

“Urinary Tract Infection”—Requiem for a Heavyweight

Thomas E. Finucane, MD

“Urinary tract infection” (“UTI”) is an ambiguous, expansive, overused diagnosis that can lead to marked, harmful antibiotic overtreatment. “Significant bacteriuria,” central to most definitions of “UTI,” has little significance in identifying individuals who will benefit from treatment. “Urinary symptoms” are similarly uninformative. Neither criterion is well defined. Bacteriuria and symptoms remit and recur spontaneously. Treatment is standard for acute uncomplicated cystitis and common for asymptomatic bacteriuria, but definite benefits are few. Treatment for “UTI” in older adults with delirium and bacteriuria is widespread but no evidence supports the practice, and expert opinion opposes it.

Sensitive diagnostic tests now demonstrate that healthy urinary tracts host a ubiquitous, complex microbial community. Recognition of this microbiome, largely undetectable using standard agar-based cultures, offers a new perspective on “UTI.” Everyone is bacteriuric. From this perspective, most people who are treated for a “UTI” would probably be better off without treatment. Elderly adults, little studied in this regard, face particular risk. Invasive bacterial diseases such as pyelonephritis and bacteremic bacteriuria are also “UTIs.”

Mindful decisions about antibiotic use will require a far better understanding of how pathogenicity arises within microbial communities. It is likely that public education and meaningful informed-consent discussions about antibiotic treatment of bacteriuria, emphasizing potential harms and uncertain benefits, would reduce overtreatment. Emphasizing the microbiome’s significance and using the term “urinary tract dysbiosis” instead of “UTI” might also help and might encourage mindful study of the relationships among host, aging, microbiome, disease, and antibiotic treatment. *J Am Geriatr Soc* 65:1650–1655, 2017.

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From the Johns Hopkins Bayview Medical Center, Baltimore, Maryland.

Address correspondence to: Thomas E. Finucane, MD, Johns Hopkins Bayview Medical Center, 5200 Eastern Ave., MFL-C, Suite 2200, Baltimore, MD 21224. E-mail: tfinucan@jhmi.edu

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“Urinary tract infection” (“UTI”) is among the most-common reasons for antibiotic treatment in humans. Its definition is ambiguous (Table 1), as are definitions of “significant bacteriuria” and “symptoms referable to the urinary tract”—two frequently cited diagnostic criteria. These ambiguities, sometimes accompanied by an explicit belief that “bacteria are not normal inhabitants of the urinary tract,”¹ encourage extensive antibiotic overtreatment of bacteriuria. Elderly adults are especially endangered. Current treatment paradigms rely for diagnosis on bacteriuria identified using standard laboratory cultures, hereinafter called standard bacteriuria. Clear evidence shows that urine is not sterile² but instead that the urinary tract hosts a complex, generally beneficial microbiome. These findings are not integrated into clinical practice. Recognition of the urinary microbiome’s significance should ultimately advance efforts to limit overtreatment.

This discussion has important limitations. It concerns noncatheterized, medically stable adults without structural or functional urinary tract abnormalities. Most studies focus on young and middle-aged women; data on men and elderly adults are far sparser. Pregnant women and individuals soon to undergo urologic surgery, who benefit from antibiotic treatment of asymptomatic bacteriuria,³ are not considered here. Persons with spinal cord injury and those ill enough to require urgent antibiotic treatment regardless of urinary findings are also not considered here. Invasive bacterial diseases, such as bacteremic bacteriuria and pyelonephritis, arise in the urinary tract and, like pneumonia in the respiratory tract, can be lethal without antibiotic treatment. At both sites, most “infections” should not be treated. Identifying when benefits of treatment outweigh burdens in respiratory infections and “UTI” is a complex, essential task that is considered here only in passing. Finally, rapid advances in understanding of the relationship between microbiome and disease may quickly render this discussion obsolete. The urinary tract virome,⁴ for example, is ignored in clinical decision-making but may be as important to “UTI” as the respiratory tract virome is to “upper respiratory infection.”

CURRENT DIAGNOSIS

“Bacteriuria”

Cultures done on agar-based media, used since the 19th century to determine presence or absence of bacteria, are

Table 1. Representative Definitions of “Urinary Tract Infection” (“UTI”)

Definition	Example
Bacteriuria	“in all of the included studies, UTI was defined by the presence of (bacteriuria).” ⁷
Bacteriuria and urinary symptoms	“UTI refers to significant bacteriuria in a patient with symptoms or signs attributable to the urinary tract and no alternate source. Asymptomatic bacteriuria (ASB) refers to significant bacteriuria in a patient without symptoms or signs attributable to the urinary tract. Bacteriuria is a non-specific term that refers to UTI and ASB combined.” ¹
Urinary symptoms	“study to describe the course of lower urinary tract infection . . . (included women with) . . . urgency, dysuria, suprapubic pain, and loin pain” ¹⁴
Subset of “infection of the urinary tract” ¹	“CA-UTI, CA-ASB, and CA-bacteriuria are each considered to represent infection of the urinary tract, because bacteria are not normal inhabitants of the urinary tract.”

CA=catheter associated.

used to determine whether urine is sterile or there is bacteriuria. (For brevity, the terms “asymptomatic bacteriuria” and “significant bacteriuria” will hereafter refer to bacteriuria identified using standard agar-based cultures, standard bacteriuria, as is done in current practice.)

“Significant Bacteriuria”

In 1956, it was proposed that, “contamination may be distinguished from true bacilluria by quantitation of the numbers of bacteria in the urine.” “True bacilluria” meant bacilluria resulting from “actual multiplication of bacteria within the urinary tract.” A count of 10^5 was chosen “arbitrarily as the dividing line.”⁵ Also in 1956, the phrase “significant bacteriuria” was used to indicate that “clinically significant infection is present. . . [a] degree of bacteriuria approximating 10^3 . . . is required for the certain diagnosis of infection.”⁶ In the subsequent 6 decades, the “dividing line” has remained approximate and arbitrary. Clinical studies have defined “significant bacteriuria” with thresholds ranging from 100 to 100,000 bacteria per mL.⁷ The significance of “significant bacteriuria” remains only that the bacteriuria is unlikely to have resulted from contamination. No threshold colony count identifies individuals who are more likely to become ill or to benefit from antibiotic treatment.

“Symptoms Referable to the Urinary Tract”

Definition and ascertainment of “urinary tract symptoms” are highly imprecise. A systematic review of symptoms and signs to diagnose “UTI,” which was defined as significant bacteriuria, found that “none of the identified studies described the precision of the history or physical examination in the diagnosis of UTI.” The summary prevalence of significant bacteriuria in individuals with urinary symptoms was 48%.⁷

A previous study showed that “lower urinary tract symptoms” are not related to standard bacteriuria in nondysuric ambulatory older men and women (mean age 85). Serial symptom questionnaires and urine cultures were used to identify a group of individuals who had standard bacteriuria at one time and not at another. The questionnaire asked about lower urinary tract symptoms other than dysuria (e.g., frequency, urgency, suprapubic pain) and about symptoms of well-being (anorexia, sleep disturbance, fatigue, malaise, weakness). “No differences in symptoms were found when bacteriuric subjects were compared with themselves when they were nonbacteriuric . . . bacteriuria without dysuria in the elderly seems to be asymptomatic.”⁸

Urinary tract symptoms do not reliably indicate risk or presence of “bacteremic bacteriuria” (sometimes also called “bacteremic UTI” or “urosepsis”) or pyelonephritis. In a representative study of individuals with bacteremia, the same bacterial species cultured from the urine, and ascertainment of symptoms, only one of 37 participants aged 75 and older had dysuria.⁹ In individuals diagnosed with pyelonephritis, urinary symptoms are uncommon enough that they are not integrated in many clinical definitions. Further complicating the diagnosis of pyelonephritis, “flank” and “loin” may refer generally to any non-midline lower abdominal, lumbar, or inguinal region or, in men, to scrotal contents.

Pyuria

Pyuria is common in elderly adults with bacteriuria. No evidence suggests that its presence is related to the likelihood of benefit from antibiotic treatment. “Pyuria accompanying bacteriuria is not an indication for antimicrobial treatment.”³

CURRENT TREATMENT

Acute Uncomplicated Cystitis

Antibiotic treatment for individuals with acute dysuria and significant bacteriuria is standard of care, but five randomized placebo-controlled trials show no benefit beyond modestly faster symptom improvement.¹⁰ In the two trials that reported episodes of pyelonephritis and in a separate metaanalysis of five antibiotic treatment trials, the incidence of pyelonephritis was low and approximately the same in individuals receiving placebo as in those receiving antibiotic treatment.¹¹ A randomized trial of approximately 500 women younger than 65 compared ibuprofen with fosfomycin for treatment of acute cystitis. The incidence of pyelonephritis was approximately the same in the two groups, and all affected women recovered fully with outpatient treatment. Improvement in symptom scores in women with acute cystitis assigned to ibuprofen lagged approximately 1 day behind those of women treated with antibiotics. A safe, effective urinary analgesic would be an important advance in reducing antibiotic use. At 28 days, the group assigned to fosfomycin had received 283 course of antibiotics, compared with 81 in the ibuprofen group.¹²

Lower urinary tract symptoms do not herald serious illness. “Acute uncomplicated cystitis rarely progresses to

severe disease, even if untreated; thus, the primary goal of treatment is to ameliorate symptoms.”¹³ The situation is fluid, with frequent spontaneous resolution of bacteriuria and of symptoms.^{8,14} “The generally benign (other than symptoms) nature of ‘symptomatic UTI’ is suggested by the billions of persons around the world and over the eons who have suffered ‘UTI’ without access to antibiotics and have recovered fully.”¹⁵

Asymptomatic Bacteriuria

Pregnant women and individuals scheduled to undergo invasive urinary tract procedures benefit from treatment of asymptomatic bacteriuria. Strong evidence confirms that antibiotic treatment is not beneficial in most other groups that have been studied, including elderly men and women living at home or in institutions, persons with spinal cord injury, catheterized individuals while the catheter remains in place, women with diabetes mellitus, and premenopausal, nonpregnant women.³ Despite this evidence, antibiotic treatment of asymptomatic bacteriuria is common, perhaps because it may be diagnosed as a “UTI” and out of concern that “bacteria are not normal inhabitants of the urinary tract”¹ (Table 1).

“UTI” in the Emergency Department

Of 25.4 million U.S. adult emergency department (ED) visits over 8 years during which “UTI” was diagnosed, urinary symptoms were identified in only 32%. Of individuals aged 85 and older, 17% had urinary symptoms.¹⁶

Delirium and Other Geriatric Syndromes

No evidence suggests that antibiotic treatment of bacteriuria improves outcomes in individuals with delirium, falls, confusion, or other geriatric syndromes.^{17,18} Guidelines and consensus statements do not recommend testing for, making the diagnosis of, or treating a “UTI” in otherwise asymptomatic, noncatheterized long-term care residents who become delirious, even if they are febrile (Table 2). Antibiotic treatment for the combination of fever and delirium is accepted, regardless of urinary tract findings, elsewhere in the statement.²⁹

Nonetheless, the practice is extremely common. One study followed 551 nursing home residents for 1 year, for example, and found that the three most-common reasons for suspecting “UTI” and sending a urine culture were altered mental status (39%), change in behavior (19%), and change in character of the urine (16%), trailed by dysuria (8%), falls, syncope, and several other indications. Approximately one-third of these residents who had cultures done had standard bacteriuria.¹⁹ The prevalence of standard bacteriuria discovered incidentally in nursing home residents who are well ranges from 15% to 50%.³

Sepsis

Initiatives encouraging prompt antibiotic treatment of early sepsis necessarily set low thresholds for diagnosis. In individuals with suspected infection who are not in the intensive care unit, the Quick Sequential [Sepsis-related]

Table 2. Expert guidance about delirium and bacteriuria in institutionalized, non-catheterized patients who become delirious. None identify delirium as a reason to culture the urine or initiate antibiotic treatment

1. Surveillance Definitions of Infections in Long-Term Care Facilities: Revisiting the McGeer Criteria.²⁷

“Surveillance Definitions for Urinary Tract Infections [abridged]

- A. For residents without an indwelling urinary catheter (both 1 and 2 must be present)
 1. At least one of
 - a. Acute dysuria or acute pain, swelling or tenderness of testes, epididymis, or prostate.
 - b. Fever or leukocytosis and at least one of Pain at (i) costovertebral angle or (ii) suprapubic area Gross hematuria (iii) New or worse urinary incontinence (iv), urge (v), or frequency (vi)
 - c. Without fever or leukocytosis, at least 2 of (ii) – (vi).
 2. Significant bacteriuria

Comment. UTI should be diagnosed when there are localizing genitourinary signs and symptoms and a positive urine culture result. A diagnosis of UTI can be made without localizing symptoms if a blood culture isolate is the same as the organism isolated from the urine and there is no alternate site of infection. In the absence of a clear alternate source of infection, fever or rigors with a positive urine culture result in the non-catheterized resident or acute confusion in the catheterized resident will often be treated as UTI. However, evidence suggests that most of these episodes are likely not due to infection of a urinary source.”

Note: Non-catheterized residents who become delirious and who have bacteriuria, fever and leukocytosis do not meet the definition of “UTI.”

2. Clinical Practice Guideline for the Evaluation of Fever and Infection in Older Adult Residents of Long-Term Care Facilities: 2008 Update by the Infectious Diseases Society of America.²⁸

“13. In noncatheterized residents, the diagnostic laboratory evaluation of suspected UTI should be reserved for those with acute onset of UTI-associated symptoms and signs (e.g., fever, dysuria, gross hematuria, new or worsening urinary incontinence, and/or suspected bacteremia) (A-II).”

Note: For non-catheterized residents of long-term-care facilities, delirium is not a reason to send laboratory tests for UTI.

3. Development of Minimum Criteria for the Initiation of Antibiotics in Residents of Long-Term Care Facilities: Results of a Consensus Conference²⁹

(re: UTI). “For residents who do not have an indwelling catheter, minimum criteria for initiating antibiotics include acute dysuria alone or fever (>37.9°C [100°F] or 1.5°C [2.4°F] increase above baseline temperature) and at least one of the following: new or worsening urgency, frequency, suprapubic pain, gross hematuria, costovertebral angle tenderness, or urinary incontinence.”

Note: For non-catheterized residents of long-term-care facilities who are febrile, delirium is not a reason to initiate antibiotics for “UTI”. Elsewhere in the Consensus, however, antibiotic treatment for the combination of fever and delirium is accepted, regardless of urinary tract findings.

4. American Geriatrics Society identifies five things that healthcare providers and patients should question³⁰

“Don’t use antimicrobials to treat bacteriuria in older adults unless specific urinary tract symptoms are present.”

Organ Failure Assessment identifies individuals as being at high risk and in need of “timely management” if two or three of the following criteria are met: respiratory rate greater than 22 breaths per minute, systolic blood pressure of 100 mm Hg or less, and altered mental status, defined as a Glasgow Coma Scale score less than 15.²⁰ This threshold endangers frail elderly adults, and considering “UTI” to be a “suspected infection” lowers the threshold further. Chronic stable confusion, as with dementia, will reduce the Glasgow Coma Scale score to 14, confirming “altered mental status.” If mild transient vital sign abnormalities occur, the individual qualifies for “timely management.” Unmindful application of these criteria can lead to serious overtreatment and perhaps a missed diagnosis of other causes of delirium.

Delirium accompanies several serious illnesses, but in individuals with limited cognitive reserve, minor perturbation can lead to delirium. Individuals with new delirium require careful, ongoing evaluation and prompt treatment if they become unstable. For those who are otherwise stable, it is likely that surveillance without antibiotic treatment is preferable.¹⁷ Deciding when a person has become sick enough to require antibiotics is a challenge. The presence of standard bacteriuria should not be part of that decision.

Joint Replacement Surgery

An observational study of 1,497 individuals undergoing joint replacement found asymptomatic bacteriuria in 12%. At 1-year follow-up the, rate of prosthetic joint infection was three times as high in individuals with bacteriuria (4.3%) as in those without (1.4%) ($P < .001$), but antibiotic treatment of bacteriuria did not reduce the risk of infection, and “microorganisms isolated in prosthetic joint infections were not the same as those in preoperative urine cultures in any patient with asymptomatic bacteriuria.”²¹ As with incident delirium, bacteriuria seems to be more a marker of vulnerability than a cause of disease.

INSIGHTS FROM THE MICROBIOME

Urinary Tract

The urine-bearing urinary tract extends without interruption from Bowman’s capsule to the urethral orifice, essentially a part of the body surface. Continuous production of urine presents perineal and ascending microbes with a reliable supply of nutrition. The biological plausibility of a sterile urinary tract is quite low.

Infection

The urinary tract resembles the respiratory tract, also an open system (from alveolus to nose and mouth). Both are traditionally considered sterile, and both have been demonstrated to host complex microbial communities. Gene sequencing techniques have identified a ubiquitous, diverse community of bacterial species in the urinary tract that are uncultivable using standard techniques,²² hereinafter called uncultivable bacteria. The viability of most uncultivable bacteria has been confirmed using more-sensitive expanded quantitative urine cultures.² Intracellular

bacterial colonies and a urinary virome, not detected using standard cultures and of unknown pathogenicity, have also been identified.⁴

The pathogenic role of uncultivable bacteria remains unknown. A woman with *Escherichia coli* “UTI” on standard cultures but much less *E. coli* deoxyribonucleic acid (3% of total sequences) according to gene-sequencing techniques than *Aerococcus* (40% of sequences) and *Actinobaculum* (25% of sequences) was reported.²² In current practice, a polymicrobial culture result is considered to be uninformative, but this study suggests microbial communities may play an unexpected role in pathogenicity. Basing antibiotic treatment on the results of standard cultures is difficult to justify and has not been shown to be beneficial in individuals with asymptomatic bacteriuria or acute cystitis.

A trial of 673 women (mean age 39) with asymptomatic bacteriuria and a history of recurrent “symptomatic UTI” demonstrated potential harm to the microbiome from antibiotic treatment. Women randomized to treatment were more likely to have “symptomatic UTI” over 1 year of follow-up than those randomized to no treatment. The authors conclude that asymptomatic bacteriuria “may play a protective role in preventing symptomatic recurrence.”²³ In 27 months of additional follow-up, recurrent “symptomatic UTI” and prevalence of antibiotic-resistant bacteria were significantly higher, quality of life was significantly poorer, and pyelonephritis was more common, although not significantly so, in the treated group.²⁴

CONCLUSION

Significant bacteriuria and urinary symptoms are common, often occur together, and generally resolve spontaneously. Neither is strongly linked to serious urinary tract disease or to likelihood of benefit from antibiotic treatment, with the limited exceptions discussed above. In individuals with standard bacteriuria who develop geriatric syndromes such as delirium, no data suggest benefit from treatment. Nonetheless, treatment for “UTI” is common for individuals with symptoms, bacteriuria, or both and for those with delirium and standard bacteriuria.

Attempts to improve management of bacteriuria in elderly adults face familiar clinical problems. First, clinical trials focus mainly on younger subjects and do not readily generalize to elderly adults. A greater prevalence of structural and functional urinary tract abnormalities, mobility impairment, and impaired immune function, for example, may alter benefits and burdens of treatment in unpredictable ways. Second, harms from undertreating invasive disease may be severe. Third, harms from overtreatment may also be severe. Studies of symptoms, urine dipstick findings, and colony counts on standard cultures cannot define which subsets of individuals will benefit from antibiotics directed to the urinary tract. Intervention trials will be necessary to develop an evidence base for management decisions.

Current management strategies logically require the improbable belief that only organisms identifiable using agar-based culture are worthy of concern. A more likely explanation for clinician behavior, although less logical,

would be a characteristic cognitive error that has been called WYSIATI or “What you see is all there is.” Many decisions are made unthinkingly, relying only on evidence that is easily accessible. “The confidence that individuals have in their beliefs depends mostly on the quality of the story they can tell about what they see, even if they see little.”²⁵ Treatment decisions often seem to rely on the diagnosis of “UTI” to justify treatment. In the decision to treat bacteriuria in individuals with incident delirium, for example, infection can cause delirium, “UTI” is an infection (a key step), standard bacteriuria is a “UTI,” antibiotic treatment for standard bacteriuria should help resolve delirium, and delirium frequently does resolve with treatment. The quality of this story is high enough that clinicians routinely ignore two reproducible but less immediately accessible findings. First, bacteriuria is present in all individuals, with or without delirium. Second, delirium and bacteriuria can each resolve spontaneously.

A small study further suggests that the term “UTI” plays an important role in decisions to treat. When urine specimens obtained from asymptomatic, noncatheterized medical and surgical inpatients (mean age 79) were positive, the results were not conveyed to clinicians. Instead, the following modified report was posted to the electronic medical record. “The majority of positive urine cultures from inpatients without an indwelling urinary catheter represent asymptomatic bacteriuria. If you strongly suspect that your patient has developed a urinary tract infection, please call the microbiology laboratory.” Physicians called for only five of the 37 modified reports, and antibiotic treatment rates fell from 48% to 12%. At 72 hours no patient had a “UTI” or sepsis.²⁶ Simply calling out the ambiguity of “UTI” reduced overtreatment.

Repetitively calling out the ambiguity of “UTI,” for example by annotating it with quotation marks in text and the bimodal “air quotes” sign in conversation, might be similarly effective.¹⁵ New nomenclature seems likely to be important. Replacing “UTI” with “bacteriuria” plus modifiers seems preferable (e.g., bacteriuria with dysuria, bacteriuria with delirium). The phrase “urinary tract dysbiosis” could be applicable to most scenarios now called “UTI” without the connotation that antibiotics are indicated.

It is likely that careful discussion of risks and benefits would reduce antibiotic overuse. For individuals with acute uncomplicated cystitis, the limited benefit (symptom control) and important risks of antibiotic treatment should be disclosed, and many people would accept temporizing measures. In one trial of individuals with acute cystitis, 72% of 1,605 participants agreed to placebo-controlled randomization.¹⁴ If a safe, effective urinary tract analgesic were available, the rate might be even higher. Decision-making with or on behalf of long-term care residents with bacteriuria who develop delirium should also include disclosure of the high prevalence of asymptomatic bacteriuria in stable residents, the corresponding likelihood that the bacteriuria is coincidental, lack of evidence of benefit from treatment, risks imparted by treatment, and consistent expert advice counselling against treatment. Public education would also help because some individuals and their families resolutely expect antibiotic treatment on hearing the diagnosis of “UTI.”

“UTI” remains deeply entrenched in clinical medicine, fortified by familiarity, convenience, the generally good outcomes that follow antibiotic treatment of generally self-limited syndromes, and a now-fading biological plausibility. In current practice, “I think this patient has a UTI” often means, “I want to give this patient antibiotics.” Clinicians considering intervention should not ask whether the individual has a real “UTI” but should ask instead whether there is evidence that antibiotic treatment directed at standard bacteriuria is more likely to benefit than harm this individual. Microbiome studies suggest that treatment is even less beneficial and more harmful than is already believed. Clinicians have a major opportunity to improve care and public health.

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