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Diagnosis and Management of Recurrent and Complicated UTIs in Women: Controversies and Dilemmas


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Prevalence and Economic Impact of Urinary Tract Infection (UTI)

In the United States, it is estimated that 1 in 3 women have had a UTI requiring antimicrobial treatment by the age of 24. The prevalence of UTIs increases with age and results in a lifetime risk of at least 50%. The annual healthcare cost associated with uncomplicated UTIs, including hospitalizations, is estimated to be between $1.6 and 2.8 billion in the United States. A significant proportion of these costs can be attributed to hospital admissions, antimicrobial resistance, repeated outpatient visits, and antimicrobial expense.[1,2] Resistance to common empiric treatments for UTIs is increasing. The Centers for Disease Control and Prevention (CDC) recently reported that antibiotic resistance to *Escherichia coli*, *Acinetobacter*, and *Pseudomonas aeruginosa* infections contributed to estimated healthcare costs in 2017 of $281 million, $539 million, and $767 million, respectively.[3] A study conducted by Shafrin et al compared the economic burden for patients with uncomplicated UTIs that were susceptible and nonsusceptible to initial treatment. This study revealed that patients who did not respond to initial treatment had higher UTI-related costs in the 6 months after the initial diagnosis. These patients were also 2 times more likely to progress to complicated UTI.[1] Moon et al highlighted that inappropriate/suboptimal prescriptions and antibiotic switching were associated with significantly higher healthcare costs.[4]

When Should a UTI Be Considered Complicated?

Although UTIs have demonstrated widespread occurrence and significant healthcare costs, there is not yet a "gold standard" definition for complicated UTI.[5] While general definitions of uncomplicated and complicated UTIs exist, these have been extrapolated mostly from criteria developed using terminology more consistent with male gender anatomy and physiology.

An uncomplicated UTI is defined as an infection of the urinary tract in a healthy patient in the absence of anatomical or functional urinary tract abnormalities. Traditionally, an uncomplicated UTI can be treated empirically without urine culture. The first line of treatment for uncomplicated UTI can be management without antibiotics in otherwise healthy patients or empiric treatment with nitrofurantoin, trimethoprim-sulfamethoxazole, or fosfomycin. Patients with recurrent UTIs, treatment failures, and those hospitalized for UTIs, require urine cultures not only to document the infection but also to identify the organism that caused it, hopefully prevent complications, and check for antimicrobial sensitivity/resistance. According to the CDC, culture-proven UTI is defined as a urine culture with no more than 2 organisms and at least one of which shows growth of $\geq 10^5$ colony forming units (CFU)mL on a midstream urine specimen or 10^3 CFU/mL on a catheterized specimen, with at least one of the following symptoms: fever in a patient ≤65 years, suprapubic tenderness, costovertebral tenderness, urinary urgency, urinary frequency, or dysuria. Although these criteria are generally followed, there are no absolute minimums regarding CFU/mL and in the presence of new-onset symptoms, any colony count should be assessed for infection causation. It is well documented that colony counts as low as 10^2 CFU/mL with symptoms suggestive of UTI are significant and should be treated.[5-9] A UTI is considered to be recurrent if there have been 2 documented infections in 6 months, or ≥3 documented infections in 1 year. In women, a UTI is considered to be complicated if there are documented recurrent or persistent infections, multi-drug resistant organisms, atypical speciation of putative organism, or urinary tract functional or anatomic anomalies.

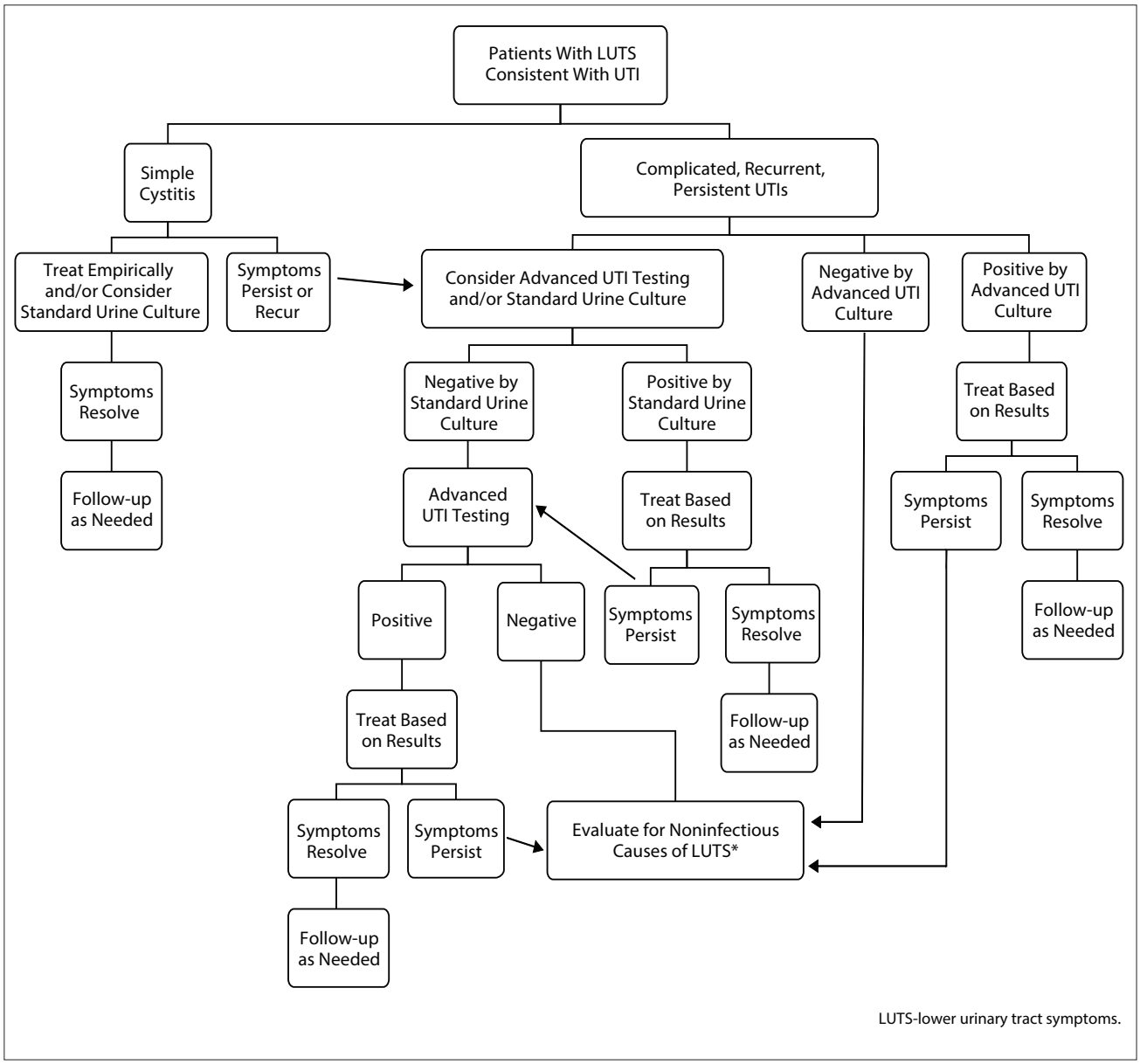

FIGURE Indications for Advanced UTI Testing in Women

Deficiencies of Standard Urine Culture

While standard urine culture (SUC) continues to be the gold standard for the treatment of recurrent or complicated UTIs, this test is only sensitive for typical micro-organisms most commonly responsible for UTIs such as *E. coli*, pathogenic *Staphylococcus saprophyticus*, *Klebsiella pneumonia*, and *Proteus mirabilis*. Newer technologies have detected some of these organisms in UTI cases that SUC missed. Recent studies have underscored the significant limitations of SUC that have unfortunately not been clinically emphasized as detailed below.

SUC is time consuming and takes a minimum of 48 hours to receive results with corresponding sensitivities, which creates a delay in treatment that can result in unwanted complications. SUC cannot reliably identify multiple organisms (approximately 30%–39% of UTIs are polymicrobial) as well as fungi; fastidious, anaerobic bacteria; or sexually transmitted diseases, which can all be etiologic factors in women with a symptomatic UTI. One study found that SUC missed 67% of uropathogens in patients with severe UTI symptoms, and 36% of the patients experienced persistent symptoms after receiving directed treatment based upon SUC results.[10] Polymicrobial interactions can also impact susceptibility results. In traditional antimicrobial susceptibility testing, each bacterium is grown in isolation against individual antibiotics, providing no opportunity to assess the effect of bacterial interactions on antibiotic effectiveness. Ignoring bacterial interactions may lead to treatment failure, which may have

serious clinical consequences or could lead to inappropriate or delayed treatments.

These deficiencies create clinical dilemmas when patients have persistent symptoms despite appropriate urine culture–based treatment or when patients have persistent symptoms with a negative culture (see **Figure**). Also, there is increasing evidence suggesting a natural microbiome within the lower urinary tract that further complicates the interpretation of cultural results.

Antibiotic Resistance

These clinical situations can often result in the repetitive use of antibiotics for many cases of uncomplicated and complicated UTIs. As a result, antibiotic resistance has recently increased. Yamaji et al found that uropathogenic *E. coli* (UPEC) is developing an increasing resistance to trimethoprim-sulfamethoxazole, with resistance reaching up to 17.1% in the outpatient population with UTI symptoms.[11] Karam et al noted that approximately 31% of hospitalized patients in the United States had UPEC strains that were resistant to fluoroquinolones.[12] Morrill et al found that approximately 40% of *E. coli* urinary isolates from inpatients and outpatients in the United States were resistant to amoxicillin or ampicillin/beta-lactamase inhibitors.[13]

Increased antibiotic resistance has direct implications for patient morbidity, resulting in increased hospitalizations and sepsis with consequent risk of permanent functional disability and even mortality. The pathogenicity of these organisms is substantially greater than organisms with more standard resistance spectrums, and the treatment choices are far fewer. Antibiotic resistance is a huge problem for UTIs compared with other infections because UTIs are so common, and the effects of antibiotic resistance are seen early on and with a high prevalence.

Need for Advanced Testing

In women who do not respond to initial empiric therapy or have complicated, persistent, or recurrent UTIs, it is essential to precisely identify organisms causative of the UTI promptly so as to have an appropriate antibiotic prescribed and prevent potential antibiotic resistance. Ideally, the pathogen and its susceptibility to antibiotics should be identified within a few hours of collection, allowing the patient to begin the appropriate treatment.

The most time-consuming step in current laboratory diagnosis is urine culture, due to time needed for bacterial isolation and growth. As a result, new technologies have been developed that analyze urine samples without the necessity of isolating or growing bacteria. In addition, these new methods account for the possibility of UTIs being caused by multiple micro-organisms and identify organisms that have not been able to be isolated by SUC.

Advanced Testing Using Polymerase Chain Reaction (PCR)

PCR testing utilizes a technologically advanced process to "copy" and amplify a portion of DNA from the patient's urine sample to identify the precise pathogen causing the UTI and to provide resistance gene information about which antibiotic may be effective and to which antibiotics the bacteria may be resistant. PCR testing is perceived to be able to address a significant portion of the deficiencies of SUC, aside from phenotypic antibiotic susceptibility testing (AST), which SUC does report and PCR does not. PCR testing has been widely used clinically in diagnosing respiratory, gastrointestinal, and sexually transmitted infections.[14]

PCR testing is gaining popularity as a diagnostic test for UTI among urologists and urogynecologists. Multiple commercially available PCR testing companies provide a test menu consisting of approximately 18 to 46 organisms, multiple antibiotic resistance markers, and result times as quickly as 5 hours or less, though results are most commonly available in 24 hours. Numerous studies have shown that PCR testing has a higher probability of detecting both single and multiple organisms in a much timelier fashion than SUC.[15,16] The main limitation of PCR is that it can identify pathogens that may be part of the normal urinary microbiome, creating the risk of overtreatment. Most of the commercially available PCR tests check for a handful of known resistance genes (genotypic), but this may be limited due to current knowledge and provide no information on the phenotypic sensitivity of the pathogen to different antibiotics.

To fully assess the potential risks and benefits of widespread use of PCR in the diagnosis of UTI, additional research on outcome measures is essential. In the interim, it appears that PCR is an additional tool for challenging UTI cases where SUC does not provide sufficient information.

There are a few UTI tests that, in addition to the genotypic testing from PCR, also provide phenotypic testing. Of these, there is one that combines PCR with pooled antibiotic susceptibility testing, or P-AST™; this yields enhanced information determining phenotypic antibiotic sensitivity.[17,18] It is designed for use in complicated, persistent, and recurrent UTIs and elevated-risk patients. This test combines genotypic assays that have traditionally been used to detect antibiotic-resistant bacterial nucleic acid sequences using PCR technology with proprietary phenotypic testing. This is important as antimicrobial resistance is more complex, and molecular assays that target only a few known resistance genes are insufficient to predict antimicrobial susceptibility since resistance genes are not always fully expressed or could be impacted by mutations. On average, genotypic results disagree with phenotypic (observed) resistance 40% of the time.[19,20] In polymicrobial infections, the interaction of various bacteria complicates antibiotic resistance and sensitivity information. P-AST™ involves simultaneously growing all the detected bacteria together in the presence of antibiotics and measuring susceptibility, which may provide useful information regarding antibiotic resistance, particularly in infections involving multiple micro-organisms. In 2020, Daly et al reported on M-PCR (multiplex PCR) and P-AST™ for diagnosis and management of UTIs. They found that the use of the combined M-PCR/P-AST™ was associated with a 13.7% decrease in hospital admissions and/or emergency department utilization when compared with the use of SUC.[17] Vollstedt et al found that antibiotic susceptibility patterns in polymicrobial specimens differed from those observed in monomicrobial specimens and P-AST™ could serve as a more accurate predictor of antibiotic susceptibility.[19]

Medicare and Third-Party Payer Reimbursement for Advanced Testing

Medicare had previously developed coverage directives for several types of PCR tests outside of UTI detection, and recently published a local coverage determination (LCD) that included the use of PCR tests for UTI detection. The LCD provides coverage for PCR testing in UTIs under clearly defined coverage criteria. This policy was issued by the MolDx program of Medicare, which includes 4 of the 7 Medicare Administrative Contractors. Coverage is generally issued to manage overutilization and to ensure test validity and utility, which means having clinical evidence of superiority to SUC is required to gain coverage.

Conclusion

In conclusion, considering the limitations of standard screening and culture, the diagnosis of a UTI needs advanced evidence for improvement and refinement. To provide physicians with a better guide for managing UTIs, there are new rapid and dependable assays available. The role of these methods in the clinical setting is currently unclear, but it appears that they may be useful in more complicated cases of UTI in which conventional urine culture will not provide all the necessary information for an accurate diagnosis and treatment (see **Figure**).

Specific clinical situations where the authors feel advanced testing would be helpful including the following:

1. Women with recurrent or persistent UTIs based on SUC
2. Women who continue to have symptoms of a UTI after appropriate treatment based on SUC
3. Women who have urinary complaints consistent with a possible UTI but have negative SUC results
4. Women who have atypical symptoms of a UTI, such as bladder pain or isolated urgency, who seem to empirically respond to a course of antibiotics
5. Women who have heightened risk of complications, including significant comorbidities.

The most studied UTI testing currently available includes both genotypic and phenotypic testing to appropriately determine the infecting organism(s) and provide specific sensitivity for accurate treatment. The ordering physician should be fully aware of the specific panel of organisms the PCR test is targeting, including that they are known uropathogens.

The key to ordering any advanced testing is accurately interpreting results. These highly sensitive assays can detect bacteria in low counts that may have no clinical implications. Therefore, clinicians should not base their treatment decisions on genotypic test results alone, as doing so can have adverse consequences for patients. To avoid the overuse of antimicrobial agents and their associated side effects, cost, and selection of antimicrobial resistance, it is vital that clinicians evaluate test results in the context of a patient's overall risk and history of UTIs and current clinical presentation and utilize testing that enables more informed treatment decisions. ●

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