To Treat or Not to Treat: UTI or Bacteriuria?

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INTRODUCTION

An 85-year-old male nursing home resident with dementia is admitted with altered mental status and decreased oral intake in the last 3 days. There has been a recent medication change and his dose of quetiapine had to be decreased due to a prolonged QT interval. He was afebrile and hemodynamically stable. On exam, he was found disoriented to time and place. He had no costovertebral or suprapubic tenderness on palpation. His complete blood count showed a WBC of 7000 per microliter. The staff noted some cloudiness in the urine the day prior to admission. Urine was sent for urinalysis (UA) showing +Leukocyte esterase (LE), pyuria [40–60 white blood cells (WBCs)], and few bacteria. Reflex urine culture grew >100,000 colony-forming units (CFU)/mL of *E. coli*.

a. Start ciprofloxacin for *E. coli* UTI
b. Start broad-spectrum antibiotics pending infectious work-up
c. Restart the higher dose of quetiapine and give Haldol to calm the patient down
d. Hold antibiotics, hydrate and continue a careful work-up for metabolic issues and medication side effects.

This case may seem familiar to many of us in medicine. When we see a patient with a positive urine test, there is an automatic need to react to it. As a result, many patients like the one described above end up receiving unnecessary antibiotics. Inappropriate use of antibiotics is associated with an increased risk for complications affecting not only our patients but also healthcare systems.

This article provides a summary of UTIs, catheter-associated UTIs, and asymptomatic bacteriuria. Understanding the difference between these etiologies is crucial for appropriate diagnosis and management.

URINARY TRACT INFECTIONS (UTIS)

To accurately diagnose a UTI, patients must have symptoms with or without a positive urine culture. Symptoms of UTI include dysuria, urgency, hesitance, frequency, new incontinence. Other constitutional symptoms such as fever, chills, can also be present in the acute setting. An infection of the lower urinary tract can progress in an ascending fashion until reaching the kidneys, causing pyelonephritis. Patients with significant constitutional symptoms and hemodynamic instability may present with changes in mental status. However, altered mental status, change in urine color, cloudy urine or foul-smelling urine alone should NOT be used to diagnose a UTI.[1]

Urine is often easy to collect and is often "positive." The bladder is not as sterile as we are taught, particularly in the elderly. We have relied on using pyuria for the definition of UTI and although its absence is associated with a 96% negative predictive value (NPV) for bacteriuria, its presence has a low (39%) positive predictive value (PPV) for bacteriuria. About 75–90% of patients with asymptomatic bacteriuria (ASB) do not develop a systemic inflammatory response or other signs or symptoms to suggest infection. Treatment of ASB does not effectively prevent symptomatic UTI.

The clinical significance of asymptomatic bacteriuria in catheterized patients is undefined. A significant proportion, 15-25% of hospitalized patients, may receive indwelling catheters. In many cases, catheters are placed for inappropriate indications and healthcare providers are often unaware that their patients have catheters, leading to prolonged unnecessary use. National data from NHSN acute care hospitals in 2006 showed a range of a pooled mean CAUTI rates of 3.1–7.5 infections per 1000 catheter days. The highest rates of CAUTIs were in burn ICUs followed by inpatient medical wards and neurosurgical wards. The lowest rates are in med-surg ICUs. An estimated 17–69% of CAUTI may be preventable with recommended infection control measures, up to 380,000 infections and 9000 deaths related to CAUTI per year could be prevented.

In addition, catheters may be used disproportionately in long-term care (LTC) facilities. The rate of catheter use for managing chronic voiding dysfunction in LTC residents ranges from 7–10%.[2] In non-catheterized residents, asymptomatic bacteriuria has been estimated at 18% to 57% for women and 19% to 38% for men.

ASYMPTOMATIC BACTERIURIA (ASB)

Asymptomatic bacteriuria (ASB) is defined as the absence of clinical symptoms suggesting a UTI in the setting of presence of at least one type of bacteria in the urine at a concentration of >10^5 cfu/mL or >10^8 cfu/mL, independent of the presence of white blood cells.

The estimated prevalence of ASB varies based on the age

cohort and patient population. ASB is more prevalent in men and women living in a long-term care facility (up to 50%) followed by elderly persons (>70 years old) living in the community (10.8 to 16% in women and 3.6 to 19% in men).[3] Persons with spinal cord injury requiring intermittent catheterization and sphincterotomy/condom catheter was as high as 69% and 57%, respectively.[4,5] One study has even reported a 100% prevalence of asymptomatic bacteriuria in persons with indwelling catheters.[6]

The risk of developing bacterial colonization in patients with indwelling catheters is directly proportional to the length of time the catheter will remain in place. Bacteriuria due to catheterization is acquired at a rate of 3–10% per day, the majority of whom are asymptomatic.[7] By 30 days, 100% of patients with a catheter will show bacteria in a urine specimen. The duration of catheterization and antibiotic use also influences the incidence of bacteriuria and candiduria.

As we describe in the recommendations below, the vast majority of people with asymptomatic bacteriuria do not need screening or treatment, except for two groups: pregnant women (rates of asymptomatic bacteriuria can be as high as 9.5%)[8] and patients undergoing invasive urological procedures. Urological procedures can be classified as low, intermediate and high risk, depending on mucosal irritation, length of procedure, or potential invasion of colorectal space (class III/contaminated procedures as transrectal prostate bx).

IDSA RECOMMENDATIONS FOR MANAGEMENT OF ASB

The Infectious Diseases Society of America (IDSA) guidelines for asymptomatic bacteriuria were released in March 2019. These guidelines highlight the importance of identifying patients in whom screening for ASB is needed in order to prevent UTIs. Most importantly, they provide recommendations regarding which groups should or should not be screened for the presence of bacteria in the urine.

Table 1 summarizes these recommendations, which include different groups of adults with asymptomatic bacteriuria. In regard to the management of asymptomatic candiduria, which are not included in these guidelines, IDSA guidelines for the management of candidiasis,[9] recommends removal of predisposing factors (ie indwelling catheter), when feasible. No antifungal treatment is recommended unless patient is at risk for disseminated infection (neutropenic patients or patients undergoing urologic invasive procedure).

Compared to 2005 guidelines, current guidelines highlight the importance of recognizing non-focal symptoms that historically have been attributed to a UTI. Many patients, especially the elderly, are at higher risk for delirium, changes in mental status, and falls. Similarly, these people are at higher risk for having bacteriuria. This association has led to many overdiagnosis of UTIs, thus overutilization of antibiotics and higher likelihood for patients to develop complications.

Table 1.

Group	Recommendation	
	Screening	Treatment
Healthy, premenopausal, non-pregnant women	NO screen	NO
Pregnant women	YES, screen with urine culture (UCX)	YES
Older person (men or women) functionally impared or living in long-term care facilities	NO screen	NO
Older person (men or women) functionally or cognitively impaired and non-localizing symptoms for UTI	NO screen -->Look for other causes of delirium	NO
Diabetic patients	NO screen	NO
Patients who have received a kidney transplant (>1 month prior)	NO screen	NO
Patients s/p non-renal solid organ transplant	NO screen	NO
Patients with high-risk neutropenia [absolute neutrophil count (ANC) <100 cells/mm3, ≥7 days' duration following chemotherapy]	Recommendation deferred	Recommendation deferred
Patients with spinal cord injury (SCI) leading to impaired voiding	NO screen	NO
Patients with a short-term (<30 days) indwelling urethral catheter	NO screen	NO
Patients undergoing elective non-urologic surgeries	NO screen	NO
Patients undergoing endoscopic urinary tract procedures/manipulation (Prior to transurethral resection of the prostate (TURP) or any other urologic procedure with a risk of mucosal bleeding)	YES, screen with UCX	YES Short course (1-2 doses) of targeted antimicrobial therapy 30-60 min prior to procedure
Patients planning to undergo surgery for an artificial urinary sphincter or penile prosthesis implantation	NO screen	NO

Outcomes or concerns include but are not limited to adverse drug reactions (ADRs), drug-to-drug interactions, polypharmacy, increased risk for antimicrobial resistance, and other (sometimes lethal) complications such as *Clostridioides difficile* infection.

With increasingly complex patients having multiple comorbidities and polypharmacy, it may be difficult to tell whether patients are symptomatic for UTI. Previous studies have tried to tease out antibiotic appropriateness. One study showed that 54% (224/414) of patients treated on an acute medical ward with antimicrobials showed that UTI was the most common diagnosis (N=49). Of those who were treated for a UTI, 32.6% had no symptoms suggestive of a UTI.[10] Catheterized patients were looked at in another study at a VA hospital. More than 50% of these patients were considered to have bacteriuria but 32% of these received inappropriate treatment.[11] Another observational study found that the average length of inappropriate treatment for ASB was around 6.6 days, resulting in two cases of C. *difficile* infection and one case of QT prolongation.[12] Treating patients who do not need to be treated could result in colonization with increasingly resistant urinary bacteria, untoward patient adverse events or hospital-acquired infections.

PHARMACOLOGICAL MANAGEMENT OF UTIS

When a patient does have urinary symptoms or a medical presentation consistent with a UTI, goal-directed therapy is aimed at evaluating and relieving urinary stasis or obstruction, removing unnecessary devices (i.e. indwelling catheters) and choosing antibiotic therapy to treat typical urinary pathogens. Urinary bacteria are most often coliform gram-negative organisms in the community at large. *E coli* causes 70–95% of both upper and lower UTIs. Other organisms to consider are *S saprophyticus* (younger women), *Proteus species* (spp), *Klebsiella spp*, *Enterococcus faecalis* (older men), and other enterobacteriaceae. For purposes of a concise overview, we will focus on treatment of community-acquired bacterial pathogens.

Current first-line recommendations for the treatment of acute uncomplicated cystitis includes nitrofurantoin monohydrate/macrocrystals 100 mg BID for 5 days or trimethoprim-sulfamethoxazole (TMP/SMX) 160/800 mg BID for 3 days. TMP/SMX use is restricted to facilities with local uropathogen resistance rates less than 20%.[13] Fosfomycin, typically dosed as a one-time 3 g sachet, is a novel antibiotic that can be considered for treatment of uncomplicated cystitis. It boasts limited collateral damage and low reported resistance due to its unique mechanism of action. Use of fosfomycin should be restricted to patients with allergies to first-line antimicrobial agents or infections with multi-drug resistant organisms.[14] Complicated cystitis that extends beyond the bladder should raise concerns for pyelonephritis. In these patients, duration of therapy can be extended to 10 or 14 days. The preferred antibiotic should have high bioavailability and great penetration. In these scenarios, fluoroquinolones are frequently preferred by many providers due to their extensive spectrum of activity, its excellent bioavailability (near 100%), and high penetration into the prostate.

Commonly used agents have risks for adverse drug reactions (ADRs) and/or drug interactions. Elderly patients who are most likely to receive treatment, are particularly at higher risk to develop antibiotic associated ADRs.[15] This risk is most likely due to decreased clearance of the drug (reduced renal or hepatic metabolism), drug interactions from polypharmacy, and increased pharmacodynamic sensitivity.[16]

Fluoroquinolones can prolong the QT interval, especially in patients receiving other QT-prolonging medications such as antipsychotics or antifungals. More concerning is the extensive list of black box warnings associated with this drug class. These warnings include hypoglycemia, tendonitis and tendon rupture, peripheral neuropathy, CNS effects, and potential myasthenia gravis exacerbations. In late 2018 the FDA warned for increased risk of life-threatening aortic aneurysms or dissections, especially in the elderly and patients with hypertension or vessel abnormalities.[17] Prescribers should be aware of the association between fluoroquinolone use and risks for adverse outcomes. Thus, careful evaluation of patients, their comorbidities, and review of active medications is highly recommended prior to initiating treatment with fluoroquinolones.

Alternative agents to fluoroquinolones are not without associated ADRs and drug interactions. TMP/SMX can cause dermatological reactions (including life-threatening Stevens Johnson Syndrome), acute kidney injury, and hyperkalemia; the latter two being most common in the elderly or when compounded with potassium sparing diuretics, ACE inhibitors, and other nephrotoxic agents. TMP/SMX also influences INR levels in patients on warfarin therapy by increasing the levels of warfarin, thus, increasing the risk of bleeding. Frequent INR monitoring along with a reduction of warfarin dosing is recommended in these patients.

Nitrofurantoin is contraindicated in patients with impaired renal functions. Previously, the creatinine clearance cut-off for use of nitrofurantoin was below 60 mL/min. In 2015, the American Geriatric Society decreased the threshold of creatinine clearance cut-off to less than 30 mL/min.[18] Risks associated with nitrofurantoin use include pulmonary and hepatic toxicity, hemolytic uremia, and peripheral neuropathy.

Beyond ADRs and potential side effects associated with antimicrobial use, inappropriate prescribing of these agents potentiates antibiotic resistance. Common uropathogens such as *E. coli* and *K. pneumonia* have been associated with the development of extended spectrum beta lactamase (ESBL) and even Carbapenemase-producing conferring resistance to the most commonly used "broad-spectrum

antibiotics." Increased exposure to these antibiotics is also associated with secondary opportunistic infections such as *Clostridioides difficile* (*C. difficile)* and yeast infections. The potential of ADRs, antibiotic resistance, and secondary infections associated with antibiotic use should reinforce judicious prescribing practices when considering antibiotics for a patient presenting with a low suspicion for UTI.

OTHER INTERVENTIONS TO IMPROVE OUTCOMES

Two-Step Urine Culture Ordering[19]

Alongside careful clinical judgement, one large academic medical center implemented a "two-step process" to justify treatment of UTI. Researchers utilized a specialized container to hold urine samples at room temperature for up to 48 hours at the time of presentation to the ED. Urine was not sent for culture until a validated diagnostic screen was completed by the ED physician with a subsequent order for culture.

Following implementation of this protocol, there was a decrease in the percentage of weekly ED visits associated with a processed urine cultures (UC) (5.97% vs 4.68%, p<0.001), a decrease in the percentage of monthly ED visits requiring callback for positive UC (1.84% to 1.12%, p<0.001), and a decrease in antimicrobial prescriptions for urinary indication among admitted patients (20.6% to 10.9%, p<0.01). The researchers reported a false omission rate of 1.35% (95% CI 0.7% to 2.2%), yet no identified cases of untreated urinary tract infection (UTI), or significant change in repeat ED visits or ED length of stay. Placing urinary specimens on hold (up to 48 hours) for further testing with urinary cultures may be a potential intervention to consider in medical centers to reduce the overuse of antimicrobials in the setting of ASB. The applicability of this intervention should be individualized as operational processes may differ at each medical center.

ANTIBIOTIC STEWARDSHIP AND EDUCATION

Data supporting the effectiveness of hospital antibiotic stewardship programs have been long-standing and voluminous. In 2017, the Joint Commission established inpatient AMS programs to be an accreditation standard for hospitals and expanded this standard to the outpatient arena in 2019.

Most of the studies on limiting treatment of asymptomatic bacteriuria have included participants from the community and healthy women. The excluded populations from many of these early studies are hospitalized or institutionalized patients, patients with chronic urinary tract conditions or stents, transplant patients, and spinal cord patients. Ironically these are the patients who need our attention and expertise. Education, combined with audit and feedback, can change clinician behavior. It is possible to incorporate interventions to guide providers toward thoughtful process and corrective action rather than reflex prescribing.[20] AMS programs led by physicians, pharmacists and nurses are able to offer educational guidelines, alternatives for prescribing (low likelihood cases), case-based learning for small group feedback, and evidenced-based lectures which can modify clinician practice.

HOSPITAL REIMBURSEMENT AND QUALITY STANDARDS

Antimicrobial stewardship goes hand in hand with infection control. Hospitals have an incentive to approach bacteriuria cautiously, testing only when needed, using antibiotics only when warranted, and removing unnecessary genitourinary catheters. In 2008 there was a significant policy change by which Medicare ceased reimbursement for hospital-acquired infections (HAIs), such as catheter-associated urinary tract infections (CAUTI). In 2015, *C. difficile* colitis was included in this HAI group. Treating HAIs proves to be more expensive than preventing them. As a result of monetary penalization, hospitals have implemented quality improvement initiations aimed at improving outcomes and reducing infection rates.

GOING BACK TO OUR CASE

In this 85-year-old gentleman, we may want to closely monitor clinical status, hydrate, assess for any metabolic abnormalities, and carefully evaluate what antipsychotics should be used (if any at all) in this elderly man with dementia. If he has urinary retention, this could be relieved and worked up, but if he has no systemic or localized signs of infection, his urine should not be tested or treated (unless he was going for cystoscopy with biopsy in the near future). Alternatively, you could consider a 2-step urine testing while continuing to monitor clinical status off antibiotics.

DISCUSSION AND CONCLUSION

Asymptomatic bacteriuria is defined as bacteria in the urine without symptoms referable to the urinary tract. Prevalence ranges from 1–5% of normal healthy women to 40–50% of those in long-term care facility. Diagnostic uncertainty in the institutionalized elderly leads to inappropriate antimicrobial use. The majority of patients with ASB require no treatment except pre-operative state for invasive urological procedure and in pregnancy.

Delirium or falls, especially in the elderly, should have a wide net cast for etiology of "mental status change." Mental status changes alone without symptoms referable to the urinary tract or systemic symptoms of infection does not accurately translate into UTI. In these instances, NO urine cultures or empiric antimicrobials for UTI are encouraged.

Antibiotics should be used judiciously for the treatment of UTIs. Targeted therapy is recommended when a causative organism has been identified.

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