35). When multiple organisms are isolated from urine collected through the replacement catheter, organisms present in quantitative counts <10^5 cfu/ml tend not to persist (36).
Thus, only organisms isolated in counts \( \geq 10^5 \) cfu/ml should be interpreted as bacteriuria for patients with an indwelling urethral catheter (29).

### Pyuria and Other Inflammatory Markers

Pyuria is a non-specific marker for inflammation within the genitourinary tract. Asymptomatic bacteriuria is usually accompanied by pyuria, but the prevalence of pyuria varies among different bacteriuric populations (Table 2). Pyuria accompanies bacteriuria in 20% to 50% of young women and girls, 50% of pregnant women (1), and 70% of diabetic women of any age (37).

From 60% to 100% of bacteriuric institutionalized elderly men or women have pyuria (38–40), 30% to 75% of bacteriuric patients with a short-term indwelling catheter (41), and virtually all patients with a chronic indwelling catheter (42).

Other inflammatory markers are present in the urine of patients with asymptomatic bacteriuria but usually vary substantially among patients and in the same patient over time. Urine interleukin-6 (IL-6) levels >20 units/ml were present in 86% of young women initially identified with bacteriuria in childhood and with persistent bacteriuria for 2 to 16 years’ follow-up (43). A similar proportion of women with pyelonephritis had these levels, but none of the bacteriuric patients had elevated serum levels of IL-6. IL-6 was present in the urine of 16% of healthy young women with asymptomatic bacteriuria; significantly increased urine interleukin-8 (IL-8) levels in these women correlated with neutrophil count (44). Chemokine ligand 5 (CXCL-5), chemokine ligand 6 (CXCL-6), and intracellular adhesion molecule 1 (ICAM-1) were not increased. When persistent asymptomatic bacteriuria was established with the avirulent E. coli 83972 strain, 21 of 23 male and female patients had pyuria and elevated urine IL-8, while IL-6, interleukin 1 receptor antagonist (IL-1RA), monocyte chemotactic protein-1 (MCP-1), and interleukin 1 (IL-1) \( \alpha \) varied over time in the same patient (45). Bacteriuric patients older than 80 years of age living in the community had significantly increased urine interleukin-12 (IL-12), chemokine ligand-1 (CXCL-1), IL-8, IL-6, and IL-10 compared with elderly individuals without bacteriuria, but there was a wide variation among patients (46). Urine levels of CXCL-1, IL-8, and IL-6 in this population were generally lower in urine from asymptomatic patients compared with patients who had symptomatic infection. For institutionalized elderly residents, 43% of bacteriuric patients had urine IL-6 present, whether asymptomatic or symptomatic (47).

#### Table 2: Prevalence of pyuria in populations with asymptomatic bacteriuria

<table>
<thead>
<tr>
<th>Population</th>
<th>Pyuria</th>
<th>Diagnostic method</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community populations:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swedish schoolgirls</td>
<td>26%</td>
<td>hemocytometer &gt;50 cells/mm³</td>
<td>94</td>
</tr>
<tr>
<td>Canadian pre-school and schoolgirls</td>
<td>37%</td>
<td>≥5 leukocytes/hpf</td>
<td>205</td>
</tr>
<tr>
<td>Female college students</td>
<td>24%</td>
<td>hemocytometer ≥8 cells/mm³</td>
<td>16</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>47%</td>
<td>leukocyte esterase/reagent strip/nitriteurinalysis &gt;10</td>
<td>157</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>81%</td>
<td>leukocytes/hpf plus reagent strip positive</td>
<td></td>
</tr>
<tr>
<td>Diabetic women</td>
<td>70%</td>
<td>hemocytometer ≥10 cells/mm³</td>
<td>37</td>
</tr>
<tr>
<td>Elderly male/female, Sweden</td>
<td>47%</td>
<td>leukocyte esterase dipstick</td>
<td>46</td>
</tr>
<tr>
<td>Institutionalized elderly:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male nursing home U.S.</td>
<td>27–67%</td>
<td>≥5 leukocytes/hpf</td>
<td>74</td>
</tr>
<tr>
<td>Condom catheter</td>
<td>50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incontinent/no catheter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canadian nursing home – male/female</td>
<td>93%</td>
<td>≥10 leukocytes/hpf</td>
<td>206</td>
</tr>
<tr>
<td>Mexican women/nursing homes</td>
<td>77%</td>
<td>≥10 leukocytes/hpf</td>
<td>207</td>
</tr>
<tr>
<td>U.S. nursing home, women</td>
<td>93%</td>
<td>&gt;10 leukocytes/mm³, uncentrifuged urine</td>
<td>38</td>
</tr>
<tr>
<td>U.S. nursing home, men/women</td>
<td>59%</td>
<td>leukocyte esterase dipstick</td>
<td>39</td>
</tr>
<tr>
<td>U.S. nursing home, men/women</td>
<td>100%</td>
<td>leukocyte esterase and/or nitrite reagent strip</td>
<td>208</td>
</tr>
<tr>
<td>U.S. nursing homes, incontinent women</td>
<td>65%</td>
<td>&gt;10 leukocytes/hpf</td>
<td>168</td>
</tr>
<tr>
<td>Other:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal cord injured/intermittent catheterization</td>
<td>86%</td>
<td>hemocytometer &gt;10 cells/mm³</td>
<td>209</td>
</tr>
<tr>
<td>Indwelling catheter, short-term</td>
<td>30–75%</td>
<td>hemocytometer &gt;20 cells/mm³</td>
<td>41</td>
</tr>
<tr>
<td>Indwelling catheter, chronic</td>
<td>66%</td>
<td>≥5 leukocytes/hpf</td>
<td>42</td>
</tr>
<tr>
<td>Ileal neobladder</td>
<td>99%</td>
<td>cytoflowmetry &gt;10/μL</td>
<td>58</td>
</tr>
</tbody>
</table>

*a hpf: high-powered field.*
EPIDEMIOLOGY

Prevalence

The prevalence of asymptomatic bacteriuria in healthy patients varies with age and gender (Table 3). Reported surveys may not be comparable because of differences in diagnostic criteria (i.e., number of positive specimens required) or laboratory methods. In the first year of life, bacteriuria is more common in boys than girls. Subsequently, asymptomatic bacteriuria is absent in boys with a normal urinary tract but the prevalence increases with increasing age in girls. For sexually-active young women the prevalence is about 1.5% at age 20 years, increasing to 3% to 5% by age 50 years (48). Married American women between 25 and 44 years of age had a prevalence of bacteriuria of 4.6%, while nuns of the same age had a prevalence of only 0.7% (12). At least one episode of asymptomatic bacteriuria was identified in 22% of 348 young, healthy, sexually active American women monitored with weekly urine cultures for 4 weeks, then monthly to 6 months (16). The prevalence in pregnant women ranges from 2% to 7% and is similar to age-matched nonpregnant women. Bacteriuria continues to increase as women age, and becomes common in men older than 50 years. By age 80 years, between 5% and 10% of men and 15% and 20% of women living in the community have bacteriuria (48–50). The prevalence of bacteriuria in residents of long-term-care facilities without indwelling urinary catheters is exceptionally high — 25% to 50% of women and 15% to 40% of men (49). In one institution, male residents had a monthly prevalence of 26% to 47%, while 24% of new residents were bacteriuric at the time of admission to the unit (51).

Patients with genitourinary abnormalities who experience recurrent symptomatic urinary infection also have an increased likelihood of asymptomatic bacteriuria, irrespective of gender or age (Table 4). Diabetic women, but not men, have a higher prevalence of bacteriuria than non-diabetic individuals (37). Men with spinal cord injuries have a prevalence of bacteriuria of 25% to 50% whether voiding is managed by intermittent catheter or by sphincterotomy with condom drainage (52, 53). When a chronic indwelling catheter is used, the prevalence of bacteriuria is 100%. Between 50% and 70% of patients with urethral stents are bacteriuric (54). At removal of ureteral stents, 17% to 24% of patients have bacteriuria, while the stents themselves are culture positive in 34% to 42% of patients (55, 56). Following urinary diversion using an abdominal stoma conduit, virtually all patients have bacteriuria, usually with mixed gram-positive skin flora (57). Between 30% and 80% of patients with orthoic bladder substitution are bacteriuric (58, 59), and bacteriuria is also common following augmentation cystoplasty, particularly for patients using clean intermittent catheterization (57).

Incidence

The incidence of asymptomatic bacteriuria is less well described (Table 5). It is reported to be 100-fold higher in sexually active women compared with school-aged girls. The incidence of bacteriuria in pregnant Swedish women was 1.3% between 8 and 16 weeks of pregnancy

<table>
<thead>
<tr>
<th>TABLE 3 Prevalence of asymptomatic bacteriuria in patients with a normal genitourinary tract</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Infants</td>
</tr>
<tr>
<td>Preschool</td>
</tr>
<tr>
<td>School age</td>
</tr>
<tr>
<td>Adolescent</td>
</tr>
<tr>
<td>Premenopausal women</td>
</tr>
<tr>
<td>Nuns</td>
</tr>
<tr>
<td>Pregnant women</td>
</tr>
<tr>
<td>Postmenopausal women</td>
</tr>
<tr>
<td>Elderly, community:</td>
</tr>
<tr>
<td>50 to 59 years</td>
</tr>
<tr>
<td>60 to 69 years</td>
</tr>
<tr>
<td>≥70 years</td>
</tr>
<tr>
<td>Elderly institutionalized</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 4 Prevalence of asymptomatic bacteriuria in populations with abnormalities of the genitourinary tract</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Spinal cord injury:</td>
</tr>
<tr>
<td>spontaneous voiding</td>
</tr>
<tr>
<td>intermittent catheter</td>
</tr>
<tr>
<td>sphincterotomy/condom</td>
</tr>
<tr>
<td>Indwelling catheter:</td>
</tr>
<tr>
<td>short-term</td>
</tr>
<tr>
<td>chronic</td>
</tr>
<tr>
<td>Urologic stents:</td>
</tr>
<tr>
<td>urethral</td>
</tr>
<tr>
<td>ureteral</td>
</tr>
<tr>
<td>ileal neobladder</td>
</tr>
</tbody>
</table>
Another study reported 2% of pregnant women without bacteriuria at initial screening developed bacteriuria during the remainder of the pregnancy (60). For elderly bacteriuric women resident in a nursing home, monthly urine cultures identified an incidence of new infection of 0.87 to 1.67/patient-year (21). The incidence of asymptomatic bacteriuria was 45/100 patient-years in elderly institutionalized men, and 10% of nonbacteriuric men acquired bacteriuria every 3 months (49). Acquisition of bacteriuria while an indwelling catheter remains in situ is between 3% and 7% per day. The acquisition of new strains remains 4% to 7% per day, or 3.2 new organisms per month, when there is a chronic indwelling catheter (61). In patients with spinal cord injuries, the incidence of bacteriuria was 5/100 patient-days for patients using indwelling catheters, 2.95/100 person-days for patients with an intermittent catheter, and 2.41/100 person-days for men using condom catheter drainage (62).

The incidence of urinary infection in elderly institutionalized populations has also been described as a turnover of bacteriuria. Female residents in U.S. life-care communities, self-care, and nursing homes from whom urine cultures were obtained every 6 months had conversion from negative to positive cultures in 5%, 11%, and 8%, respectively, at 6 months, and from positive to negative in 33%, 34%, and 31%, respectively (63). Female residents in U.S. community housing and long-term care from whom monthly urine cultures were obtained had a probability of transition from positive to negative urine culture on two consecutive monthly specimens of 0.3, and from negative to positive of 0.12 (64). In a Greek nursing home population, 23% of initially negative women and 11% of men had bacteriuria at one year, while 27% of positive women and 22% of positive men became negative (65). Residents with bacteriuria present on the initial culture but a negative culture at 6 months had recurrent bacteriuria at one year in 77% of men and 44% of women.

### TABLE 5  Incidence of asymptomatic bacteriuria in selected populations

<table>
<thead>
<tr>
<th>Population</th>
<th>Female</th>
<th>Male</th>
<th>Both</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schoolgirls</td>
<td>0.35/100 person-years</td>
<td>–</td>
<td>–</td>
<td>13</td>
</tr>
<tr>
<td>Premenopausal women, sexually active</td>
<td>39–53/100 person-years</td>
<td>–</td>
<td>–</td>
<td>16</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>1–1.3% after 12 weeks</td>
<td>–</td>
<td>–</td>
<td>15</td>
</tr>
<tr>
<td>Postmenopausal women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-diabetic</td>
<td>3.0/100 person-years</td>
<td>–</td>
<td></td>
<td>214</td>
</tr>
<tr>
<td>diabetic</td>
<td>6.7/100 person-years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteriuric institutionalized elderly</td>
<td>87–67/100 patient (pt)–years</td>
<td>45/100 pt-years</td>
<td></td>
<td>21, 51</td>
</tr>
<tr>
<td>Intermittent catheter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indwelling catheter:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-term</td>
<td>11/100 days</td>
<td>2% to 7%/day</td>
<td></td>
<td>48, 215</td>
</tr>
<tr>
<td>Long-term</td>
<td>2.72/100 pt-days</td>
<td>0.56/pt-week; 5/100 pt-days</td>
<td></td>
<td>62, 72</td>
</tr>
<tr>
<td>Suprapubic</td>
<td>0.96/100 pt-days</td>
<td></td>
<td></td>
<td>62</td>
</tr>
<tr>
<td>Spinal cord injured, normal voiding</td>
<td></td>
<td></td>
<td></td>
<td>62</td>
</tr>
<tr>
<td>Condom drainage:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elderly</td>
<td>6.1/100 pt-days</td>
<td></td>
<td></td>
<td>216</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>2.41/100 pt-days</td>
<td></td>
<td></td>
<td>62</td>
</tr>
</tbody>
</table>

and 0.2% from 16 weeks to term (15). Another study reported 2% of pregnant women without bacteriuria at initial screening developed bacteriuria during the remainder of the pregnancy (60). For elderly bacteriuric women resident in a nursing home, monthly urine cultures identified an incidence of new infection of 0.87 to 1.67/patient-year (21). The incidence of asymptomatic bacteriuria was 45/100 patient-years in elderly institutionalized men, and 10% of nonbacteriuric men acquired bacteriuria every 3 months (49). Acquisition of bacteriuria while an indwelling catheter remains in situ is between 3% and 7% per day. The acquisition of new strains remains 4% to 7% per day, or 3.2 new organisms per month, when there is a chronic indwelling catheter (61). In patients with spinal cord injuries, the incidence of bacteriuria was 5/100 patient-days for patients using indwelling catheters, 2.95/100 person-days for patients with an intermittent catheter, and 2.41/100 person-days for men using condom catheter drainage (62).

The incidence of urinary infection in elderly institutionalized populations has also been described as a turnover of bacteriuria. Female residents in U.S. life-care communities, self-care, and nursing homes from whom urine cultures were obtained every 6 months had conversion from negative to positive cultures in 5%, 11%, and 8%, respectively, at 6 months, and from positive to negative in 33%, 34%, and 31%, respectively (63). Female residents in U.S. community housing and long-term care from whom monthly urine cultures were obtained had a probability of transition from positive to negative urine culture on two consecutive monthly specimens of 0.3, and from negative to positive of 0.12 (64). In a Greek nursing home population, 23% of initially negative women and 11% of men had bacteriuria at one year, while 27% of positive women and 22% of positive men became negative (65). Residents with bacteriuria present on the initial culture but a negative culture at 6 months had recurrent bacteriuria at one year in 77% of men and 44% of women.

### PATHOGENESIS

#### Host Factors

Genetic and behavioral factors associated with acute uncomplicated urinary infection in healthy girls and women are also major contributing factors for asymptomatic bacteriuria. Women and girls with asymptomatic bacteriuria are more likely to have recurrent symptomatic urinary infection (13, 16, 66, 67) and recurrent bacteriuria (68). A population-based study enrolled Swedish women initially screened between 38 and 60 years of age. When evaluated 6 years after enrollment, 18% of women with bacteriuria at the initial screening had bacteriuria again, compared with only 3.2% without initial bacteriuria (risk ratio 6.92; 95% CI 3.53–13.53) (87). At 12 years’ follow-up, there was still significantly increased bacteriuria in women with bacteriuria on the initial screening (RR 3.13; 95% CI 1.45–6.73). Another long-term Swedish study reported
that 20% of women bacteriuric at enrollment had bacteriuria at 15 years' follow-up, but only 3 (7.5%) women without bacteriuria at enrollment (69).

Nonsecretors of the blood group substance have an increased risk for symptomatic infection, but this association has not been evaluated for asymptomatic bacteruria. Genetic variation in components of the host innate immune response appear to influence the risk of acquisition of bacteriuria as well as the clinical presentation of infection (45, 70). Selected genetic polymorphisms of TLR-2 and CXCR1 have been reported to be associated with asymptomatic bacteriuria in healthy young women (44).

The most important behavioral risk factors for asymptomatic bacteriuria in premenopausal women are sexual intercourse and spermicide use, with or without a diaphragm (16). For young university students, the relative risk for bacteriuria was 1.6 (95% CI 1.4–1.9) with recent diaphragm use with spermicide, 1.4 (95% CI 1.1–1.7) for spermicide use with cervical cap, and 1.3 (95% CI 1.1–1.4) for recent sexual intercourse. For older premenopausal women risks were 1.5 (95% CI 1.2–1.8) for diaphragm with spermicide, 2.4 (95% CI 1.4–4.4) for spermicide use alone, and 1.2 (95% CI 1.1–1.5) for recent sexual intercourse. Spermicide kills or inhibits many organisms of the normal vaginal flora, facilitating replacement with potential uropathogens, while sexual intercourse allows organisms colonizing the periurethral and vaginal mucosa to ascend into the bladder.

Following menopause, the age-related increase in bacteriuria prevalence continues, but is not accelerated (71). Loss of the estrogen effect on the genitourinary mucosa correlates with changes in colonizing flora of the vagina and periurethral area, but these changes have not been shown to promote bacteriuria (72). The presence of bacteriuria in elderly women living in the community correlates with urinary incontinence, reduced mobility, and systemic estrogen treatment and, for men, is associated with prostate disease, prior stroke, and living in an institutional care facility (73). Bacteriuria does not correlate with age in the institutionalized elderly population. The highest prevalence of bacteriuria in institutionalized elderly individuals is among the most functionally impaired residents (49). Male nursing home residents who use a condom catheter for voiding management have an increased prevalence and incidence of bacteriuria compared with those without condom drainage (74). Bacteria was present in 29% of men using continuous condom drainage, 15% with a night condom only, 10% of incontinent men not using a condom, and 3% who were continent.

Bacteriuria in women with diabetes correlates with duration of diabetes and the presence of long-term complications such as retinopathy and neuropathy, but not with parameters of glucose control such as hemoglobin A1C (37, 75). The increased prevalence of bacteriuria observed in diabetic women is likely secondary to impaired voiding attributed to diabetic neuropathy rather than metabolic or immune changes accompanying diabetes. Obstruction and urine stasis with abnormalities such as cystocele, bladder diverticuli and, in men, prostate hypertrophy, is associated with asymptomatic bacteriuria. A review of 342 urodynamic studies undertaken in a British center, however, reported no significant association of residual urine volume, stratified as <100 cc or >100 cc and bacteriuria for men (9.9% and 17.6%, respectively) or women (24.6% vs 20.0%) (76). A retrospective review of 176 renal transplant patients reported that independent associations with bacteriuria in addition to age and female sex were days of bladder catheterization following transplant surgery, presence of genitourinary anatomic abnormalities, and urinary infection within one month of transplant (77). Routine stenting at the time of transplant surgery also increases the likelihood of bacteriuria.

Intermittent catheterization promotes bacteriuria by repeated introduction of organisms into the bladder (62). Acquisition of bacteriuria in patients with urethral catheters or other indwelling urologic devices is a consequence of biofilm formation on the device. The duration the device remains in situ predicts bacteriuria. There may also be a genetic influence on the clinical presentation of infection in patients with complicated urinary tract infection. Patients with long-term E. coli 83972 bacteriuria associated with a low urinary neutrophil count, IL-6 and MCP-1 were more likely to have TLR4 polymorphisms and IRF3 genotypes previously reported to be associated with asymptomatic bacteriuria (45).

Organism Factors
E. coli is the most common organism isolated from healthy women with asymptomatic bacteriuria. E. coli occurred in 72% of bacteriuric school-aged girls (13), 77% of young, sexually active American women (16), 65% to 84% of pregnant women (2, 58), 75% of postmenopausal women (78), and 60% of diabetic women (18). Other organisms commonly isolated are Klebsiella spp. and P. mirabilis; Streptococcus agalactiae occurs more frequently in diabetic and pregnant women.
E. coli strains isolated from asymptomatic healthy women may have a lower frequency of virulence factors, such as specific lipopolysaccharide types, adhesins, motility determinants, toxins, and other proteins compared with strains isolated from asymptomatic or symptomatic urinary tract infection (45, 78). Decreased virulence characteristics are also described for strains isolated from pregnant women (79), diabetic women (80–82), and women with spinal cord injury (83) (Table 6). There is, however, overlap in virulence expression among E. coli strains isolated from asymptomatic or symptomatic infection, and some reports describe similar virulence factors for asymptomatic and symptomatic strains (16, 84). E. coli strains isolated from asymptomatic bacteriuria may originate either from a clonal lineage lacking the virulence genes generally associated with uropathogenic E. coli (UPEC), or by attenuation of a UPEC strain so urovirulence characteristics are no longer present or expressed (45, 85). The prototypic, well-characterized, avirulent E. coli strain 83972, originally isolated from a girl with persistent asymptomatic bacteriuria, is a UPEC strain with attenuation of the adhesin virulence determinants fimH, P, and F1C fimbriae (85, 86).

E. coli is also a common organism isolated from bacteriuria in patients with a complicated genitourinary tract. However, the proportion of isolates accounted for by E. coli is lower and a much wider variety of organisms occurs (Table 7). E. coli appears to be less frequent in males in some populations. For instance, in patients using intermittent catheterization, E. coli accounted for 19% and 53% of isolates (61) and 42% and 68% (52) from males and females, respectively. E. coli strains isolated from hospital-acquired asymptomatic bacteriuria possessed similar virulence profiles whether an indwelling catheter was present or not (87). Two E. coli isolates causing long-term ileal neobladder colonization genetically resembled commensal/gastrointestinal adapted E. coli rather than UPEC, potentially explaining the persistence of these strains in the gut-derived neobladder (88).

Attributes of other organisms isolated from patients with complicated asymptomatic bacteriuria are not well described. Klebsiella pneumoniae, Citrobacter species, P. mirabilis, other Enterobacteriaceae, Pseudomonas spp, Enterococcus, and coagulase-negative staphylococci are all common (Table 7). Relatively avirulent organisms, including coagulase negative staphylococci (other than Staphylococcus saprophyticus), Enterococcus species, and Candida spp. are more common with asymptomatic bacteriuria, particularly when devices with biofilm are present. Strains of K. pneumoniae isolated from bacteriuric patients with and without catheters were characterized by less serum resistance, but had a similar frequency of Type 1 fimbriae and capsular K2 serotype compared to cystitis strains (89). For Providencia stuartii, the MRK hemagglutinin correlates with catheter adherence and persistence of infection (90). P. mirabilis is common and frequently associated with catheter obstruction resulting in

**TABLE 6** Studies of E. coli virulence factors in strains isolated from asymptomatic bacteriuria

<table>
<thead>
<tr>
<th>Population</th>
<th>E. coli virulence factors</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nosocomial; male/female; age 54 year; bacteriuria (ABU) vs cystitis (c), pyelonephritis (p)</td>
<td>ABU strains decreased genes for pap G II, sfaS, afaBC, fewer fimbrial markers, hlyA, iha, fyuA. Expression of adhesins, hemolysin, and siderophores lower for ABU than c/p.</td>
<td>78</td>
</tr>
<tr>
<td>11 ABU isolates, 3 virulent UPEC, one fecal strain</td>
<td>ABU strains genetically related to UPEC had altered virulence genes – point mutations, DNA rearrangements, deletions; ABU strains unrelated to UPEC lacked most virulence genes.</td>
<td>203</td>
</tr>
<tr>
<td>ABU, pyelonephritis (p) cystitis (c) strains; complicated and uncomplicated</td>
<td>Comprehensive genotyping could not differentiate between strains isolated from ABU or c/p.</td>
<td>84</td>
</tr>
<tr>
<td>Pregnant women: asymptomatic and pyelonephritis strains</td>
<td>ABU strains had decreased adherence and MRHA, with different serotypes compared with pyelonephritis; hemolysin and MSHA similar.</td>
<td>79</td>
</tr>
<tr>
<td>Nosocomial, catheterized vs noncatheterized (male/female, 56 year)</td>
<td>Catheter-acquired and not catheter-ABU strains had similar virulence profiles, including biofilm formation.</td>
<td>87</td>
</tr>
<tr>
<td>Diabetic women</td>
<td>Virulence factors for ABU E. coli similar for diabetic and non-diabetic with ABU.</td>
<td>80, 82</td>
</tr>
<tr>
<td>Diabetic women</td>
<td>Virulence characteristics of ABU strains similar to fecal strains from healthy women.</td>
<td>81</td>
</tr>
<tr>
<td>Premenopausal women, asymptomatic and cystitis (c) strains</td>
<td>Proportion of strains with pap G (39% ABU vs 41% c) and class I, II, III papG alleles similar.</td>
<td>16</td>
</tr>
<tr>
<td>Neobladder</td>
<td>Neobladder strains distinct from UPEC; more similar to GI strains.</td>
<td>88</td>
</tr>
<tr>
<td>Spinal cord injured (indwelling, condom, and intermittent)</td>
<td>76% MSHA, 31% MRHA, 17% P, 27% hemolysin, 27% aerobactin, 54% virulent serotypes.</td>
<td>83</td>
</tr>
</tbody>
</table>

*afa/S: sialosyl-specific fimbriae; pap GII: P fimbria adhesin; afaBC: afa fimbrae; hlyA: hemolysin; iha: siderophore receptor; fyuA: yersiniabactin receptor; ABU: asymptomatic bacteriuria; MRHA: mannose-resistant hemagglutination; MSHA: mannose-sensitive hemagglutination.*
from crystalline biofilm formation. One report isolated *P. mirabilis* from 86% of obstructed catheters (91). Patients with complex urologic abnormalities or indwelling devices frequently have polymicrobial bacteriuria. When a chronic indwelling catheter is present, 77% or more of urine specimens have more than one organism isolated (42, 92). Bacteria isolated from patients with complicated genitourinary tracts are more likely to be antimicrobial resistant. This higher prevalence of resistance is attributed to repeated antimicrobial exposure as well as healthcare acquisition for many patients.

### NATURAL HISTORY OF BACTERIURIA

#### Microbiology

Potential microbiologic outcomes of asymptomatic bacteriuria include spontaneous resolution, resolution with concomitant antimicrobial therapy given for any indication, persistence of bacteriuria with the same or different organisms, or progression to symptomatic urinary tract infection. Of these, progression to symptomatic infection is the least common. In the absence of indwelling devices, *E. coli* is the organism most often associated with persistent bacteriuria. The likelihood of resolution or persistence is dependent on the duration of follow-up as well as patient characteristics. Patients frequently have recurrent bacteriuria following resolution.

### Infants and children

A Swedish study of infants with asymptomatic bacteriuria identified on screening and confirmed by suprapubic aspiration monitored 50 bacteriuric patients with six urine cultures in the first year, four in the second, two in the third and fourth, and yearly thereafter (93). There were 12 girls and 25 boys followed for the full 6 years; 45 infants with normal urography at enrollment were not treated with antimicrobial therapy. Bacteriuria cleared spontaneously in 36 infants and following antibiotics given for concomitant respiratory tract infections in 8. Ten of 50 children who cleared bacteriuria had a recurrence during follow-up.

Of 116 Swedish school-aged girls with bacteriuria on screening confirmed by a second culture, 11% who did not receive antimicrobials had spontaneous resolution by 1 year (94). Another Swedish study followed 54 girls aged 3 years to 15 years referred to a specialty outpatient clinic with asymptomatic *E. coli* bacteriuria, for a median of 2.5 years (95). All patients with evidence of renal scarring were included in the follow-up cohort, and a random sample of girls with normal kidneys. Spontaneous strain change identified by epidemiologic typing of *E. coli* was uncommon—only 1/11.6 patient-years of follow-up. Eleven (46%) of 24 strain changes occurred following antimicrobials given for other infections. A US cohort of 156 school-aged girls with persistent bacteriuria defined by 3 consecutive cultures were all treated with antimicrobials and followed for 10 years; 50% of white and 20% of black girls had recurrent bacteriuria by 1 year, and 70% and 45% by 3 years, respectively; 80% of recurrences were with a different organism (96). Thus, asymptomatic bacteriuria may persist for a prolonged time in some children, and recurrence is common following resolution with or without antibiotics.

### TABLE 7 Microbiology of asymptomatic bacteriuria in selected populations with complicated urinary tract infection

<table>
<thead>
<tr>
<th>Population (reference)</th>
<th>% of urine specimens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spinal cord/male (217)</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>18</td>
</tr>
<tr>
<td><em>K. pneumoniae</em></td>
<td>15.1</td>
</tr>
<tr>
<td><em>P. mirabilis</em></td>
<td>4.9</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>16</td>
</tr>
<tr>
<td>Providencia spp.</td>
<td>4.6</td>
</tr>
<tr>
<td>Other Enterobacteriaceae</td>
<td>15.1</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>13.5</td>
</tr>
<tr>
<td>Group B streptococcus</td>
<td></td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>6.0</td>
</tr>
<tr>
<td>CNS*</td>
<td></td>
</tr>
<tr>
<td>Other gram-positive</td>
<td>3.3</td>
</tr>
<tr>
<td>Candida spp.</td>
<td>0.8</td>
</tr>
<tr>
<td>Acinetobacter spp.</td>
<td>7.9</td>
</tr>
</tbody>
</table>

*CNS: coagulase-negative staphylococcus.*
Healthy women
Ten of 65 bacteriuric *E. coli* episodes identified on a single urine culture in 348 sexually active American women aged 18 years to 40 years were followed by symptomatic cystitis (6 with *E. coli* isolated) (16). A second culture obtained 1 week or 1 month later showed bacteriuria had resolved spontaneously in 34, 17 had persistent bacteriuria with the same strain, and 4 had *E. coli* bacteriuria with a different strain. However, *E. coli* bacteriuria persisted for 2 months or longer in only 5 women. Of 45 untreated healthy women aged 20 years to 65 years with bacteriuria on two specimens, 11% cleared spontaneously by 14 days, 20% by 4 weeks, 33% at 6 months, and 36% at 1 year (97, 98). The variation in persistence of bacteriuria appears largely to reflect the number of urine specimens obtained to define the bacteriuric population and the frequency of interval antimicrobial therapy.

Pregnant women
Bacteriuria in pregnant women confirmed by two or three consecutive cultures generally persists with the same organism throughout pregnancy or until antimicrobial therapy is given. Of 145 untreated pregnant women less than 32 weeks gestation in whom bacteriuria was identified by three positive cultures, only 20 (14%) cleared spontaneously during the remainder of the pregnancy, 98 remained bacteriuric, and 27 developed pyelonephritis and were treated (60). In 106 women bacteriuric on three consecutive urine specimens, 72 remained bacteriuric and untreated throughout the pregnancy, and only 8 (7.5%) cleared spontaneously, while 26 developed symptomatic infection (9). Women with bacteriuria during pregnancy are likely to have recurrent or persistent bacteriuria after delivery. At 2 to 4 years after delivery 27% of 285 bacteriuric women who had received antimicrobial treatment and had sterile urine at discharge were bacteriuric (99).

Diabetic women
Diabetic women with untreated bacteriuria and urine cultures repeated every 3 months remained bacteriuric in 50% at 12 months, 40% at 24 months, and 50% at 36 months (100). Persistent bacteriuria with the same *E. coli* strain occurred in 30% at 12 months, 20% at 24 months and 20% at 36 months (82). In another study, 53 diabetic women with *E. coli* bacteriuria confirmed in a second specimen at 2 months to 4 months had the same strain in 9 (63%) of 16 pairs available for typing (19). Thus, *E. coli* bacteriuria frequently persists for extended periods in women with diabetes.

Older women and men: community
A population-based study in Sweden screened persons aged 72 years to 79 years; bacteriuric patients were subsequently screened intermittently and nonsystematically. In patients who underwent repeated screening, bacteriuria persisted for at least 12 months only in women and only when the organism isolated was *E. coli* (101). Another Swedish study screened men and women older than 80 years of age in the community with urine cultures repeated at 6 months and 18 months (50). When bacteriuria was present at the initial screening, 60% of patients remained bacteriuric with any organism at both 6 and 18 months and, for *E. coli* bacteriuria, 76% had the same strain at 6 months and 40% at 18 months. Male outpatients at a Veteran’s hospital followed every 3 months for 1 to 4.5 years had at least one spontaneous resolution in 76%, while 38% had persistence of bacteriuria with the same species for 2 to 21 months; 21% had intermittent bacteriuria (102).

Institutionalized elderly
A cohort of elderly American women and men who were residents in assisted-living facilities or nursing homes had urine cultures persistently positive with a single species for 18 months in 6% of women and 2.6% of men (63). Ten of 12 women with recurrent *E. coli* bacteriuria following antimicrobial therapy had the pre-therapy strain isolated while 11 of 14 untreated women had a persistent *E. coli* strain for up to 18 months (103). Five of 7 initially bacteriuric women resident in an American nursing home had persistence of the initial strain during 6 months of monthly urine cultures (64). A Canadian long-term care facility reported persistent bacteriuria with the same species in 71% of untreated women monitored with monthly urine cultures for 12 months, but epidemiologic typing was not performed; 25% of the women had spontaneous resolution but experienced reinfection at 1 month to 1 year (21). In another Canadian study, bacteriuria persisted during 1-year follow-up in 77% of 1,387 urine specimens obtained monthly from 83 initially bacteriuric men and women (40). While 20 (24%) patients had persistent bacteriuria with the same organism only 13 (16%) had periods of at least 4 months free of bacteriuria. For 11 of these 13 patients, the nonbacteriuric period followed an antimicrobial course given for another indication. Nineteen bacteriuric elderly institutionalized men who did not receive antimicrobial therapy remained bacteriuric at 24 months, and 55% of all monthly urine cultures were positive during follow-up (49). At 24 months, 84% had bacteriuria with the same species isolated at the first culture,
and 3 had replacement with a new organism at 5, 7, and 13 months. Thus, spontaneous resolution of bacteriuria is uncommon in elderly institutionalized patients, while the same strain frequently persists for months or years.

**Other populations**

Bacteriuria persists in patients with a chronic indwelling catheter but there is continuous replacement of strains (29, 92, 104). Different species remain for different durations. Enterococcus species persisted for a mean of 2.9 weeks, *E. coli*, *P. mirabilis*, *K. pneumoniae*, and *P. aeruginosa* for 4 to 6 weeks, and *Providencia stuartii* for 10.4 weeks in a prospective study of patients with chronic catheters when weekly urine cultures were obtained (92). In contrast, 75% of non-enterococcal gram positive cocci persisted less than 1 week. Patients maintained on intermittent catheterization experience repeated episodes of bacteriuria with new organisms, but persistence of a single organism for extended periods may also occur. For 50 spinal cord injury patients using indwelling catheters followed for 24 to 270 days, relapsing bacteriuria following antibiotics was 35.6/1,000 days and reinfection 55.8/1,000 days (104). Patients with relapsing bacteriuria were more likely to acquire symptomatic infection. In a prospective study, 18 (67%) patients with a continent ileal reservoir had persistent bacteriuria, 5 of whom had *E. coli* persisting for 5 or more months (62).

**Morbidity and Mortality**

Potential adverse outcomes following acquisition of asymptomatic bacteriuria include short-term events, such as symptomatic urinary tract infection, and long-term outcomes, including chronic renal failure, hypertension, or increased mortality.

**Infants and Children**

Early screening studies of infants and preschool children reported an association of bacteriuria with obstructive uropathy and vesicoureteral junction deformities (105). Only 2 of 50 infants with bacteriuria identified on population based screening and followed prospectively developed pyelonephritis, both within 2 weeks of the initial identification of bacteriuria (95). Infants with normal urography were not given antimicrobial therapy and, with a median follow-up of 32 months, none of 36 patients developed renal damage. Renal concentrating ability at the end of follow-up was comparable to a reference non-bacteriuric population. An American study that enrolled 1,817 infants and preschool girls reported evidence of upper tract damage in 17% of bacteriuric infants and 13% of bacteriuric preschool children (105). Vesicoureteral reflux was present in 46% of infants and 9% of preschool girls. At 3 to 5 years follow-up, infants with bacteriuria and a normal urinary tract, with or without reflux, were more likely to experience recurrent bacteriuria, but the kidneys remained anatomically normal. Infants with high-risk lesions, such as obstructive uropathy and vesicoureteral junction ectopy and deformity, were more likely to experience both bacteriuria and recurrent symptomatic infection.

School-aged girls with bacteriuria on screening were more likely to have renal parenchymal reduction, pyelonephritic scarring, vesicoureteral reflux, and past history of symptomatic urinary infection (13, 67, 106). One of 28 Swedish school-aged girls with untreated *E. coli* bacteriuria developed pyelonephritis during 9 months’ follow-up, but the strain isolated from the symptomatic episode was different from that isolated at screening (94). In this cohort, at 3 years, renal scarring or arrested renal growth only occurred in patients who experienced symptomatic pyelonephritis (107). In fact, treatment of asymptomatic bacteriuria was associated in the short-term with an increased incidence of symptomatic infection (107, 108). During 9 to –18 years’ follow-up of 60 American school-aged girls identified with asymptomatic bacteriuria on screening, five had reflux repair, two had nephrectomy, and one, with atrophic pyelonephritis, had reduced inulin clearance (109). Renal scars or caliectasis were present in 16 bacteriuric girls and no controls, but blood pressure remained similar for both groups during the extended follow-up. Girls with asymptomatic bacteriuria were more likely to have bacteriuria identified at subsequent follow-up, including during pregnancy. The authors concluded that bacteriuria in school-aged girls identifies patients at risk of recurrent symptomatic infection and renal scars, but at low risk of reduced renal function. Thus, infants and school-aged girls with asymptomatic bacteriuria identified at routine screening are more likely to have genitourinary abnormalities, including renal scars and vesicoureteral reflux, and at greater risk of experiencing symptomatic urinary infection. Persistent untreated asymptomatic bacteriuria, however, is not associated with an increased risk for new or progressive renal scars, symptomatic infection with the same organism, hypertension, or renal failure. The few children at risk for progression of renal abnormalities are identified by the occurrence of symptomatic infection.

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Asymptomatic Bacteriuria and Bacterial Interference

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ASMscience.org/MicrobiolSpectrum
Healthy non-pregnant women
Young, sexually active American women with *E. coli* ≥10⁵ cfu/ml isolated in one urine specimen developed symptomatic infection with the same strain in 8% of bacteriuric episodes, invariably within 1 week of initial identification of bacteriuria (16). British women with untreated asymptomatic bacteriuria had symptomatic infection develop in 36% by 1 year compared with 7% of control women without bacteriuria (97). A Swedish study re-evaluated 40 women 15 years after identification of bacteriuria, and compared these with 40 age-matched controls without bacteriuria (69). The median age was 58 years (35–72 years) at the long-term assessment. In the 15-year interval, 22 (55%) women with bacteriuria and 4 (10%) controls were treated for symptomatic urinary infection, including 3 episodes of pyelonephritis. Diagnosis of hypertension and renal function at 15 years were similar for patients with and without bacteriuria. There was a significant reduction in renal concentrating ability compared to the initial assessment, but the rate of decline was similar for both bacteriuric and non-bacteriuric patients. Renal imaging of selected women identified no evidence for progression or development of new renal abnormalities. A 24-year Swedish follow-up study also reported no differences in renal disease between women initially identified as bacteriuric or nonbacteriuric (68). American (12), Japanese (110), and Jamaican (111) studies have reported no association of hypertension with bacteriuria at long-term follow-up.

Women enrolled in prospective population based surveys in Wales and Jamaica were combined for an analysis of mortality stratified by bacteriuria or not at initial screening (112). There was significantly increased mortality at 10 to 13 years for women who bacteriuric at the first survey [RR 2.5 (1.73, 2.68)], or at two consecutive surveys [RR 4.2 (2.23, 8.04)]. However, when adjusted for age and weight, the association was lower [RR 1.5 (0.96, 2.32) and 2.0 (1.05, 3.92)], respectively. Other potential confounding factors were not addressed. The analysis was not stratified by geographic origin and pooling of these different populations for the analysis was likely not appropriate. The 24-year Swedish study did not report any association of mortality with asymptomatic bacteriuria (68).

Thus, bacteriuric women are at increased risk of symptomatic urinary tract infection, but the strain isolated from asymptomatic infection seldom progresses to symptomatic infection. When this does occur, the symptomatic episode usually develops shortly following acquisition of the strain. Women with bacteriuria are not at risk for long-term negative renal outcomes, hypertension, or increased mortality. Several studies report an increased risk of symptomatic infection following antimicrobial therapy in women (113, 114). This observation has been attributed to disruption of normal vaginal flora by the antimicrobial, thus promoting colonization with potential uropathogens (114). However, an alternate explanation is that eradication of asymptomatic bacteriuria in a woman with a biologic predisposition to both bacteriuria and recurrent symptomatic infection is followed by reinfection with a more virulent organism, resulting in the symptomatic infection.

Diabetic women
Diabetic women with asymptomatic bacteriuria are also at increased risk for symptomatic urinary infection (83, 115). In a Dutch cohort study of 589 diabetic women followed for 18 months, 20% developed symptomatic urinary infection. For women with type 2 diabetes 19% without and 34% with bacteriuria at enrollment developed symptomatic infection, and for type 1 diabetes 12% and 15%, respectively (115). Bacteriuric women with type II diabetes had poorer renal function at enrollment compared with those without bacteriuria, but the decline in renal function at 6 years was similar for patients with and without bacteriuria at enrollment (116). Thus, bacteriuric diabetic women are more likely to experience symptomatic urinary infection, but are not at increased risk for long-term negative renal outcomes.

Pregnant women
From 19% to 36% of untreated pregnant bacteriuric women will develop acute pyelonephritis later in pregnancy, usually with the same organism isolated early in the pregnancy (1, 2, 14, 60) (Table 8). Pyelonephritis occurring at the end of the second or early third trimester

**Table 8** Asymptomatic bacteriuria in pregnancy and the frequency of pyelonephritis

<table>
<thead>
<tr>
<th>Number with bacteriuria (prevalence)</th>
<th>Pyelonephritis in pregnancy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antimicrobial treated</td>
</tr>
<tr>
<td>265 (5.3%)</td>
<td>3.2</td>
</tr>
<tr>
<td>145 (4.0%)</td>
<td>2.8</td>
</tr>
<tr>
<td>144 (4.7%)</td>
<td>2.8</td>
</tr>
<tr>
<td>110 (6.5%)</td>
<td>4.3</td>
</tr>
<tr>
<td>179 (NS)</td>
<td>–</td>
</tr>
<tr>
<td>173 (4.9%)</td>
<td>–</td>
</tr>
<tr>
<td>203 (6.0%)</td>
<td>1</td>
</tr>
</tbody>
</table>

NS: not stated
precipitates preterm delivery and increases neonatal death rates (60, 117). Asymptomatic bacteriuria in pregnant women is also associated with intra-uterine growth retardation and low birth weight (118).

Progression of asymptomatic bacteriuria to pyelonephritis in these women is attributed to the physiologic hormonal changes of pregnancy, as well as ureteric obstruction (119). Progesterone induces relaxation of the genitourinary autonomic musculature, leading to impaired voiding and urine stasis. Decreased muscle tone also increases the likelihood of reflux of urine from the bladder into the kidneys. Pressure of the fetal head on the pelvic brim, usually on the right side, obstructs drainage from the kidney. These changes are maximal at the end of the second trimester and early third trimester, when pyelonephritis carries the greatest risk for preterm delivery and poor fetal outcomes.

**Elderly patients**

The 15- (69) and 24-year (68) Swedish follow-up studies of women in the community enrolled both pre and post-menopausal women. Outcomes did not differ for older compared with younger women. A prospective, longitudinal study in ambulatory outpatient men (102) in the United States reported 5 of 34 bacteriuric men were treated for symptomatic infection during 1- to 4.5-years follow-up, but symptoms were not described.

Ambulatory women in a supervised living facility experienced chronic genitourinary or non-specific symptoms with similar frequency and intensity whether bacteriuria was present or not (120). Bacteriuria in elderly institutionalized women was not associated with alterations in mental status or increased rates of hospitalization for urinary infection (121). There is evidence of increased systemic immune activation in some frail elderly patients with asymptomatic bacteriuria (122). Elevated circulating levels of soluble tumor necrosis factor receptors (sTNFR-1) and a higher number of blood neutrophils were reported in frail bacteriuric men and women, compared to individuals without bacteriuria. Bacteriuric elderly patients with increased systemic antibody to *Enterobacteriaceae* have decreased survival compared with bacteriuric patients without elevated antibody (40, 123). However, the mortality of patients with increased antibody is similar to elderly residents without bacteriuria (123). The clinical relevance of these observations is not clear, and they may represent epiphenomena accompanying aging-associated alterations of immune function.

The clinical diagnosis of symptomatic urinary infection is often problematic in elderly institutionalized populations with impaired communication, a high frequency of chronic genitourinary symptoms, and underlying urologic abnormalities (124). One adverse outcome is the promotion of antimicrobial resistance in this population when unnecessary antimicrobial treatment is given for nonspecific clinical deterioration in the bacteriuric resident (121, 125). Given the very high prevalence of bacteriuria in these populations, clinical deterioration without localizing signs or symptoms is frequently diagnosed as urinary infection. However, for residents without indwelling catheters, localizing genitourinary signs or symptoms should be present to support a diagnosis of symptomatic infection (49, 120, 126, 127).

Early studies in Finland (128) and Greece (129) reported increased 5-year mortality for bacteriuric compared with non-bacteriuric institutionalized elderly women and men. Subsequent reports with follow-up of 5 and 9 years of elderly residents in Finland (130), Sweden (131), the United States (132), and Canada (133) reported no differences in survival between bacteriuric and nonbacteriuric residents. It is, in fact, somewhat surprising that asymptomatic bacteriuria is not associated with decreased survival, as functional impairment is an independent predictor of mortality in elderly institutionalized populations and the more functionally impaired residents are more likely to be bacteriuric (134).

**Indwelling urinary catheters**

Catheter-acquired bacteriuria in patients with a short-term indwelling catheter is infrequently associated with symptomatic infection. In 1,497 patients with a newly inserted indwelling catheter, 235 of whom developed bacteriuria, potential symptoms of urinary infection occurred with similar frequency in patients with or without bacteriuria. Only one episode of bacteremia was attributed to catheter-acquired bacteriuria (135). Another prospective study reported presumed symptomatic urinary tract infection in 1.43 to 1.61/100 catheter-days, with concordant blood and urine isolates for 0.53% of all catheters and 4.8% of catheters with bacteriuria (136). In critical care units, less than 3% of bacteremic episodes in patients are attributed to catheter-acquired urinary infection (29). Increased mortality was reported in hospitalized patients with indwelling catheters in one study, but receiving antimicrobials either before or during catheterization did not predict lower mortality in the multivariate analysis (137). Other studies report no association of bacteriuria with mortality. Confounding attributed to the substantial clinical dif-
ferences between catheterized and noncatheterized patients seems the likely explanation for any mortality differences (29).

Elderly institutionalized residents with chronic indwelling catheters have increased morbidity and mortality compared with bacteriuric residents without an indwelling catheter, presumably at least partially attributable to bacteriuria (138). The usual presentation of symptomatic infection in these residents is fever alone (127). Urinary infection is usually a diagnosis of exclusion, as localizing symptoms are seldom present. Febrile episodes of presumed urinary source occur at a rate of 0.69 to 1.1/100 catheter-days (127, 139) and bacteremia is 3- to 39-times more frequent in bacteriuric residents with indwelling catheters (140, 141). Local complications, such as purulent urethritis, paraurethral abscesses, and, in men, epididymoorchitis and prostatitis, may also develop. Transient bacteremia has been described in 4% of residents when a chronic indwelling catheter is replaced, but is of low quantitative count and not associated with morbidity (142–144).

Intermittent catheterization
A prospective observational study of 14 children with neurogenic bladder managed with intermittent catheterization reported 70% of urine specimens had ≥10^4 cfu/ml of organisms isolated. Persistent carriage for 4 weeks or longer was common, but only 5 symptomatic infections were observed during 323 patient weeks, less than 1 per patient-year. There was no deterioration of renal function during follow-up (145). In a small number of men with spinal cord injury, symptomatic urinary infection was uniformly attributed to organisms previously isolated from weekly urine cultures, with a median time of 72 days from first isolation to symptomatic infection for patients not receiving antibiotics (146). In this study, neither the intensity of pyuria nor trend over time predicted progression to symptomatic infection.

Invasive genitourinary procedures
Patients who are bacteriuric and undergo a traumatic genitourinary procedure have a high frequency of post-procedure bacteremia, with sepsis in 4% to 10% (147, 148). Transurethral resection of the prostate is the procedure best described, but any urologic procedure with a high likelihood of mucosal bleeding likely carries a similar risk. This may include extracorporeal shock wave lithotripsy, bladder tumor resection, ureteroscopy, percutaneous stone extraction, and some open procedures (148).

Other populations
Retrospective cohort studies do not report increased morbidity or impaired graft survival with bacteriuria alone in renal transplant patients (149). When asymptomatic bacteriuria is present and there is decline in renal graft function, alternate explanations for deterioration are invariably present, including symptomatic pyelonephritis or urologic complications. A study completed before antimicrobial prophylaxis became the standard of care for hematologic patients with profound neutropenia reported bacteremia developed in a high proportion of patients who acquired bacteriuria (150). However, urosepsis is uncommon with current approaches of antimicrobial prophylaxis in these patients. Morbidity has not been attributed to bacteriuria in patients with continent ileal reservoirs or other neo-bladders (151).

Some clinicians recommend treatment of asymptomatic bacteriuria prior to elective surgical procedures outside the genitourinary tract to prevent post-operative wound infections. There are conflicting observations from cohort studies, including report of an increased occurrence of post-operative surgical infections when there is pre-operative bacteriuria (152) or of no increase (153, 154). The organisms isolated from surgical wound infections following bone and joint surgery differ from those isolated from the urine of bacteriuric patients prior to surgery (154). An association of bacteriuria with post-operative wound infection may be attributable to confounding by host risk factors associated with surgical site infections, such as age and functional impairment, which are also risk factors for bacteriuria.

SCREENING FOR AND TREATMENT OF ASYMPOTOMIC BACTERIURIA
Early clinical trials evaluating antimicrobial treatment or nontreatment of asymptomatic bacteriuria in pregnant women consistently reported compelling benefits with antimicrobial therapy (Table 8). However, prospective, randomized clinical trials in all other non-surgical populations have reported no benefits with treatment of bacteriuria (Table 9). In addition, treatment of asymptomatic bacteriuria in school-aged girls (94, 95, 108) adult women, (113, 114), and diabetic women (18) is reported, in the short term, to be followed by an increased frequency of symptomatic urinary tract infection. In the absence of evidence for improved outcomes with treatment of bacteriuria, screening of populations to identify asymptomatic bacteriuria is also not indicated.
Children
A controlled trial randomized bacteriuric American school-aged girls to antimicrobial treatment or no treatment (155). At 2 years, 84% of controls and 74% of treated school-aged girls had persistent or recurrent bacteriuria, 63% and 41% at 3 years, and 59% and 46% at 4 years, respectively. Similar numbers of children in both groups developed clinical pyelonephritis or radiologic evidence of new scars by 2 years following enrollment. The radiologic changes were all minor and did not affect renal growth. Swedish school-aged girls without vesicoureteral reflux or renal parenchymal reduction who remained bacteriuric for 6 months were treated with 10 days of nitrofurantoin or received no antibiotics (94). For the treated girls, 93% had a negative urine culture at 1 year compared with 11% of those not treated. Only one girl in each group developed pyelonephritis. The authors concluded that therapy for bacteriuria is not necessary for school-aged girls and screening for covert bacteriuria of childhood could not be recommended. An analysis of the costs and benefits of screening for bacteriuria in toilet trained asymptomatic children concluded there was no evidence that detection and treatment of asymptomatic bacteriuria prevents subsequent pyelonephritis, renal scarring or renal failure, and that screening for bacteriuria in asymptomatic children was costly and ineffective (156).

Premenopausal, Nonpregnant Women
A prospective, 12-month trial randomized 94 women aged 20 years to 65 years to treatment with nitrofurantoin, followed by ampicillin if nitrofurantoin was not effective, or no antimicrobial treatment (97, 98). Two weeks following treatment 76% of treated and 20% of untreated patients had sterile urine, and, at 12 months, 45% of treated and 36% untreated. Symptomatic urinary tract infection occurred with equal frequency in 37% of treated and in 36% of untreated patients, during 12 months’ follow-up. However, 12 of 15 patients with reinfection developed symptomatic infection compared with only 20 of 44 with persistent or relapsing infection, a significant difference (97). Thus, treatment of asymptomatic bacteriuria had no clinical benefits and may have been harmful.

Pregnant Women
Screening for and treatment of asymptomatic bacteriuria in early pregnancy decreases the risk of pyelonephritis during the pregnancy by 90% (Table 8). Treatment is also associated with decreased preterm labor and improved fetal survival (118). Thus, all pregnant women should be screened for bacteriuria in early pregnancy and treated if bacteriuria is present (1, 119). A culture method should be used for screening. Tests for pyuria, such as dipstick or urinalysis, are insensitive and identify only 50% of pregnant women with bacteriuria (157–160). A second urine culture should be obtained to confirm bacteriuria. From 20% to 50% of pregnant women may not have bacteriuria persist on a second specimen (9, 60, 161) and antimicrobial therapy can be avoided in these women. A strategy of screening and treatment was concluded to be cost effective in the American context if the prevalence of bacteriuria exceeded 2% and the risk of pyelonephritis exceeded 13% (162).

### TABLE 9
Symptomatic infection in patients enrolled into prospective, randomized clinical trials of treatment or non-treatment of asymptomatic bacteriuria in populations other than pregnant women

<table>
<thead>
<tr>
<th>Population</th>
<th>Trial characteristics</th>
<th>Symptomatic urinary infection</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schoolgirls</td>
<td>N=63; ampicillin, NF, or T/S; 24 mo</td>
<td>Treated: 6.9% Not treated: 6.3%</td>
<td>155</td>
</tr>
<tr>
<td>Women</td>
<td>N=94; 12 months, cultures, q 6 months</td>
<td>Treated: 37% Not treated: 36%</td>
<td>97, 98</td>
</tr>
<tr>
<td>Elderly ambulatory women</td>
<td>N=61; 6 months</td>
<td>Treated: 7.9% Not treated: 16.4%</td>
<td>169</td>
</tr>
<tr>
<td>Elderly institutionalized men</td>
<td>N=36; 24 months; monthly cultures</td>
<td>Treated: 12.5% Not treated: 10%</td>
<td>21</td>
</tr>
<tr>
<td>Elderly institutionalized women, incontinent</td>
<td>N=50; 12 months; monthly cultures</td>
<td>Treated: 42% Not treated: 35%</td>
<td>21</td>
</tr>
<tr>
<td>Diabetic women</td>
<td>N=105; double-blind first 6 weeks; 36 months, cultures every 3 months</td>
<td>Treated: 0.93/1,000 days Not treated: 1.1/1,000 days</td>
<td>18</td>
</tr>
<tr>
<td>Spinal cord patients</td>
<td>N=46; mean 993, 1,180 days; cultures 4 and 14 days post-therapy</td>
<td>Treated: 1.86/100 pt days Not treated: 1.11/100 pt6 days</td>
<td>182</td>
</tr>
<tr>
<td>Chronic indwelling catheter</td>
<td>N=35; weekly cultures; 15–43 wk and 12–44 wk</td>
<td>Treated: 0.18 febrile days/ patient-week Not treated: 0.22 febrile days/ pt-wk</td>
<td>177</td>
</tr>
</tbody>
</table>

*a* NF: nitrofurantoin; T/S: trimethoprim/sulfamethoxazole.
organism isolated, and given for as short a duration as possible (Table 10). Recommended first-line agents include amoxicillin, amoxicillin/clavulanic acid, cephalexin, or nitrofurantoin. Pivmecillinam and fosfomycin trometamol are also safe in fetal cartilage development. A Cochrane review concluded that pregnant women should be treated with standard durations of antimicrobial regimens until more data becomes available (163). Although single-dose antimicrobial treatment was not significantly inferior at 4 to 7 days, there was a trend to lower efficacy and the studies were judged to be of poor quality. A subsequent prospective, randomized comparative trial enrolling pregnant women in Thailand, the Philippines, Vietnam, and Argentina randomized bacteriuric pregnant women to nitrofurantoin monohydrate/macrocrystals 100 mg twice a day for 1 day or for 7 days (164). The microbiologic cure rates at 14 days post-treatment were 76% and 86%, respectively, a significant difference. Thus, short courses of antimicrobial therapy for treatment of asymptomatic bacteriuria in pregnancy are not currently recommended.

Following one episode of either asymptomatic bacteriuria or symptomatic urinary infection in a pregnant woman, urine cultures should be monitored monthly throughout the remainder of the pregnancy (158, 165). If a second episode of asymptomatic or symptomatic infection occurs, prophylactic antimicrobial therapy should be initiated and continued for the duration of the pregnancy and, optimally, 6 weeks post-partum. Cephalexin or nitrofurantoin are preferred, but nitrofurantoin should be discontinued at 32 to 34 weeks gestation.

The management of pregnant women with genitourinary abnormalities which promote an increased frequency of asymptomatic bacteriuria, is not well studied. Some of these women (e.g., women with spinal cord injuries) managed with intermittent catheterization, always have a high prevalence of bacteriuria. Current guidelines recommend screening for bacteriuria and treatment of all positive urine cultures in such women (166). However, the effectiveness of this approach in preventing pyelonephritis and adverse fetal outcomes balanced against the risk of acquisition of resistant organisms has not been rigorously evaluated.

### Women with Diabetes

A prospective, randomized 36-month trial of treatment or non-treatment of bacteriuria in diabetic women, the majority of whom had type 2 diabetes, reported no benefits with antimicrobial treatment (18). Continued screening for and treatment of bacteriuria, including prophylactic antimicrobial therapy following repeated recurrences, did not alter the frequency of symptomatic infection, including pyelonephritis, compared with non-treatment. Hospitalization for urinary infection or any other cause was also similar with or without treatment, and there was no evidence for renal functional decline in either group. Women randomized to treatment, however, had substantially greater antimicrobial exposure and, in the short term, an increased incidence of pyelonephritis. A prospective, cohort study followed 53 Polish diabetic patients with bacteriuria and 54 diabetic patients without bacteriuria for 14 years, with clinical and bacteriological assessment every 3–6 months. Acute pyelonephritis occurred with similar frequency in both groups (11% and 9.3%, respectively), and there were no differences in renal functional decline or development of hypertension (167). Thus, routine screening for or treatment of asymptomatic bacteriuria for diabetic women is not beneficial.

### Older Women in the Community

There are no prospective, randomized trials of treatment or nontreatment of bacteriuria specifically evaluating older community residents. Some post-menopausal women were enrolled into a prospective, randomized study of healthy women who reported no benefits with treatment (97, 98). For diabetic women, there were no differences in outcomes with treatment of bacteriuria.

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### Table 10 Recommended antimicrobial regimens for the treatment of asymptomatic bacteriuria in pregnancy

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferred:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>500 mg tid</td>
<td>7 days</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>500 mg qid</td>
<td>7 days</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>50–100 mg qid or 100 mg bid</td>
<td>5 days</td>
</tr>
<tr>
<td>Pivmecillinam*</td>
<td>400 mg bid</td>
<td>3–7 days</td>
</tr>
<tr>
<td>Fosfomycin trometamol</td>
<td>3 g</td>
<td>single dose</td>
</tr>
<tr>
<td><strong>Other options</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMP/SMZ*</td>
<td>80/400 mg</td>
<td>3 days</td>
</tr>
<tr>
<td>Amoxicillin/clavulanate</td>
<td>500 mg tid or 875 mg bid</td>
<td>7 days</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>500 mg bid</td>
<td>5 days</td>
</tr>
<tr>
<td>Cefixime</td>
<td>400 mg od</td>
<td>5–7 days</td>
</tr>
</tbody>
</table>

*Not licensed in North America;  
*For women with intolerance or resistance to preferred regimens;  
*Avoid in first trimester; TMP/SMZ: trimethoprim/sulfamethoxazole; tid: three times daily; qid: four times daily; bid: twice daily; od: once daily.
for older compared with younger women (18). The absence of adverse outcomes in long term prospective cohort studies also supports a lack of benefit for screening and treatment (68, 69, 102). Thus, current evidence does not support screening for or treatment of asymptomatic bacteriuria in elderly women or men resident in the community, but clinical trial evidence is limited.

Elderly Institutionalized Populations
Prospective, randomized, clinical trials enrolling men and women resident in long-term care facilities have reported no benefits with treatment of asymptomatic bacteriuria (21, 168, 169). Studies have enrolled residents of differing functional levels and are relevant across the spectrum of institutionalized elderly patients. Treatment of bacteriuria does not decrease the likelihood of subsequent symptomatic urinary tract infection or alter mortality. The prevalence of asymptomatic bacteriuria is decreased only modestly in the treated arm, and for only a short duration. There was also no improvement of chronic incontinence in women with treatment of bacteriuria (168). An increased likelihood of reinfection with a more resistant organism follows antimicrobial treatment, and there are increased antimicrobial adverse drug effects and costs (21). Thus, screening for and treatment of asymptomatic bacteriuria in elderly long-term care residents is not recommended. As most elderly institutionalized individuals with bacteriuria have pyuria, the presence of pyuria does not identify patients with a poorer outcome or for whom antimicrobial treatment is indicated (123).

Indwelling Urethral Catheter
Most patients with short-term indwelling catheters receive concomitant antimicrobial therapy (32, 170). Antimicrobial therapy given for any indication delays the onset of bacteriuria and decreases the prevalence of bacteriuria at catheter removal (170). A randomized, controlled trial of catheter irrigation with either neomycin-polymyxin or saline reported no decrease in bacteriuria with the antimicrobial solution, perhaps because irrigation required disconnecting the catheter tubing (171). Bacteria isolated from patients receiving the antimicrobial irrigation solution had increased antimicrobial resistance. A clinical trial enrolling intensive care unit patients reported no differences in mortality, duration of intensive care unit stay or duration of hospitalization in patients randomized to catheter replacement with treatment of bacteriuria compared with the catheter remaining in situ without antimicrobial treatment (172).

Clinical trials evaluating treatment of asymptomatic bacteriuria when an indwelling catheter is discontinued report conflicting results. A non-blinded Swiss study of patients not otherwise receiving antimicrobials reported a significantly decreased frequency of symptomatic infection (4.9% vs 21.6%) and of bacteriuria when three doses of TMP/SMX were given at catheter removal (173). However, a blinded trial in male surgical patients comparing a single dose of ciprofloxacin, TMP/SMX, or no antibiotics at catheter removal reported no differences in bacteriuria or symptomatic infections for 14 days following removal, but increased isolation of ciprofloxacin resistant organisms from infections (174). Another blinded pilot study enrolling patients not otherwise receiving antimicrobials reported a 48 hour course of ciprofloxacin or placebo at catheter removal was followed by a similar frequency of symptomatic infection in the two groups, but patients who received ciprofloxacin were more likely to have resistant organisms isolated (175). In women requiring a short-term indwelling catheter, with a negative urine culture at catheter insertion, and with bacteriuria persisting 48 hours following catheter removal, TMP/SMX treatment at 48 hours significantly decreased the frequency of symptomatic urinary infection during the subsequent 14 days, from 17% of untreated patients to none (176). This was a highly selected patient population and the generalizability of the effect needs confirmation in further clinical trials.

A prospective, randomized trial in nursing home residents with chronic indwelling catheters reported that cephalexin treatment of bacteriuria did not decrease subsequent symptomatic episodes compared with no antibiotics, but in the treated population cephalexin resistant organisms were isolated from 30% of re-infections (177). A prospective, non-comparative study of consecutive courses of antimicrobial treatment given to eradicate bacteriuria in elderly patients with chronic catheters also reported no decrease in fever episodes compared with the historical pretreatment period and immediate recurrence of bacteriuria following therapy, often with an organism of increased resistance (178). Patients with chronic indwelling catheters given trimethoprim/sulfamethoxazole or no antimicrobials had a similar incidence of bacteriuria (59). A randomized, double-blind study enrolled 89 patients with neurologic conditions and indwelling catheters to one of 3 bladder irrigations—sterile saline, acetic acid, or neomycin/polymyxin (179). During the 8-week study, none of the three irrigating solutions altered the frequency of bacteriuria or pyuria in the 52 patients who completed the study.
Thus, studies consistently report no benefits with treatment of asymptomatic bacteriuria while the catheter remains in situ. The risks or benefits of treatment of asymptomatic bacteriuria acquired during catheterization and persisting following catheter removal remain controversial. Currently, treatment of bacteriuric patients at the time of catheter removal cannot be recommended, but further studies to address this question are necessary.

**Patients with Spinal Cord Injury**

A randomized, double-blind, placebo-controlled, 16-week trial enrolled 112 men and 17 women with acute spinal cord injury managed with intermittent catheterization (180). Treated patients received TMP/SMX one-half tablet daily, with additional treatment for breakthrough bacteriuria. The 50% weekly prevalence of bacteriuria decreased to 30% in antimicrobial treated patients compared with 56% of placebo patients. At least one episode of symptomatic infection was experienced by 7% of men receiving TMP/SMX and 35% with placebo, but there was no decrease for women. However, 95% of recurrent bacteriuria episodes in the treatment group and 50% in placebo were with TMP/SMX resistant organisms. Men with chronic spinal cord injury for at least 6 months and using any type of bladder management were randomized to continue or discontinue daily TMP/SMX prophylaxis and followed with weekly urine cultures for a minimum of 3 months (109). Episodes of asymptomatic bacteriuria were 0.241 per week in controls and 0.243 with continued TMP/SMX, while 76% of control urine cultures and 65% from TMP/SMX patients were positive. Symptomatic urinary tract infection occurred with similar frequency in the two groups. Organisms isolated were resistant to TMP/SMX in 78% of controls and 94% receiving TMP/SMX.

In a non-comparative study with uniform treatment of asymptomatic bacteriuria in a cohort of primarily men with spinal cord injury, patients managed with intermittent catheterization or condom drainage reported prompt recurrence of bacteriuria after antimicrobial treatment (181). Following a course of antibiotics of 7 or 14 days, 93% of patients were again bacteriuric by 1 month. When the duration of antimicrobial therapy was increased to 4 weeks, 85% were bacteriuric within 1 month. A prospective, randomized controlled trial of antimicrobial treatment or no treatment of bacteriuria in a small number of patients with spinal cord injury and bacteriuria reported a similar frequency of symptomatic urinary tract infection in the two groups during an average of 50 days follow-up (182).

Thus, clinical trials report no benefits with treatment of asymptomatic bacteriuria in patients with spinal cord injury irrespective of bladder management. The National Institute on Disability and Rehabilitation Research Consensus Statement recommends that asymptomatic bacteriuria in patients with spinal cord injury should not be treated (183).

**Invasive Genitourinary Procedures**

Antimicrobial therapy initiated for bacteriuric patients prior to an invasive urologic procedure decreases the risk of post-procedure bacteremia and sepsis (1). This is a strategy of peri-operative surgical prophylaxis rather than treatment of asymptomatic bacteriuria, per se (148). Antimicrobial therapy is indicated for any bacteriuric patient undergoing an invasive genitourinary procedure associated with mucosal trauma and bleeding (184–188). Clinical trials do not identify a preferred regimen, but a single dose given 1 hour prior to the procedure is usually effective, similar to other surgical prophylaxis regimens (189).

**Other Populations**

Renal transplant patients receive antimicrobial prophylaxis, usually with TMP/SMX, for 6 months following transplantation, and this reduces the frequency of asymptomatic bacteriuria as well as of symptomatic infections. A non-randomized retrospective case-control study from Switzerland described 334 episodes of *E. coli* or Enterococcal bacteriuria in 77 renal transplant recipients (190); 101 (30%) episodes were treated with antimicrobials. Subsequent symptomatic urinary tract infection was similar for treated or untreated patients, but resistant organisms were isolated from 78% of the treated group with recurrent infection. Current renal transplant guidelines do not recommend routine screening for bacteriuria in renal transplant patients.

A prospective cohort study stratified women with multiple sclerosis into three groups—those using intermittent catheterization, those with post-void residual (PVR) >100 ml but not using intermittent catheterization, and women with no evidence of bladder dysfunction (191). Bacteriuria present at study enrollment was treated and urine cultures repeated monthly for 6 months, with further appropriate antimicrobial therapy given for eradication of recurrent bacteriuria. After a first episode of recurrent bacteriuria, long-term prophylaxis with nitrofurantoin 100 mg daily was initiated for all women, and if there was further recurrent bacteriuria on nitrofurantoin, norfloxacin prophylaxis was instituted. The prevalence of any episode of bacteriuria
during 6 study months was 90% of women using intermittent catheterization, 34% with increased PVR but not using a catheter, and 24% in the normal-voiding group. Bacteriuria developed on prophylactic antimicrobial therapy in 31% of the intermittent-catheter group and 22% of women with elevated PVR, but in none of the patients with normal bladder function; 14% of patients in the intermittent-catheter group developed symptomatic infection but none in the other groups. Thus, a strategy of treatment of bacteriuria and antimicrobial prophylaxis was not effective for patients using intermittent catheterization.

A double-blind, placebo-controlled study of patients with asymptomatic candiduria, about one-half of whom had indwelling catheters, reported a significantly lower prevalence of candiduria at the end of 14 days fluconazole treatment, but no difference 2 weeks following the end of treatment (192).

**BACTERIAL INTERFERENCE**

Bacterial interference describes the therapeutic strategy of establishing persistent asymptomatic bacteriuria using an avirulent bacterial strain with the goal of preventing symptomatic infection. This approach was suggested following observations from clinical and epidemiologic studies that repeatedly describe an increased frequency of acute symptomatic urinary tract infection shortly after antimicrobial therapy in girls (108), adult women (97), diabetic women (18) with bacteriuria, and in the general adult female population (113, 114). Asymptomatic bacteriuria is hypothesized to prevent symptomatic infection by interfering with persistence of virulent uropathogens in the bladder. Potential mechanisms include inhibiting adherence by blocking uroepithelial cell receptors, competition for nutrients, or production of toxins that inhibit the virulent strain (193).

An initial study described eight women with chronic symptomatic urinary infection and catheter instillation into the bladder of either the avirulent *E. coli* 83972 strain (85, 86, 194), the same strain transformed with pap and pil adhesins, or both strains together (195). The avirulent *E. coli* 83972 strain persisted beyond 30 days in more than 50% of patients, while the virulent transformant elicited a vigorous local inflammatory response leading to elimination within 2 days. These observations were the basis for further clinical studies of the *E. coli* 83972 strain, and an *E. coli* HU2117 strain derived from *E. coli* 83972 by deletion mutation of the papG gene (196, 197). Preliminary studies confirmed that extended bacteriuria was achieved in selected patients and appeared safe (195, 198–200), and that incomplete bladder emptying was necessary to establish bacteriuria (198). Coating indwelling catheters with the strain was one effective means of introducing the organism into the bladder (198).

Three prospective, randomized clinical trials have evaluated bacterial interference using the *E. coli* 83972 strain in selected patients experiencing frequent recurrent symptomatic infection. A blinded, prospective, randomized trial in the United States enrolled male patients with spinal cord injury, most with indwelling catheters (201); there were 21 experimental patients and 6 controls. Following a course of antibiotic therapy to resolve pre-existing bacteriuria, the therapeutic strain was instilled by catheter twice daily for 3 consecutive days. Colonization was successful in 13 (62%) experimental patients for an average duration of 3.5 months; 4 (31%) patients remained colonized for more than 12 months. For the clinical efficacy analysis, the 8 patients who failed colonization were combined with the 6 control patients and compared with successfully colonized patients while they remained colonized. The frequency of at least one symptomatic infection was significantly lower in the *E. coli* 83972 colonized patients. There were no serious toxicities, but 1 of 13 colonized patients developed symptomatic infection with a mixed bacterial culture, including the therapeutic strain isolated.

These same investigators proceeded to a multicenter randomized trial of patients with chronic spinal cord injury managed with indwelling or intermittent catheters and who had experienced two or more symptomatic infections in the previous year (196). Colonization with *E. coli* 83972 was achieved for only 30% of the experimental group. There was a significant difference in time to first symptomatic episode in colonized or saline inoculation placebo patients, but the analysis used a one-sided confidence interval and 66% of the experimental group and 37% of the placebo group were not included in the analysis. The occurrence of symptomatic infection in the two study arms did not diverge until more than 100 days following inoculation.

A randomized, blinded Swedish study using the *E. coli* 83972 strain enrolled only patients without an indwelling catheter (202). Twenty of 26 patients enrolled completed the full trial and were included in the analysis. Of the 20 patients who completed the trial, 12 patients were women, 12 patients used an intermittent catheter, and 8 patients used no catheter. Antibiotics were given to clear pre-existing bacteriuria and
the therapeutic strain instilled by catheter once daily for 3 days. In the first phase of the study, 13 of 18 (72%) patients were successfully colonized; the 5 not colonized were combined with 6 patients randomized to saline control for the outcomes analysis. At 1 year, colonized patients had significantly fewer symptomatic episodes. In a second phase of the study, patients were crossed over after 12 months or following a symptomatic episode. There were also significantly fewer symptomatic episodes in colonized patients after the crossover.

Bacterial interference to prevent symptomatic urinary infection is an attractive concept, which could limit morbidity and antimicrobial exposure for some patients with frequent symptomatic infections. Evidence to date suggests this approach may be effective for a limited number of selected individuals for a limited duration. However, the randomized clinical trials supporting efficacy are compromised by problems with study design and analysis. Further clinical studies are needed to characterize patient populations most likely to benefit from this approach, standardize effective instillation techniques, and explore strategies to increase the duration of colonization. The impact of host genetic variation on the likelihood of establishing colonization should be evaluated. Given the propensity for genetic evolution of E. coli strains isolated from persistent bacteriuria, deliberate instillation of a potentially pathogenic organism remains conceptually problematic (85, 203). Other safety issues include the need for antimicrobial therapy prior to instillation and repeated bladder catheterization to establish bacteriuria.

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REFERENCES

Asymptomatic Bacteriuria and Bacterial Interference


Asymptomatic Bacteriuria and Bacterial Interference


