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State of the Science Review

Promoting appropriate urine culture management to improve health care outcomes and the accuracy of catheter-associated urinary tract infections

Robert Garcia BS, MT(ASCP), CIC, FAPIC [a,*], Eric D. Spitzer MD, PhD [b]

[a] Healthcare Epidemiology Department, Stony Brook University Hospital, Stony Brook, NY
[b] Department of Pathology, Stony Brook University Hospital, Stony Brook, NY

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Published literature indicates that the unjustified ordering or improper collection of urine for urinalysis or culture from either catheterized patients or those without indwelling devices, or misinterpretation of positive results, often leads to adverse health care events, including increased financial burdens, overreporting of mandated catheter-associated urinary tract infection events, overtreatment of patients with antimicrobial agents, selection of multidrug-resistant organisms, and *Clostridium difficile* infection. Moreover, national guidelines that provide evidence-based direction on core processes that form the basis for subsequent clinical therapy decisions or surveillance interpretations; that is, the appropriate ordering and collection of urine for laboratory testing and the treatment of patients with symptomatic urinary tract infection, are not widely known or lack adherence. This article provides published evidence on the influence of inappropriate ordering of urine specimens and subsequent treatment of asymptomatic bacteriuria and associated adverse effects; reviews research on bacterial contamination and preservation; and delineates best practices in the collection, handling, and testing of urine specimens for culture or for biochemical analysis in both catheterized and noncatheterized patients. The goal is to provide infection preventionists (IPs) with a cohesive evidence-based framework that will assist them in facilitating the implementation of a urine culture management program that reduces patient harms, enhances the accuracy of catheter-associated urinary tract infection surveillance, improves antibiotic stewardship, and reduces costs.

Since the Institute of Medicine report "To Err is Human" 19 years ago,[1] hospitals across the United States have modified practices and conducted extensive educational programs aimed at enhancing patient safety. In response to the occurrence of harms, hospital executives have become aware of the importance of not only creating a culture of safety, but also creation of a culture of systems; that is, a culture in which systems of care are carefully assessed, standardized across organizations, and change effectively over time.[2,3] The competency model for infection preventionists (IPs) contains domains needed for instituting successful practices, such as performance improvement and implementation science. The competency model is an essential tool for "...translating evidence into practice, addressing gaps between theory and practice, and serves as a useful clinical model to accomplish improvement in safety, quality, and effectiveness of patient care."[4]

Urinary tract infections (UTIs) are among the most common infections in adults,[5] accounting for nearly 10 million health care visits[6] and 100,000 hospitalizations annually.[7] A subset of UTIs, catheter-associated UTIs (CAUTIs), account for up to 25% of health care-associated infections,[8] with more than 35,600 events reported by acute care hospitals to the National Healthcare Safety Network (NHSN) in 2013.[9] In addition, unjustified ordering or improper collection of urine for urinalysis (UA) or culture from either catheterized patients or those without indwelling devices, or misinterpretation of positive results, often leads to adverse health care events, including increased financial burdens,[10] overreporting of mandated CAUTI events,[11] overtreatment of patients with antimicrobial agents,[12] selection of multidrug-resistant organisms (MDROs),[13] and *Clostridium difficile* infection (CDI).[14] Moreover, national guidelines that provide evidence-based direction on core processes that form the basis for subsequent clinical therapy decisions or surveillance interpretations; that is, the appropriate ordering and collection

* Address correspondence to Robert Garcia, BS, MT(ASCP), CIC, FAPIC, Healthcare Epidemiology Department, Stony Brook University Hospital, 100 Nicolls Rd, Stony Brook, NY 11794.
E-mail address: robert.garcia@sbumed.org (R. Garcia).
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of urine for laboratory testing and the treatment of patients with symptomatic UTI, are not widely known or lack adherence.[15-18]

The purpose of this article is to provide published evidence on the influence of inappropriate ordering of urine specimens and subsequent treatment of asymptomatic bacteriuria (ASB) and associated adverse effects; review research on bacterial contamination and preservation; and delineate best practices in the collection, handling, and testing of urine specimens for culture or for biochemical analysis in both catheterized and noncatheterized patients. The review focuses on adult patients and does not address issues related to neonatal, pediatric, or specialized populations such as transplant patients or those receiving chemotherapy. The goal is to provide IPs with a cohesive evidence-based framework that will assist them in facilitating the implementation of an innovative health care program that reduces patient harms, enhances the accuracy of CAUTI surveillance, improves antibiotic stewardship, and reduces costs.

DEFINITIONS

The existence of varied definitions for symptomatic and asymptomatic UTI can cause disagreements between clinicians and IPs when they attempt to diagnose and/or categorize individual cases. For example, a nonpregnant catheterized female patient presenting with symptomology of a UTI, an abnormal UA, and a urine culture (UC) of $\geq 10^3$ CFU/mL gram-negative bacteria might be diagnosed as having a clinically significant CAUTI based on Infectious Diseases Society of America (IDSA) guidelines.[15] Prior NHSN CAUTI definitions would also have categorized this patient with a reportable CAUTI. However, according to the revised NHSN 2015 CAUTI definition, an IP would not classify this event as a reportable health care-associated infection because the criterion now requires the bacterial colony count to be a minimum of $\geq 10^5$ CFU/mL. This 2-log (100-fold) increase in the threshold for the colony count is among several changes that were introduced in this revision to simplify and increase the specificity of CAUTI surveillance definitions.[19] Conversely, a patient with an indwelling urinary catheter exhibiting fever and identified with $\geq 10^5$ CFU/mL *Escherichia coli* in a UC fulfills NHSN CAUTI surveillance criteria but may not be considered to be a clinical UTI if the patient has a secondary condition causing the fever. Table 1 illustrates the variety of clinical and epidemiologic definitions currently used in health care institutions to assist in diagnosing patients and to determine reportable conditions. Regardless of which definition is being used, a UC comprises the core element of each definition and it must be ordered judiciously, and collected and handled in a manner that increases the accuracy of the outcome.

REASONS FOR INAPPROPRIATE UC AND UA ORDERING

Understanding the underlying reasons why clinicians and nurses order and collect urine specimens is fundamental to formulating an improvement strategy. A recent survey of resident physicians (100 out of 280 responded) used clinical management vignettes to gauge knowledge deficits in urine testing and management.[21] Questions were posed based on commonly encountered scenarios, including elderly patients with confusion, preoperative screening, ASB in a patient undergoing transurethral resection of the prostate, and patients with cloudy urine in the drainage bag. The authors reported a poor overall mean percentage of correct answers of 48%. Questions directed at treatment of ASB were answered correctly only 23% of the time. Further evidence examining potential underlying causes for inappropriate ordering of UCs is found in the exploration of the perceptions of focused groups consisting of physicians and nurses caring for institutionalized elderly patients.[22] A primary finding of the study was that treatment for nonspecific indicators of UTI was common, often considered due to a patient's inability to articulate his or her symptoms; however, there is no evidence in guidelines to support the ordering of UCs and treating positive cultures for patients other than those who are symptomatic. Another survey of medicine and surgery resident physicians reiterated the finding that UCs are often ordered for inappropriate indications, including foul-smelling urine, cloudy or dark urine, or hematuria.[23]

Nurses' knowledge, training, and practices regarding the appropriate reasons for the collection of UCs in catheterized patients was assessed in a 2016 published survey conducted in 5 hospitals of a health care system.[24] Of the 19 questions directed at determining which conditions trigger the collection of a UC on a catheterized patient, a total of 12 (63.2%) were answered incorrectly; that is, did not conform to published clinical guidelines.[15] Among the incorrect selections were collection of urine when foul-smelling or cloudy, during routine catheter insertion, and chronic catheterization on admission. Of interest, the authors found that although 83% of all nurses indicated that they never obtain a urine sample from a drainage bag, only 58.4% reported observing others being compliant with this collection standard.

Identifying complex behaviors contributing to unnecessary urine collection in an emergency department study by using frontline ownership methodology uncovered several issues that may reflect typical practice in many hospitals.[25] Poor compliance with published UC guidelines,[15] staff practice based on outdated policies, the inclusion of urine collection containers in catheterization kits encouraging inappropriate collection, and manual point-of-care urine testing all were contributors to inappropriate UC collection.

EVIDENCE OF INAPPROPRIATE ORDERING OF UC AND UA TESTING

Examples of hospital-based studies documenting the ordering of urine for testing without appropriate clinical reasons are found in the literature. Medical records of a randomly selected group of newly admitted patients over a period of 1 year at the University of Michigan Health System were examined for adherence to guideline recommendations when ordering UCs.[26] Results of the study indicated several glaring findings: of 208 patients in the study, 120 (57.7%) did not meet guideline-based criteria for a UC; 62.5% of those had a reason for culturing that was inappropriate; no documented reason for ordering the UC was found in 37.5% of patients; specific clinical indications were documented in only 23.9% of patients; and for patients meeting criteria, fever was the sole indication for obtaining a UC in nearly three-quarters. In another study conducted at 2 hospitals, it was reported that 68% of UCs were ordered without clinical indication, including 21% from catheterized patients.[27]

A significant number of urine screening tests originate in hospital emergency departments. One group of researchers at a large, tertiary care center retrospectively studied the appropriateness of UA orders on admission to a general medicine service of an emergency department.[28] Assessment of these cases included whether the patient exhibited symptoms of UTI. The study found that the majority of the 198 patients who had UA orders did not have symptoms of a UTI. More importantly, 21.8% of asymptomatic patients who had a positive UA received empirical antibiotic therapy. Likewise, in another emergency department-based examination of UA and UC in elderly patients, results indicated that positive UC rates were only slightly higher in patients exhibiting vague symptoms of UTI than they were in asymptomatic patients treated for nonurologic problems. This suggests that many positive UCs in elderly patients without UTI symptomology were false-positive tests in that they represented ASB and not UTI.[29] These results are not unique. In a third study of 195 emergency department patients who had UAs ordered, the authors reported that 43% had nonspecific signs or symptoms and 19% had no symptoms at all. Physicians ordered

Table 1
Definitions and diagnostic criteria for urinary tract infection (UTI)

Term	Definitions/diagnostic criteria	Source of definition	Reference
Contaminated Urine Culture	Defined as the presence of more than 2 isolates at ≥10,000 CFU/mL	Clinical laboratory	20
Symptomatic UTI	Defined as the presence of significant bacteriuria* in a patient with signs or symptoms referable to the urinary tract and no alternate source	Clinical	15
	Defined by clinical symptoms and a positive urine culture that demonstrates colony counts ≥10^3 CFU/mL	Clinical	10
Asymptomatic bacteriuria	Defined as the presence of significant bacteriuria in a patient without signs or symptoms referable to the urinary tract	Clinical	15
	Defined as the presence of bacteria within the urinary tract in the absence of symptoms and is generally not considered clinically significant except in pregnant women (because if the risk of later development of pyelonephritis), and patients who are to undergo an invasive procedure involving the urinary tract	Clinical laboratory	17
	Defined as the isolation of a specified quantitative count of bacteria in an appropriately collected urine specimen obtained from a person without symptoms or signs referable to urinary infection	Clinical	18
	In women: 2 consecutive clean-catch midvoid specimens with same bacteria ≥10^5 CFU/mL In men: 1 clean-catch midvoid specimen with single bacteria at ≥10^5 CFU/mL Catheterized patients: A single straight catheter specimen with 1 bacterial species ≥10^2 CFU/mL	Clinical	18
Catheter-associated symptomatic bacteriuria	Catheter-associated symptomatic bacteriuria in patients with indwelling urethral, indwelling suprapubic, or intermittent catheterization is defined by the presence of ≥10^5 CFU/mL of ≥1 bacterial species in a single catheter urine specimen in a patient without symptoms compatible with UTI	Clinical	15
Acute uncomplicated cystitis	Term applied to UTI presumed to be confined to the bladder and characterized by symptoms suggesting bladder involvement, such as dysuria or urinary frequency	Clinical laboratory	17
	A symptomatic bladder infection characterized by frequency, urgency, dysuria, or suprapubic pain in a woman with a normal genitourinary tract and it is associated with both genetic and behavioral determinants	Clinical	18
Acute pyelonephritis	A clinical diagnosis of infection that involves the kidney and renal pelvis and is often associated with signs and symptoms of systemic infection, such as fever and rigors. Other findings can include back pain or tenderness and nausea.	Clinical laboratory	17
	A renal infection characterized by costovertebral angle pain and tenderness, often with fever; it occurs in the same population that experiences acute uncomplicated urinary infection	Clinical	15
Complicated UTI	An infection that occurs in patient with a structural or functional abnormality impeding urine flow or in a host with altered defenses that predispose the patient to a higher risk of treatment failure and/or complications. The existence of complicated UTI may predispose the patient to multidrug-resistant organisms and make treatment more difficult. Complicated UTIs occur in <5% of patients who have a UTI	Clinical laboratory	17
	May involve the bladder or the kidneys, and is a symptomatic urinary infection in individuals with functional or structural abnormalities of the genitourinary tract. Uncomplicated UTI rarely occurs in men, and urinary infection in men is usually considered complicated	Clinical	15
Catheter-associated UTI	Catheter-associated UTI in patients with indwelling urethral, indwelling suprapubic, or intermittent catheterization is defined by the presence of symptoms or signs compatible with UTI with no other identified source of infection along with ≥10^3 CFU/mL of ≥1 bacterial species in a single catheter urine specimen or in a midstream voided urine specimen from a patient whose urethral, suprapubic, or condom catheter has been removed within the previous 48 h.	Clinical	15
	A UTI where an indwelling urinary catheter was in place for >2 calendar days on the date of the event, with day of device placement being day 1, and an indwelling urinary catheter was in place on the date of event or the day before. If an indwelling urinary catheter was in place for >2 calendar days and then removed, the date of event for the UTI must be the day of discontinuation or the next day for the UTI to be catheter-associated. Symptomatic UTI, symptomatic UTI 1a, catheter-associated UTI—patient must meet 1, 2, and 3 below: 1. Patient had an indwelling urinary catheter that had been in place for >2 d on the date of event (day of device placement = day 1) and was either: a. Present for any portion of the calendar day on the date of event, or b. Removed the day before the date of event 2. Patient has at least 1 of the following signs or symptoms: a. Fever (>38.0°C), suprapubic tenderness, costovertebral angle pain or tenderness, urinary urgency, urinary frequency, dysuria 3. Patient has a urine culture with no more than 2 species of organisms identified, at least 1 of which is a bacterium of ≥10^5 CFU/mL	Surveillance	19

*Significant bacteriuria is the quantitative level of bacteriuria consistent with bladder bacteriuria, rather than contamination, determined on the basis of growth from a urine specimen collected in a manner to minimize contamination and transported to a laboratory in a timely fashion to limit bacterial growth.

antibiotics in 28% of patients who had no UTI symptoms or non-specific symptoms.[30] These examples focusing on UA and UC orders and empiric treatment of patients provide strong evidence of the need to include EDs in antibiotic stewardship programs addressing UTIs.[31] Indications for appropriate and inappropriate ordering of UCs in patients with and without symptoms of UTI are summarized in Table 2.

EVIDENCE OF INAPPROPRIATE TREATMENT OF ASBS

ASB is defined as “isolation of a specified quantitative count of bacteria in an appropriately collected urine specimen obtained from a person without symptoms or signs referable to urinary infection.”[18] Translating this definition and applying it to an actual patient population is often difficult. Reports indicate that ASB occurs in more

Table 2
Appropriate and inappropriate indications for urine cultures (UC) in asymptomatic and symptomatic patients[11,15,18,24,32,33]

Asymptomatic patients to screen for bacteriuria	Symptomatic patients to screen for a UTI	Asymptomatic patients to avoid screening for bacteriuria	Avoid UC collection or antimicrobial treatment if basing decision solely on 1 or more of the following findings
Before transurethral resection of the prostate Before urologic procedures for which mucosal bleeding is anticipated Pregnant women	In acute uncomplicated UTI, persons exhibiting: Frequency Urgency Dysuria Suprapubic pain In acute nonobstructive pyelonephritis, persons exhibiting costovertebral angle pain and tenderness Complicated UTI: involves bladder or kidneys, and is symptomatic in individuals with functional or structural abnormalities of the genitourinary tract Catheterized patients exhibiting New-onset of or worsening of fever, rigors, altered mental status, malaise, or lethargy with no other identified cause Flank pain Costovertebral angle tenderness Acute hematuria Pelvic discomfort In those whose catheters have been removed the day before any of the following events: dysuria, urgent or frequent urination, or suprapubic pain or tenderness Catheterized patients who have had a catheter in place for >2 wk and have symptoms of catheter-associated UTI with no other recognized source. Urine culture should be obtained only when the catheter has been replaced (if required). If a catheter is not required, obtain a voided midstream urine specimen Spinal cord injury patients: increased spasticity, autonomic dysreflexia, or sense of unease As part of an evaluation for sepsis without a clear source	Premenopausal, nonpregnant women Patients with diabetes Elderly patients (community or institutionalized) Patients with spinal cord injuries Patients with an indwelling urinary catheter On admission for a patient with a chronic urinary catheter	Pyuria Odorous urine Cloudy urine Change in color Sediments Turbidity Screening urine cultures such as on admission Standing orders for urinalysis or urine culture without an appropriate indication Panculturing Repeat urine culture to document clearing of bacteriuria Upon routine catheter insertion

UTI, urinary tract infection.

than 30% of nursing home residents and 100% of those who are chronically catheterized.[34] Complicating these findings is the realization that some hospitalized or institutionalized patients are unable to communicate their specific symptoms[32] and therefore may have nonurinary symptoms attributed to bacteriuria. Such clinical interpretations often trigger unwarranted events, including unnecessary urine testing and false-positive results followed by overtreatment with antibiotics. Guidelines issued by the IDSA on treatment of ASB recommends antibiotic therapy only for pregnant women and for patients undergoing transurethral resection of the prostate or other urologic procedures for which mucosal bleeding is anticipated. Among the patients who should not be screened or treated for ASB are those with indwelling urinary catheters.[15,18,35]

Because ASB is so often associated with inappropriate antimicrobial agent use, performance improvement initiatives should target UC management as a cornerstone in every hospital's antibiotic stewardship program.[36] Several international and national health organizations and accrediting agencies strongly support implementation of initiatives that reduce the use of antibiotics. The World Health Organization,[13] and the federal Centers for Disease Control and Prevention (CDC)[37] have issued alerts and promoted plans for restriction of antimicrobial agents and improving bacterial resistance trends in outpatient and inpatient settings. The recent national action plan looks to reduce the incidence of such organisms as carbapenem-resistant Enterobacteriaceae by 60% by the year 2020[38] using attainable goals that emphasize that each patient will receive "the right antibiotic at the right time at the right dose for the right duration." Of the top-5 recommendations issued by members of the Society of Healthcare Epidemiologists of America and the American Board of Internal Medicine under the Choosing Wisely Campaign, which directs efforts at reducing patient harms, is "don't perform urinalysis [or] urine culture. . ..unless patients have signs and symptoms of infection. . .tests can be falsely positive leading to overdiagnosis and overtreatment."[39] The Agency for Healthcare Research and Quality acknowledges avoiding excessive UCs in catheterized patients as a means to improve antibiotic stewardship.[33] The Joint Commission's new antimicrobial stewardship standard suggests that hospitals assess the appropriateness of antibiotics for UTIs starting January 2017.[40] A position paper jointly issued by the Association of Professionals in Infection Control and Epidemiology (APIC) and Society of Healthcare Epidemiologists of America delineates the key role played by IPs in implementing strategies aimed at appropriate therapeutic use of antimicrobial agents.[41]

Despite the extensive evidence to support proper management,[42] inappropriate treatment of ASB remains widespread. Estimates are that 23%-50% of antibiotic-days for UTI are unnecessary treatment of ASB.[43] Among catheterized patients, mismanagement occurs, in part, because of failure to distinguish between symptomatic and asymptomatic CAUTI. Inappropriate treatment of catheter-associated asymptomatic bacteriuria (CAABU) has been researched.[44] UCs obtained over a 3-month period from catheterized patients at a large Veterans Affairs medical center were reviewed to determine the appropriateness of antimicrobial therapy in patients diagnosed with CAUTI. Of 280 episodes, 164 (58.6%) were deemed to have CAABU and 116 (41.4%) CAUTI. Of the 164 cases of CAABU, 53 (32%) were treated inappropriately with antibiotics. A reason for treatment was stated in 19 of the CAABU events—peripheral leukocytosis (11%), hematuria (8%), pyuria (6%), and other (11%). The authors suspected that these adverse outcomes were due to physician gaps in knowledge, attitudes, and behavior as they relate to guidelines on the management of ASB.

Similar outcomes have been identified in several other studies. Researchers in a study conducted at a large, tertiary care teaching hospital reported that clinicians treated more than half of all catheterized patients with positive UCs with antibiotics although the decision was not based on signs and symptoms of infection but based on age and type of organism.[45] A blinded expert panel reviewing the antibiotic therapy in catheterized patients found discordance among patients with positive UCs (23 of 24 not indicated) and in those having negative urine findings (5 of 6).[46] It was also determined that 69% of antibiotic therapy days related to UCs in the inpatient and outpatient settings were unnecessary. Rates of inappropriate use of antibiotics for ASB among varied inpatient and outpatient populations have ranged from 17%-83% in 10 additional studies, according to a recent review.[32]

EVIDENCE OF COMPLICATIONS STEMMING FROM INAPPROPRIATE TREATMENT OF ASB

Positive UA or UCs collected without the presence of UTI symptoms often leads to overdiagnosis followed by the inappropriate prescribing of antibiotics. Overexposure to antibiotics has been documented to lead to a variety of adverse events. First is the occurrence of untoward drug effects. A Cochrane Library review of 9 randomized controlled trails examining the safety and effectiveness of antimicrobial therapy for ASB in noncatheterized patients concluded that significantly more adverse events occurred in those persons who received antimicrobial agents.[47] The adverse events included diarrhea, rash, dizziness, candidiasis, swollen mouth, and vertigo.[48] Second is the spread of MDROs. The CDC estimates that 20%-50% of all antibiotics prescribed in acute care hospitals are inappropriate and at least 2 million people become infected with bacteria that are resistant to antibiotics with 23,000 deaths annually. The CDC's Core Elements for Hospital Antibiotic Stewardship Programs lists avoiding unnecessary UCs and proper treatment of UTIs among the top-6 infection-specific interventions.[49] The third adverse consequence of antibiotic use is the potential development of CDI. The most important risk factor for CDI is antibiotic agent use.[14,50,51] A recent analysis reported that hospitals with "better" levels of CDI standardized infection ratios used fewer broad-spectrum antibacterial agents and for shorter durations.[52] The fourth consequence of overuse of antibiotics is increased health care costs, with CDI alone contributing from $264 million to $2.9 billion to the burden due to the 107,600 hospital onset cases occurring each year.[53]

TECHNICAL ASPECTS OF UA TEST MARKERS

It is important for IPs to understand the technical aspects of UA processing and interpretation. UA is typically performed in 2 parts, with many laboratories using automated analyzers to perform both portions.[54] The chemical UA portion uses a "reagent strip" that contains various chemically impregnated reaction pads that produce color changes upon contact with urine. Leucocyte esterase (LE) and nitrite reaction pads are 2 of those contained in the strip and are most useful for UTI detection.

LE is an enzyme that is produced by intact leukocytes; that is, white blood cells (WBCs) and the remnants of lysed cells and is a gauge for pyuria.[17] Proteins produced by neutrophils react with ester substrates to produce reactions read as color changes that are proportional to the amount of esterase in the specimen. Clinical laboratories report the result semiquantitatively as negative, trace, moderate, or large.

Nitrite is formed from the conversion of nitrate, a normal substance in urine, specifically by gram-negative members of the Enterobacteriaceae family.[30] Common organisms causing this reaction include *E coli*, *Klebsiella*, *Enterobacter*, and *Proteus.* Because not all pathogens are capable of converting nitrate to nitrite (eg, *Pseudomonas* or enterococci), a patient can still have a UTI despite a negative nitrite test.[5] The nitrate reduction test is most accurate on a first-morning sample or one that has been taken 4 hours or more after the last voiding because this allows organisms sufficient time to metabolize the nitrite.[17] Results are stated as positive or negative. Dipstick tests are most useful in screening symptomatic patients.

The microscopic UA portion serves as a rapid confirmatory test for the presence of leukocytes and bacteria. Concerning leukocytes, the advantage of urine microscopy is that cells and casts can be detected visually; however, they deteriorate quickly in urine that is not fresh and has not been preserved. Leukocytes, the marker for pyuria, are reported as the number of WBCs per high power field (hpf). Bacteria are detected by wet-mount microscopy or Gram stain. The test has been reported to be sensitive for detection at higher colony counts but insensitive for counts $\leq 10^5$ CFU/mL.[5] Results for bacteria are commonly noted as negative, few, moderate, or large.

PERFORMANCE CHARACTERISTICS OF LE AND NITRITE TESTS

The relationship between UA tests for pyuria and bacteriuria, namely LE and nitrite, and the colony counts of UC results is important to note. When evaluating these relationships, Wilson and Gaido[5] came to the following conclusions: the 2 tests when used together perform better than either test individually; the tests' sensitivity rise as the criterion for a significant colony count increases; that is, sensitivity is highest when the definition of a "positive" UC is $\geq 10^5$ CFU/mL; when LE and nitrite are negative, the likelihood is that a UC obtained from the patient will also be negative; that is, the tests have high negative predictive values.[17]

WHEN TO COLLECT CULTURES IN CATHETERIZED PATIENTS

Several national guidelines emphasize that collection of urine for culture from an indwelling catheter should be limited to patients who exhibit symptoms of UTI. The IDSA recommends that "a urine specimen for culture should be obtained before initiating antimicrobial therapy for presumed CAUTI. . .". The guideline provides insight on obtaining a UC in a catheterized patient suspected of CAUTI, recommending that if the catheter is removed, a ". . .UC should be obtained from the freshly placed catheter prior to the initiation of antimicrobial therapy to help guide treatment."[15] APIC concurs with this approach in their publication *Guide to Preventing Catheter-Associated Urinary Tract Infections*.[55] The Society of Urologic Nurses and Associates in their clinical practice advocates that ". . .routine collection of UCs is not recommended. If a patient has a CAUTI, the old catheter should be removed and the specimen should be collected using sterile technique when the new catheter is placed."[56] The intent of collecting urine after replacement of a catheter is to obtain a true specimen of urine from the bladder rather than sampling bacteria contained in biofilms that have formed on the pre-existing catheter tubing wall.[10]

PROPER COLLECTION AND HANDLING OF URINE FOR ANALYSIS AND CULTURE

Laboratory urine specimens are classified by the type of collection conducted. Random specimens are collected at any time and have no specific recommendations on collection. First morning specimens are the preferred choice for UA because the urine will be more concentrated and contains higher levels of cellular and other elements. A midstream clean-catch specimen is the preferred collection method for culture from noncatheterized patients and is less likely to contain contaminants compared with a random specimen. Midstream specimens are typically collected by patients themselves, particularly in clinic settings. If collected by the patient, he or she should be verbally instructed and provided written instructions on the proper procedure to follow.[15] Health care workers assisting in the collection of midstream samples should also receive formal training. Regardless of who collects the sample, specimens collected from women are more likely to be contaminated than those from men due to anatomic considerations. An accepted procedure for collection by women includes several seemingly important steps: the cleansing of the periurethral area and perineum with 2 or 3 cleansing pads with a front-to-back motion, separation of the labial folds, voiding the first few milliliters of urine into the toilet and without stopping the stream, collect the midstream portion of the urine avoiding contact with the inner surfaces of the container or lid.[15,17] However, a recent systematic review of 5 studies found no difference in the odds of contamination between midstream urine specimens collected with or without cleansing.[57] The overall value of the clean-catch midstream urine collection methodology in reducing contamination is difficult to assess because it is problematic to standardize the procedure throughout an organization. Nevertheless, there exist several good examples of posters and videos providing step-by-step instructions for patients.[10,58,59]

For catheter collection specimens, the sampling port should be the only access used to collect a specimen for UA or UC. Specimens should never be collected from the urine collection bag, drainage ports, or other sites.[60,61] Regardless of the collection device used, the collection procedure requires initial clamping of the tubing a minimum of 12 inches below the sampling port allowing urine to fill the tubing, scrub the hub (ie, swabbing of the sampling port with a disinfectant before access), and unclamping of the drainage tube. Urine can be collected using a Luer-lock syringe; however, this method introduces the additional step of connection to a transfer device, followed by insertion of the collection tube. This extra step increases opportunities for contamination. A potentially simpler method is using a dedicated transfer device designed to Luer-fit directly onto a sampling port, thus eliminating the additional step required when using a syringe.[62] Collection tubes with preservatives should be filled to the fill line, generally 4 mL urine, to ensure a proper urine-preservative dilution. Devices intended for other types of collection (eg, clean-catch midstream), should not be used in the collection from a catheterized patient.

It must be re-emphasized that UCs should never be collected from a collection bag. Similarly, foul odor, cloudy appearance, sediment in urine, hematuria, or change in urine color should not be the sole indication for collection of urine samples for testing.[15]

UC CONTAMINATION AND PRESERVATION

Previous literature on important collaborations between IPs and clinical microbiology laboratory personnel stressed the need for enhanced communication on topics that included surveillance for health care-associated infections, outbreak detection and management, generation of timely patient-specific culture and sensitivity data, and education of IPs on testing methodologies and microbiology.[63,64] Evidence presented in this article substantiates the need for IPs to expand collaboration with the laboratory and clinical leaders to address not only limiting UA and UC ordering, but ensuring that samples are obtained in a manner that limits bacterial contamination or overgrowth.

The gold standard for diagnosis of a UTI is identification of a pathogen in a freshly collected specimen of urine.[5] Common methods of collection are either clean-catch midstream specimens from noncatheterized patients or those obtained from an indwelling urinary catheter. Voided samples of urine may be contaminated by organisms from the urethra, skin, genitals, fecal flora,[65] or introduced into the sample by the collector. Hence, the proper collection of urine for culture should have several goals: identify a causative pathogen if present, preserve the organism at a colony count that reflects the patient's clinical condition at the time of collection, and avoid introduction of a contaminant into the specimen. The overgrowth of a pathogen or interpretation of a contaminant organism as a pathogen may trigger unnecessary antibiotic therapy.

Urine can serve as a culture medium for the growth of bacteria and therefore complicates accurate diagnosis of UTI unless collected appropriately. The largest studies conducted to date on outpatient urine contamination and interventions used to control this outcome were directed by the College of American Pathologists. Outpatient urine specimens included those collected in emergency departments, preadmission, and in ambulatory care settings. The 1998 Q-Probes survey of 906 institutions reported a contamination rate as high as 36.8%.[66] A second Q-Probes study of 14,739 specimens processed by 127 laboratories, published in 2008, found that no progress had been made, and that in fact, the low-performance laboratories, with an average rate of 41.7%, had a higher contamination rate than in the previous study.[20] The most effective intervention was refrigeration, which reduced contamination by an average of 50%. Verbal instructions on proper collection also played an important role in those laboratories with low rates of contamination. Researchers reviewing 3 published observational studies on differences in colony counts between immediate and delayed processing of urine specimens stored at room temperature found moderate increases of 10% at 4 hours, but a large increase (>135%) after storage at 24 hours.[57]

Analysis of UC contamination rates across 8 hospitals of a health care network uncovered an average rate of 27.6%. This finding led to a comprehensive performance improvement plan consisting of standardization of collection techniques and products, expediting transport, expanding use of preservatives (refrigeration was found to be impractical), and provision of collection instructions for staff and patients, along with establishment of a systemwide standardized definition and tracking mechanism for UC contamination. These interventions resulted in reducing contamination rates to below the goal of 5%.[67]

A recent investigation suggests that unnecessary clinical interventions stemming from contaminated UCs are a frequent occurrence. A 1-year retrospective study in which emergency department patients or inpatients with contaminated UCs (defined as a UC with >2 organisms at ≥10,000 CFU/mL) were randomly selected for review, identified 139 complications in 64 of 131 patients (48.8%).[68] Among the events attributed to a contaminated UC included initiation of antibiotics (44.3%), urinary catheter removal (13%), placement of a new catheter (12%), and collection of an additional UC (8.4%). Extrapolation for a 1-year period would have resulted in 869 unnecessary interventions.

Current recommendations for urine collection, transport, and culture advocate that if a specimen cannot be transported and plated on culture medium within 2 hours of collection, then the specimen should be refrigerated (2°C-8°C) or preserved during transport; if delayed beyond 24 hours, a collection tube containing a preservative should be used.[15,17,57,69] For many health care institutions, transport and culturing within this time frame is not consistently achievable due to such factors as the physical distances separating ancillary clinics and laboratories, nurse workloads in emergency departments and inpatient critical care units that contribute to delays in transportation, and collection times that may not coincide with laboratory processing schedules. Refrigerators specifically designated for specimens are not available in every clinic setting, emergency department, or inpatient unit, and require temperature monitoring, space, and funding, factors that make this recommendation unrealistic for many health care organizations.

Due to these logistic challenges, many institutions are routinely using UC collection tubes with preservatives. The preservative most often used in UC tubes is buffered boric acid visible in a UC tube as a crystalline pellet. Confirmatory studies have demonstrated that tubes containing boric acid preservation will maintain the original organism load over a 48-hour period at room temperature compared with tubes with no preservation under refrigeration.[70] Researchers at the Johns Hopkins University School of Medicine compared 110 clinical urine specimens initially collected in sterile cups followed by plating on culture medium. Thereafter, specimens were divided into 3 storage criteria and cultured at set time intervals: nonpreserved, refrigerated; nonpreserved, room temperature; and preserved at room temperature. Significant growth occurred in the samples that had no preservative and were stored at room temperature. The authors concluded that use of a preservative at room temperature was equal or better at maintaining organism colony counts than those using a refrigeration strategy.[65]

MODIFICATION OF UA AND UC TESTING PROTOCOLS

A current trend in US health care institutions is to modify clinician ordering practices for UA or urine for culture to limit overuse and better control medical and clinical microbiology laboratory resources. An example of this methodology is reflex urine testing, which restricts UC testing unless a UA sample for a patient is found to be positive for 1 or a combination of 4 specific test parameters that assist in determining a UTI; that is, LE, nitrite, and the presence of WBCs or bacteria.

Reflex urine testing: Retrospective assessment addressing emergency department populations

One study that examined the feasibility of implementing a reflex testing protocol used data gathered from patients aged 5 years and older seen in an emergency department, a hospital unit that often screens for UTI in high numbers.[71] UA criteria included the 4 test parameters, including WBC restriction to >10/hpf. Thirty-nine percent of 1,546 samples would have been eliminated because they were found to have a negative UA and a negative culture. Conversely, 11 of 314 positive cultures (3.5%) would have been missed using this methodology because the UA in these cases was negative. Hertz et al,[72] using data on 4,849 urine samples collected in an emergency department over a 1-year period, reported that if UCs had been canceled based on negative findings in the 4 parameters of the criteria, including WBC >10/hpf, 34.6% fewer cultures would have been performed. The false negative rate in this study was 4.7%.

Reflex urine testing: Retrospective assessment addressing hospital and clinic populations

Using retrospective information obtained on male patients seen through a tertiary-care urology clinic, researchers tested a reflex testing protocol utilizing a UA limitation of >5 WBC/hpf[73] Based on findings that identified the potential avoidance of 69% of UCs while missing 7% of UCs that were positive, the authors concluded that implementation of such a protocol was clinically reasonable for most patients in this population.[73] For patients undergoing planned instrumentation or who have other significant risks, UC should be requested regardless of the UA outcome. The negative predictive value (ie, the probability that a negative UA result would yield a negative UC) were 98.2%, 95.3%, and 97.0% in the 3 previously cited studies[71-73] and nearly 100% in another study of 32,998 hospital and outpatient on clean-catch samples.[74] Foc et al[73] reported a potential cost savings of $46,800 in their urine reflex study.

Reflex urine testing: Pre- and poststudy addressing hospital populations

Using evidence of pyuria at a cutoff of >10 WBC/hpf to trigger UC across 7 ICUs at a large, tertiary care hospital, researchers measured the influence on treatment of ASB as well as overall antimicrobial use over a 2-year study period.[75] Immediately following the intervention, there was a 30% decrease in the rate of UCs performed followed by a 6% month-to-month relative decrease during January-December 2013; bacteriuria decreased 28%; and although there was no significant change in antimicrobial agent use, the number of patients not previously taking antibiotics who were prescribed a new antimicrobial agent decreased from 41%-23%.

A reflex testing protocol has also been trialed among a population of catheterized patients across 5 ICUs at an academic tertiary care hospital in Maryland with assistance from the CDC.[76] The hospital identified significantly high CAUTI rates compared with NHSN benchmarks despite the introduction of a Comprehensive Unit-Based Safety Program 1-year prior. As part of a new intervention plan, the hospital instituted a protocol aimed at reducing unnecessary UCs. As with other studies, pyuria was used as the trigger element, whereby a UC was performed only when WBC were found to be >10/hpf. Results indicated that UC and CAUTI rates across all 5 ICUs decreased significantly for 12 months following the intervention.

Summarizing reflex urine testing

The findings and limitations of reflex urine testing studies as contained in this section can be summarized as follows. First, reflex urine testing relies on addressing UA results after clinicians have already ordered tests rather than trying to elicit informed decisions before placing UA or UC orders. Second, the only study that included both clean-catch and catheter-collected specimens did not report results separated into these categories.[71] Third, when all UA markers test negative, it is likely that the patient does not have a UTI, a finding also applicable among febrile, catheterized ICU patients[77]; however, false-negatives can occur as previously mentioned.[71,72] In contrast, positive UA markers found in emergency department or urology clinic patients have a higher probability of significant UTI than that observed in febrile hospitalized patients who do not have localizing signs and symptoms.[71-73] Individual markers, particularly those for pyuria, are less predictive of a UTI in catheterized patients.[78,79] Positive UA markers often become the sole basis for antimicrobial therapy rather than reliance on patient symptoms.[80] Lastly, and perhaps of most importance, patient symptoms for UTI were not reported in any study.[71-76] Reflex urine testing relies on a strategy of assessment of UA markers whose results when positive, whether singularly or in combination, have not been demonstrated to be reliable as the sole identifier of UTIs. A point–counterpoint review of reflex testing strategies[81] reached the same conclusion, emphasizing that "...careful evaluation of the patient's symptoms before ordering such testing is imperative..." and "...will in turn reduce UA and culture orders, thereby decreasing the utilization of laboratory resources, reducing unnecessary antimicrobial therapy, and improving overall health care costs." This viewpoint has been reiterated by several authors who reviewed the issue of proper ordering of UCs.[77,82]

Study modifying laboratory reporting

A very different but simple approach to control UC processing of specimens obtained from noncatheterized inpatients has been examined. In the trial, UC results were suppressed and physicians were notified by a computer posting to call the microbiology laboratory if they suspected the patient had a symptomatic UTI. Analysis of the UCs found 86% were associated with ASB, whereas 14% were true UTIs. As a result of the intervention, inappropriate treatment for ASB dropped from 48%-12%.[83]

PERFORMANCE IMPROVEMENT PROGRAMS

Rather than attempting to convince clinicians not to treat a positive UC, the most logical and effective strategy appears to be to have a physician not order a urine study on a patient who has nonspecific signs and symptoms of urinary infection. This was the premise of the most comprehensive program to date that attempted to change the behavior of physicians who order UCs and antimicrobial agents in patients with indwelling urinary catheters, details of which were published in 2015.[84] Study and control groups were based at 2 Veterans Affairs hospitals in Texas, with both groups having similar patient populations, house staff involvement, and infection prevention programs. The preintervention year included activities such as catheter insertion and maintenance training and CAUTI surveillance. The key components of the second-year intervention period were the introduction of a diagnostic and treatment algorithm adapted from the IDSA guideline[15] on CAUTI followed by audits, feedback, and inservice workshops aimed at educating clinicians using clinical vignettes and slide presentations. The third year of the study served as the maintenance period during which case presentations were made on a quarterly basis.

Among the study patients, UCs decreased from 41.2 per 1,000 bed-days at baseline to 23.3 per 1,000 bed-days during the intervention period. The maintenance period saw a further decrease to 12.0 per 1,000 bed-days. No significant changes were observed at the control site. Overtreatment of ASB was also significantly improved among the study patients. Rates of ASB treatment decreased from 1.8 to between 0.6 and 0.4 per 1,000 bed-days during the 3 study periods.[84] The program offered by Trautner et al provides support that intervention programs to control UC ordering and inappropriate antimicrobial agent use are an important component in quality improvement movements.

Another important study conducted at 3 hospitals involved the use of a pocket card containing appropriateness criteria for ordering UCs and antimicrobial treatment recommendations based on their institutional antibiograms. Initial educational sessions followed by pharmacist-based interventions resulted in decreases in unnecessary ASB treatment of 9.6% in patients with a urinary catheter, 40.9% in patients without a catheter, and an overall reduction of 23.5%. A key recommendation of the study suggests embedding of selection criteria for signs and symptoms into a decision-making tool within the electronic medical record, allowing for further standardization of UTI clinical decisions.[85,86] It may also be useful for hospitals to review the inclusion of automatic UC collection in electronic care plans because some of these may prove to be inappropriate.

POTENTIAL INFLUENCE OF INAPPROPRIATE URINE COLLECTION ON CAUTI SURVEILLANCE

Why should IPs make efforts to ensure the accuracy of CAUTI surveillance by improving UC management? A recent joint CDC-Centers for Medicare and Medicaid Services communique issued in response to national survey findings related to CAUTIs and forwarded to hospital administrators, reiterates the need for hospitals to ensure that diagnostic urine tests be discouraged in the absence of patient symptoms and, conversely, ordering microbiology testing when clinical symptoms are identified.[87] The APIC response provides talking points on the overall issue of urine testing.[88] As presented here, obtaining unnecessary UCs by panculturing based on nonspecific findings such as fever,[89] or inappropriately collecting or handling of urine specimens increases the risk of detecting asymptomatic CAUTI, introducing a contaminant organism, or permitting the overgrowth of the patient's bacterial pathogen from low-level colony counts to the NHSN CAUTI definition criteria level of $>10^5$ CFU/mL. Such occurrences contribute to overestimation of CAUTI rates, a comparative metric of increasing epidemiologic[11,90] and financial importance.[91] Because of adverse consequences of false-positive results, infection prevention programs cannot rely solely on compliance with insertion and maintenance bundles to reduce the number of reportable CAUTI events. Rather, what is necessary in this situation is a comprehensive CAUTI prevention program that includes a UC management component.[92]

The inclusion of a UC management component as part of an innovative 6 Cs of CAUTI bundle at the Mayo Clinic-Rochester, is a fine example of this evolutionary process in CAUTI prevention.[93] The project, winner of The Joint Commission's 2015 John M. Eisenberg Patient Safety and Quality Award, was instituted in response to high CAUTI rates that occurred despite the implementation of traditional aseptic practices in catheter placement and maintenance. A gap analysis identified several key system elements for targeting, including modification of the electronic medical record to require providers to select appropriate indications for ordering a UC, as well as education needs that were addressed in part by production of a pocket card that reminded staff of new protocols that stressed reasons for not ordering a UC (eg, foul-smelling or cloudy urine) and to not obtain samples while awaiting an order. These efforts resulted in a 30% reduction in infection rate (after factoring for the new NHSN definition changes that took effect in 2015) and a 50% decrease in UCs. In a related approach, Mullin et al[94] focused on reducing CAUTIs by applying critical care guideline recommendations for evaluating fever in critically ill patients. These interventions resulted in a 47% reduction in UCs and a CAUTI rate decrease from 3.0 per 1,000 catheter-days to 1.9 per 1,000 catheter-days over a 1-year period.[95]

GUIDELINE RECOMMENDATIONS ON UC MANAGEMENT

Table 3 summarizes recommendations on UC management as identified in published guidelines. Table 3 includes additional recommendations from the American College of Critical Care Medicine, the American Urological Association, the European Association of Urology, and the National Health Service of England.

RECOMMENDATIONS FOR PERFORMANCE IMPROVEMENT

Based on our review of the literature, UC management should employ the following elements.

Establish a preculture strategy[94] that directs efforts at how cultures are ordered rather than solely addressing issues after a UA or UC test is finalized:

- Modify the electronic medical record to include appropriate and inappropriate indications for UAs/UCs that address patient symptomology,
- Provide education for all clinicians who order UCs with emphasis on appropriate indications for UCs and UTI symptoms in catheterized and noncatheterized patients,
- Carefully evaluate patients with fever and order UCs as appropriate, and
- Reflex urine testing should be considered only if used in conjunction with careful clinical evaluation for signs and symptoms of UTI.

Table 3
Recommendations on urine culture management as contained in published guidelines*

	CLSI 2009 [16]	ASM 2009 [17]	IDSA 2005 [18]	IDSA 2010 [15]	CDC 2009 [61]	CDC-CMS 2015 [87]	SHEA 2014 [60]	ACCCM 2008 [94]	EAU 2015	DOH 2007	AUA 2014
Urine culture ordering and treatment											
Routine ordering of urine cultures is not recommended						√	√	√	√		
The diagnosis of asymptomatic bacteriuria should be based on results of a urine specimen collected in a manner that minimizes contamination			√								
Urine cultures for asymptomatic and symptomatic patients should be limited to specific populations and conditions			√	√		√		√			
Pregnant women should be screened for bacteriuria by urine culture at least once in early pregnancy			√								
Screening for asymptomatic bacteriuria before transurethral resection of the prostate is recommended			√					√			
Screening for asymptomatic bacteriuria before other urologic procedures for which mucosal bleeding is anticipated is recommended			√								
Screening for or treatment of asymptomatic bacteriuria is not recommended for the following persons: premenopausal, nonpregnant women, diabetic women, older persons living in the community, elderly, institutionalized subjects, persons with spinal cord injury, catheterized patients while the catheter remains in situ			√	√							
Urine culture collection and handling											
Obtain urine culture before starting antimicrobial therapy				√					√		
Do not collect specimens based on findings such as foul odor, cloudy urine, hematuria				√							
Collection of midstream clean catch specimens by patients should be preceded by verbal and written instructions to avoid contamination	√	√									
Specimens for urinalysis should be collected as a first morning specimen	√	√									
Specimens for culture from a patient with an indwelling urinary catheter should only be collected from the sampling port		√			√		√	√		√	
Before collection of a specimen for culture from a patient with an indwelling urinary catheter, the sampling port should be disinfected		√			√		√	√		√	
Specimens for culture should never be collected from the collection bag		√		√				√			
When a patient with an indwelling urinary catheter develops symptoms of UTI, the old catheter should be removed, and the sample obtained from a newly inserted catheter; if catheter removed, obtain a voided mid-stream urine sample or from or intermittent catheter		√		√							
Label the specimen indicating patient identifiers, method of collection, time of collection, prior or current antibiotic treatment		√									
For specimens not analyzed within two hours of collection, preserve the specimen using refrigeration or a specifically designed chemical preservative	√	√						√			
Refrigeration temperatures should be in the range of 2°C-8°C	√										
If transported, the container should have a secure closure to prevent leakage, especially important when using pneumatic tube systems	√										
Management of asymptomatic bacteriuria											
Do not treat asymptomatic bacteriuria (exceptions as below)				√	√		√	√			√
Pregnant women should be screened for bacteriuria by urine culture at least once in early pregnancy, and they should be treated if results are positive			√	√	√		√				
Screening for asymptomatic bacteriuria before transurethral resection of the prostate is recommended, and they should be treated if positive			√	√	√		√				
Screening for asymptomatic bacteriuria before other urologic procedures for which mucosal bleeding is anticipated is recommended, and they should be treated if positive			√	√	√		√				

ACCCM, American College of Critical Care Medicine; *ASM*, American Society of Microbiology; *AUA*, American Urological Association; *CDC*, Centers for Disease Control and Prevention; *CLSI*, Clinical and Laboratory Sciences Institute; *CMS*, Centers for Medicare and Medicaid Services; *DOH*, Department of Health, National Health Service of England, *EAU*, European Association of Urology; *IDSA*, Infectious Disease Society of America; *SHEA*, Society of Healthcare Epidemiologists of America.

*Additional references include Grabe M, Bartoletti, Bjerklund Johnasen TE, Cai T, Çek M, Köves B, et al. *Guidelines on Urological Infections.* European Association of Urology; 2015. epic2: National Evidence-Based Guidelines for Preventing Healthcare-Associated Infections in NHS Hospitals in England. *J Hosp Infect*. 2007;655:S1-S64. American Urological Association. Catheter-associated urinary tract infections: definitions and significance in the urologic patient. Available from: https://www.auanet.org/common/pdf/education/clinical-guidance/Catheter-Associated-Urinary-Tract-Infections-WhitePaper.pdf. Accessed October 10, 2016.

Ensure proper collection and handling of urine specimens:

- Delineate policies and procedures and educate personnel on the proper methods to collect UCs, particularly for catheterized patients, emphasizing disinfection of the sampling port and limiting collection of specimens from the port and never from the collection bag; and
- Standardize the use of refrigeration or preservative tubes in all health care settings, including ambulatory clinics and EDs.

Incorporate into the facility's quality monitoring process adherence to UC ordering and collection policies.

CONCLUSIONS

This article presents evidence from varied literature sources that the inappropriate collection and testing of urine specimens and subsequent treatment of false-positive culture results, is a frequent and widespread occurrence. Such events lead to significant patient and institutional harm, including adverse drug effects, overuse of antimicrobial agents, selection of MDROs and *C difficile*, overreporting of CAUTI events, and excess costs. Improvements in UC management will require hospitals to impose a culture change in culturing—a collaborative effort involving IPs, hospital administrators, clinicians, nurses, and microbiologists. Included in this review are important findings that will assist in system and staff behavior analysis that leads to formation of a performance improvement plan that includes appropriate indications for UC collection, modification of clinical practices for urine specimen ordering, proper methods of collection and preservation, as well as coordination with antibiotic stewardship programs.

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