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Advances and Challenges in the Diagnosis and Treatment of Urinary Tract Infections: the Need for Diagnostic Stewardship

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Abstract

Purpose of Review Urinary tract infections (UTIs), including catheter-associated UTIs, are among the most common bacterial infections in both inpatient and outpatient settings. Diagnosis of true UTI remains a clinical challenge, and excessive antimicrobial treatment of asymptomatic bacteriuria (ASB) or contaminated urine cultures is common.

Recent Findings Challenges with the appropriate diagnosis of UTIs include the lack of specific signs and symptoms, no definitive diagnostic criteria, high incidence of ASB, contamination of samples, and frequent lack of indications for ordering urine cultures. Promising interventions include education and feedback, indication requirements when ordering cultures, and use of reflex culture policies that limit urine cultures.

Summary Antimicrobial and diagnostic stewardship interventions can work synergistically to decrease ordering of urine cultures without clear indication and prevent excessive antimicrobial administration in patients without clearly defined UTI.

Keywords Antimicrobial stewardship · Diagnostic stewardship · Urinary tract infections

Introduction

Urinary tract infections (UTIs) are among the most common bacterial infections in the USA in both inpatients and outpatients [1–5]. They account for approximately one million emergency department visits annually, 100,000 hospitalizations in the USA annually, and are the fourth most commonly reported healthcare-associated infection. Additionally, over 25% of hospitalized patients are catheterized during their hospital admission, placing them at risk of developing a catheter-associated UTI (CA-UTI). However, diagnosis of UTI remains a clinical challenge, largely because signs and symptoms can be non-specific and bacteriuria is common. Asymptomatic bacteriuria (ASB) is frequently mistaken for UTI and is a major driver of inappropriate antimicrobial prescribing [6–8]. A recent meta-analysis that included over 4000 cases of ASB reported a pooled treatment rate of 45%, illustrating the magnitude of inappropriate antimicrobial use that may be attributed to this condition [6].

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Inappropriate administration of antimicrobials carries serious risks, including adverse drug events, *Clostridioides difficile* infections, and emergence of antimicrobial resistance [6, 9–12]. Antimicrobial stewardship programs aim to improve clinical outcomes by reducing unnecessary antimicrobial administration and optimizing its use [13, 14]. Strategies used by antimicrobial stewardship programs generally focus on modulating antimicrobial use after their initiation. By contrast, strategies that aim to reduce unnecessary detection of ASB can help to avoid the negative outcomes associated with unnecessary initiation of empiric antimicrobials. Diagnostic stewardship is one way to frame such strategies. It aims to improve patient outcomes by optimizing ordering of diagnostic tests; specimen collection and transport; testing practices; and test reporting. Diagnostic stewardship therefore works synergistically with (and upstream of) antimicrobial stewardship interventions by reducing unnecessary testing and over-diagnosis (Fig. 1) [15••]. This review summarizes the challenges surrounding UTI diagnosis and synthetizes published evidence pertaining to diagnostic stewardship interventions for reducing UTI over-diagnosis and unnecessary antimicrobial administration.

Challenges with Urinary Tract Infection Diagnosis

UTI diagnosis remains a difficult task. Challenges include non-specific signs and symptoms, high incidence of ASB, particularly in elderly populations; lack of a definitive gold standard for UTI diagnosis; high rates of contamination during urine collection; and variable knowledge related to appropriate indications for ordering urine cultures (UCs) in asymptomatic individuals.

Signs and Symptoms of UTI Can Be Non-specific and Difficult to Ascertain

Patients with UTI typically present with non-specific features including fever and leukocytosis in combination with localized symptoms that are referable to the urinary tract such as suprapubic tenderness, costovertebral angle tenderness, urinary frequency, urinary urgency, and dysuria [16, 17]. In cognitively intact adults with normal genitourinary tracts, the diagnosis of symptomatic UTI is generally straight forward and can be based on the presence of localized genitourinary symptoms, evidence of urinary tract inflammation (e.g., pyuria), and recovery of pathogens in UCs. Eliciting genitourinary symptoms in patients with limited ability to communicate is much more challenging. McGeer and colleagues proposed a surveillance definition of UTI for patients in long-term care facilities that required three or more of the following features to be present: fever ≥ 38 °C or chills; new or increased burning pain on urination, frequency, or urgency; new flank pain or suprapubic pain or tenderness; change in character of urine; and worsening mental or functional status [18, 19]. Similarly, Loeb and colleagues proposed that antibiotics be initiated in residents of long-term care facilities when they have fever (> 37.9 °C or 1.5 °C increase above baseline) plus one of the following: urgency, frequency, suprapubic pain, gross hematuria, costovertebral tenderness, or urinary incontinence [20]. While both sets of criteria have been widely accepted, their use in clinical settings appears to be limited as they have not been clinically validated [21, 22].

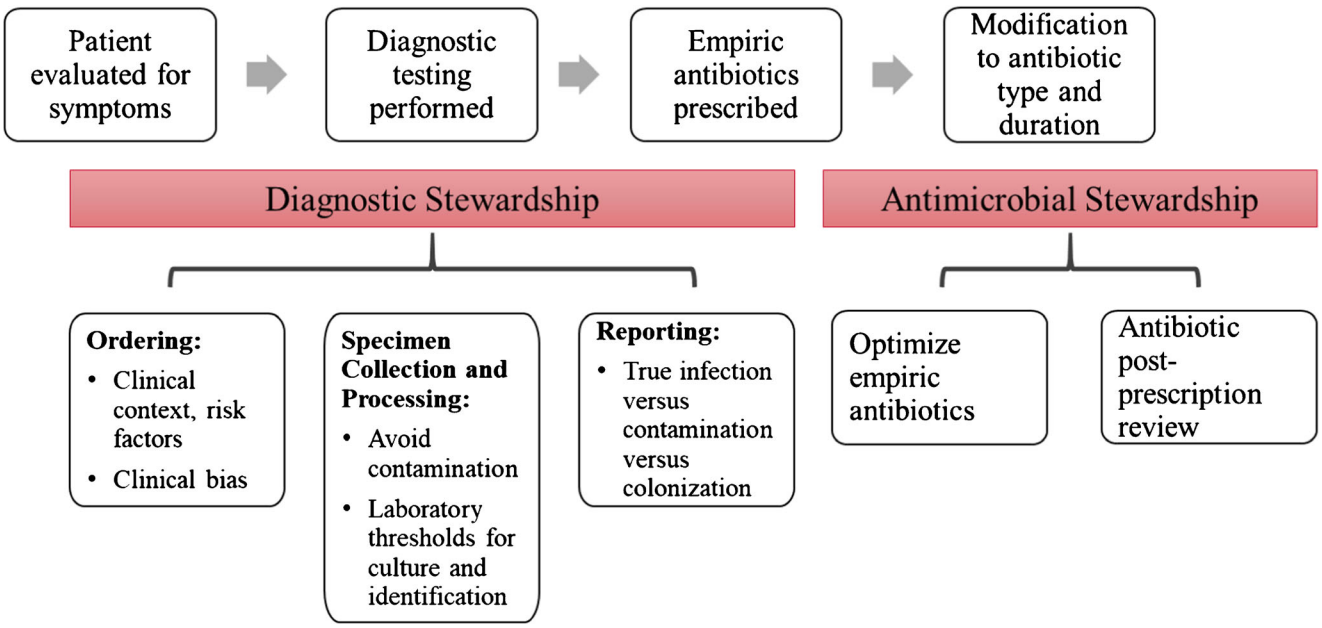

Fig. 1 Diagnostic stewardship is synergistic with antimicrobial stewardship

There Is a High Incidence of Asymptomatic Bacteriuria

The Infectious Disease Society of America (IDSA) defines ASB as the presence of bacteria in the urine in quantities of $\geq 10^5$ colony-forming units per milliliter (CFU/mL) in two consecutive urine specimens in women or one urine specimen in men in the absence of signs and symptoms of a UTI [23]. The IDSA also states that a single catheterized urine specimen with one bacterial species isolated with a quantitative count of $\geq 10^2$ CFU/mL identifies ASB in asymptomatic patients.

The incidence of ASB varies significantly by patient population. In healthy individuals, incidence is 5–15%, but in elderly patients residing in long-term care facilities, incidence has been reported to range from 30 to 60% [20–25]. In patients with indwelling urinary catheters, incidence of ASB has been reported to increase 3–10% per day following catheterization with virtually all chronically catheterized patients eventually developing ASB [26–28]. This complicates the diagnosis of CA-UTI and the application of surveillance definitions. For example, the National Healthcare Safety Network (NHSN) definition of CA-UTI currently requires that a patient has a urinary catheter in place for at least 2 days, a UC growing $\geq 10^5$ CFU/mL of at least one organism, and one pre-defined sign of infection (fever of ≥ 38 °C; suprapubic tenderness, costovertebral angle pain or tenderness, urinary urgency, urinary frequency, or dysuria). The latter three criteria do not apply when a urinary catheter is in place, as the catheter itself can be responsible for these symptoms [29]. It is important to note that a patient who is chronically catheterized with a positive UC who develops a fever would meet criteria as a reportable CA-UTI even in the absence of symptoms that are referable to the urinary tract [30].

Contamination of Urine Cultures Is Common

Despite its limitations, UC remains the gold standard laboratory test for diagnosis of UTI. However, UC specimens can easily become contaminated with periurethral, vaginal, perianal, and perineal flora at the time of collection, leading to false positive results. In a survey involving 127 microbiology laboratories and over 14,000 UCs and using recovery of three or more isolates in quantities of $\geq 10^4$ CFU/mL as the definition of a contaminated UC, the College of American Pathologists reported that laboratories at the 25th, 50th, and 75th percentiles for contamination had rates of 26.7%, 15.0%, and 4.2%, respectively [31]. They also noted that these findings were relatively unchanged from a similar survey conducted 10 years prior.

Urine Cultures Are Ordered Without a Valid Clinical Indication

Urine cultures are frequently ordered in response to nonspecific findings such as fever or leukocytosis in the absence of a clear indication [32, 33]. In a prospective audit of UCs performed at two large academic hospitals, Leis and colleagues reported that 68% were ordered without a valid clinical indication [34]. Reasons included confusion (23%), unexplained leukocytosis (21%), previous history of UTI (11%), abnormal smell or color of urine (9%), recent catheterization (8%), urinary retention (8%), weakness or dizziness (7%), and dysglycemia (4%) [34]. Knowledge deficit with respect to diagnosis and management of ASB is an important driver of inappropriate urine culturing and treatment of ASB [35–37]. A cross-sectional survey of physician residents that used clinical vignettes to assess their knowledge related to recognition and management of ASB reported that only 34% of respondents correctly diagnosed ASB [35]. Moreover, even when ASB was diagnosed correctly, 47% of respondents indicated that they would still prescribe antimicrobials. This highlights the importance of educational initiatives such as the American Board of Internal Medicine Foundation Choose Wisely Campaign [38]. In their list of "Five Things Physicians and Patients Should Question," made in collaboration with the Society for Healthcare Epidemiology of America (SHEA), they recommended that urinalysis (UA) and UC not be ordered unless patients have clear signs and symptoms of infection [39].

Diagnostic Stewardship Opportunities

Suboptimal urine culturing is common, wasteful, and potentially harmful. Various investigators and organizations have described a variety of interventions that optimize urine culture ordering, urine collection and transport, processing, and test reporting in an effort to reduce unnecessary culturing and improve the quality of UC specimens submitted to laboratories (Table 1). Implementing some or all of these interventions has the potential to decrease excessive UC ordering and antimicrobial prescribing in an additive fashion (Fig. 2).

Urine Culture Ordering

Urine cultures should be ordered only when clinical indications are met. They should not be ordered in asymptomatic patients unless there is an evidence-based indication (i.e., pregnant women, prior to transurethral resection of the prostate, or a urologic procedure likely to cause mucosal bleeding) [16, 17]. Various investigators have reported reductions in UC orders and antimicrobial treatment of ASB by providing clinical staff with written guidance coupled with education that

Table 1 Opportunities to implement diagnostic stewardship practices

Intervention Type	Pre-Analytic	Analytic	Post-Analytic	Diagnostic Stewardship Interventions for Urine Culturing
Treatment guidelines coupled with provider education	■			• Review evidence-based practices, development of institution-specific guidelines for correct UC technique and treatment of UTIs • Provider education • Active review of urine culture orders and provider feedback (peer-to-peer)
Require clinical indication when placing test order	■			• Build hard stops in the EHR that require providers to enter clinical indication when ordering UCs
EHR-integrated memorandum	■			• Build comment in the EHR that triggers when a UC is being ordered to remind the provider to avoid ordering in the absence of symptoms
Correct specimen collection technique	■			• Provide nurse training on appropriate UC collection technique • Provide ambulatory patients with education on correct clean-catch technique • Submit UC specimens with boric acid preservative
Assess specimen quality and reject poor quality specimens		■		• Laboratories should reject urine culture specimens that are submitted without preservative if >2 hours have elapsed since collection
Perform adjunctive tests to differentiate colonization infection		■		• Implement reflex urine culturing in the laboratory (perform UC only when UA meets predefined criteria) • Configure EHR to prioritize reflex UC • Remove UCs from order sets but retain reflex UC orders
Provide providers with guidance around test interpretation			■	• Build a comment in the EHR when a patient has a positive urine culture that advises providers about management of ASB.
Restrict reporting of UC results			■	• Report UCs as "mixed" without further information about identification when three or more organisms are recovered • Urine culture results (organism identification and/or antimicrobial susceptibility results) released only upon request of provider • Selective suppression of antimicrobial susceptibility results or use of cascade reporting

AMS antimicrobial stewardship, *DOT* days of therapy, *EHR* electronic health record, *UC* urine culture, *UTI* urinary tract infection

communicates appropriate indications for ordering UCs. Trautner and colleagues implemented an initiative called "Kicking CA-UTI: The No Kneejerk Antimicrobials" [40]. This initiative involved development and distribution of a "CA-UTI versus ASB" treatment algorithm and feedback in the form of in-person presentations that reviewed cases that were appropriately and inappropriately managed. At the intervention site, UC orders decreased significantly from 41.2/1000 bed days, pre-intervention, to 23.3/1000 bed days post-intervention, while incidence remained unchanged at the comparison site (incidence rate ratio (IRR) = 0.57, 95% CI 0.53–0.61). Incidence of ASB overtreatment also decreased significantly at the intervention site (1.6 to 0.6 episodes/1000 bed days, IRR = 0.35, 95% CI 0.22–0.55). Similarly, Egger

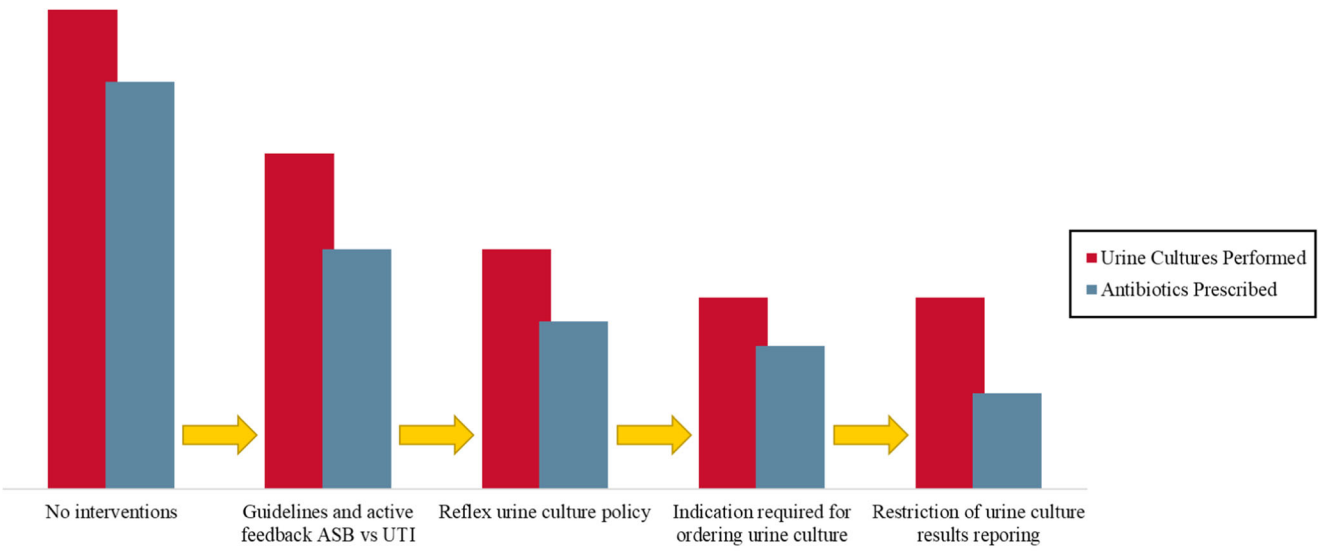

Fig. 2 Potential cumulative benefits of diagnostic stewardship interventions

and colleagues published guidelines that provided indications for ordering UCs and best practices for urine collection on the hospital intranet [41]. Concurrently, they offered web-based education to physicians. Treatment days for ASB decreased from 22 to 10 days/1000 patient days (IRR 0.46, 95% CI 0.33–0.63). Irfan and colleagues conducted a similar intervention, with education focused on medical residents [42]. Following implementation, inappropriate treatment of ASB was significantly lower in the unit that received feedback and education compared to a control unit (8% versus 52%, OR = 0.10, 95% CI 0.02–0.49). Risk factors for inappropriate treatment included pyuria (OR = 2.0, 95% CI 1.1–3.8), positive urine nitrite (OR = 2.2, 95% CI 1.1–4.5), and detection of bacteriuria (OR = 10.6, 95% CI 3.8–29.4).

In an effort to reduce unnecessary culturing, some organizations have leveraged their electronic health record (EHR) to encourage providers to actively consider the clinical indication before ordering. Keller and colleagues built a "pop-up" message that recommended against urine testing in the absence of symptoms and treatment of ASB [43]. The message accompanied EHR orders for UA, UC, and antimicrobials that were most commonly prescribed in their institution to treat UTIs. In a study that used a quasi-experimental design, the investigators reported a 6% reduction in urine culture orders ($p < 0.001$) and a 5.8% reduction in simultaneous UA and UC orders following implementation. There were also significant reductions in antimicrobial orders following UA orders (− 0.56%; $p = 0.021$) and UC results (− 0.24%; $p = 0.036$). Shirley and colleagues took the additional step of configuring their EHR to require providers on designated "pilot units" to enter an indication when placing UC orders [44]. The authors reported a 34% reduction in number of UCs ordered in catheterized patients on the pilot units and no reduction on non-pilot units ($p = 0.049$). Others have examined barriers associated with optimizing UC orders. In a qualitative study, Redwood and colleagues investigated individual- and system-level barriers that affect urine culture ordering and collection practices in an emergency department and an intensive care unit (ICU), as described by nursing staff [45]. The investigators reported misconceptions about appropriate indications for urine culturing in settings where nurses had autonomy to place orders. Also, when orders were placed by physicians, nurses reported difficulties connecting with physicians to clarify orders. They also reported that alerts built into the EHR about sending appropriate urine culturing had become a nuisance, providing evidence of "alert fatigue" associated with EHR messaging.

Optimizing Urine Collection

Once a UC is ordered, the urine specimen needs to be collected in a manner that minimizes contamination [46••]. When collecting urine using the clean-catch midstream technique, perineal cleansing is recommended for women, although a recent meta-analysis reported that contamination rates were similar between specimens obtained by midstream collection with and without cleansing [46••]. In men, obtaining a midstream urine sample reduces contamination compared to a first-void sample. However, while recommended, the value of cleansing the glans penis prior to collection is unclear. The authors also reported insufficient evidence to recommend straight catheterization over midstream urine in both men and women. Interventions focusing on patient education related to optimal urine collection technique through instructional videos, phone-based applications, and written guidance have been described, but these interventions have not been associated with sustained reductions in urine contamination rates [47–49].

Urine obtained from indwelling urinary catheters is frequently contaminated by organisms residing in biofilm that develops in the lumen of the catheter and should be collected from the sampling port and not the urine collection bag or other ports [16, 28]. Mullin and colleagues implemented a series of interventions in a sequential fashion that included initiation of catheter insertion competency assessments, implementation of a nurse-driven protocol for removal of urinary catheters, a campaign to enhance EHR documentation, and use of urine collection tubes containing preservative [50]. The authors reported a significant reduction in number of urine cultures processed (4749 pre-intervention versus 2479 post-intervention) and CA-UTI rate (3.0 per 1000 catheter days versus 1.9 per 1000 catheter days, $p = 0.0003$, rate ratio 0.629, 95% CI 0.49–0.81).

Urine Culture Processing

Urine samples should be submitted in a sterile, leak-proof container or, alternatively, in a collection tube with boric acid preservative [51]. Both refrigeration at 4–10 °C and use of boric acid preservative adequately preserves urine specimens for up to 24 h. The American Society for Microbiology (ASM) recommends that unpreserved urine culture specimens be received in the laboratory within 2 h of collection and that laboratories reject urine if an unpreserved urine specimen is more than 2 h old at the time of receipt [51].

Urine culture processing typically involves inoculation of urine on solid agar media using a calibrated loop followed by incubation in ambient air at 35–37 °C [51]. This is followed by organism identification and antimicrobial susceptibility testing. ASM indicates that organisms should proceed to further testing only if they are not normal urogenital microbiota. Growth of three or more pathogens should be considered evidence of contamination and reported as a "mixed" culture with a recommendation to submit another urine specimen. When one or two pathogens are recovered in midstream and indwelling catheter urine cultures, ASM recommends that

identification and antimicrobial susceptibility testing be pursued if $\geq 10^4$ CFU/mL are present when there is pure growth of only one uropathogen and $\geq 10^5$ CFU/mL each when two uropathogens are recovered. These recommendations are intended to avert treatment of contaminated urine cultures [51].

Reflex Urine Culturing

Reflex urine culturing is a novel approach to reducing unnecessary urine cultures. Urine cultures are only performed if predefined criteria are met on urinalysis. In an early study, Jones and colleagues conducted a retrospective review of over 1500 UAs with paired UC results with the goal of developing a predictive model for UC positivity [52]. Their univariate analysis showed statistically significant differences in leukocyte esterase status, presence of $\geq$ 10 leukocytes/high power field, nitrite status, and presence of bacteria when positive UCs were compared against those that were negative. Multivariable analysis also identified these four elements as significant predictors of UC positivity. The investigators proposed that UA results not meeting these criteria should result in cancelation of the UC. Subsequently, Hertz and colleagues showed that by canceling UCs in low-risk patients, not meeting criteria above, 34.6% fewer cultures would have been performed over a 12-month period. Only 4.7% of those UCs would have been positive for a potential pathogen, resulting in a negative predictive value of 95.4% (95% CI 94.3–96.4%) [53]. Stagg and colleagues implemented a two-step UC ordering algorithm [54]. In the first step, a urine sample with UA was completed and the urine sample was held for potential processing. Step 2 consisted of a separate order for UC based on provider assessment of need. Only 19.1% of urine specimens had a subsequent order for UC that was processed. Overall, there was 36.8% relative reduction in ED visits with a UC processed after implementation.

Finally, in a quasi-experimental study, Epstein and colleagues implemented a urine reflex policy in five intensive care units and measured the impact of the new policy on UCs processed [55•]. Urine cultures were performed only if there were $\geq$ 10 WBC/hpf on UA. Immunocompromised patients were excluded from the analysis. The authors reported a statistically significantly decrease in urine culture volumes on all five units ($p = 0.0012$) as well as CA-UTIs per 1000 patient days ($p = 0.04$). In a follow-up study, the investigators expanded the use of reflex urine culturing across more ICUs and evaluated the impact on antimicrobial use [56]. There was a decrease of 30% in UCs processed, but the antimicrobial days of therapy per 10,000 patient days did not significantly change (449 days of therapy/1000 patient days versus 425 days of therapy/1000 patient days). Among 500 randomly selected patients with orders for routine or reflex urine cultures (250 pre- and 250 post-implementation), fewer new courses of antimicrobials were started following implementation of the new policy (41% versus 23%, $p = 0.002$). Removing UC order types from the EHR "frequently ordered tests" list, with the exception of reflex UC, will aid in eliminating unnecessary cultures [57]. Investigators were able to demonstrate a significant decrease in rates of UC ordered (54.3 versus 29.7 per 1000 ED visits, $p < 0.001$) by forcing providers to order reflex UCs.

Reflex urine culturing should not be confused with automatic urine culturing in all patients with positive findings on UA. Dietz and colleagues investigated the impact of discontinuing a policy that all patients with positive nitrite or WBC $\geq$ 8 automatically have a UC performed [58]. Using a quasi-experimental study design, the authors investigated UA and UC volumes and use of ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, and nitrofurantoin (their most commonly prescribed antimicrobials for UTI treatment) before and after de-implementation of the policy. The authors reported a reduction in outpatient UC volumes in outpatients (90.1 versus 61.3, $p < 0.0001$) but not among inpatients. The policy change did not reduce urinalysis volumes or antimicrobial prescriptions.

In a survey of the SHEA Research Network, Sullivan and colleagues identified 26 institutions that implemented reflex urine culturing [59•]. The criteria used to designate a UA as "positive" varied considerably. Ninety-six percent of respondents performing reflex UCs reported criteria that included WBC/hpf. Nineteen (76%) reported that leukocyte esterase and nitrite status were part of their criteria. Following implementation of reflex urine culturing, seven (27%) respondents reported a decrease in their institutional CA-UTI rates; seven (27%) reported no change; three (11%) reported an increase; and nine (35%) stated that they were uncertain of its impact on CA-UTI rates. The authors postulated that the mixed perceived impact of implementing reflex UC practices could be explained by differences in how institutions defined "reflexing" and how reflex urine culturing was implemented.

Urine Culture Reporting

Interventions that focus on urine culture reporting practices do not mitigate unnecessary urine culturing but may reduce inappropriate initiation of antimicrobial therapy or unnecessary use of broad spectrum antimicrobials. Selective reporting of antimicrobial susceptibilities has been shown to reduce antimicrobial prescriptions for the treatment of ASB [60, 61]. In an ecological study involving primary care practices, McNulty et al. demonstrated a shift from amoxicillin-clavulanate to cephalosporin use following replacement of amoxicillin-clavulanate with cephalosporin susceptibility testing results in urine culture reports [62]. Linares et al. implemented an educational memorandum that was added to the charts of patients receiving systemic antimicrobials within

48 h of urinalysis and urine culture results becoming available in the EHR. The memorandum reminded providers of available evidence against treating ASB and referred them to the institutional guidelines for treatment of UTIs [63]. Antimicrobial utilization was significantly lower (6.3 ± 4.2 DOTs to 2.2 ± 3.1 DOTs, $p < 0.001$) in the intervention group compared to the control. Factors contributing to antimicrobial treatment of ASB in the control group included isolation of a resistant organism (OR = 3.28, 95% CI 0.74–14.54), antimicrobials initiated in the emergency department (OR = 3.06, 95% CI 0.98–10.13), and absence of spinal cord injury (OR = 3.63, 95% CI 0.93–16.5).

Leis and colleagues took a more radical approach. Their intervention involved complete cessation of the routine reporting of urine culture results in non-catheterized patients at an academic hospital. Urine cultures were processed as usual in the microbiology laboratory, but in lieu of a culture result, a message was posted advising the provider that most positive urine cultures in non-catheterized patients represent ASB and to call the laboratory for release of results [34]. Results were released when requested by the provider. The rate of antimicrobial therapy for ASB decreased from 48 (95% CI 32–65%) to 12% (95% CI 15–57%), $p = 0.002$). In a randomized controlled trial, Daley and colleagues used a similar intervention that required providers to contact the microbiology laboratory to obtain urine culture results [64]. Patients were randomized 1:1 to standard versus modified reporting. The modified report indicated if there was significant bacterial growth and that further information would be released upon request. A total of 110 consecutive UC meeting inclusion criteria were reviewed in the intention-to-treat analysis. The proportion of appropriately treated UTIs was higher (and thus inappropriately treated ABS was lower) among the modified arm (80% versus 52.7%, risk difference 27.3%, $p = 0.002$). The number needed to report in order to witness a clinical benefit was reported to be 3.7, indicating that this modified reporting has a significant impact by decreasing inappropriate antibiotic treatment.

Conclusions

Although UTIs and CA-UTI diagnoses are common in ambulatory, long-term, and acute care settings, they are poorly defined clinical entities and diagnosis of true infection remains challenging. Adding to this challenge, ASB is common, approaching 100% in chronically catheterized patients, and often misdiagnosed as UTI, resulting in unnecessary antimicrobial exposure. Diagnostic stewardship, which is upstream of antimicrobial stewardship, can assist in limiting overdiagnosis of UTI and reducing unnecessary antimicrobial treatment. Interventions such as requiring a clear clinical indication when ordering UCs, reflex UC policies, and selective reporting of results have the potential to significantly decrease false positive UCs and limit prescribing of unnecessary antimicrobials. Future research on the additive effects of these interventions and synergistic activities with antimicrobial stewardship programs are warranted to demonstrate the true clinical benefit.

Compliance with Ethical Standards

Conflict of Interest Kimberly C. Claeys receives personal fees from Luminex Corporation.

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- • Of importance
- •• Of major importance

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