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Controversies in the Diagnosis of Urinary Tract Infections

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Abstract

Urinary tract infection is one of the most commonly encountered infectious diseases in the United States, and urinalysis and urine culture are among the most commonly performed laboratory tests. Despite information in the literature, there continues to be ongoing controversy regarding the appropriate collection method for culture, the utility of urine preservation methodologies, and the work-up of urine cultures containing low numbers of bacteria. We have reviewed the literature to determine optimal specimen collection techniques, the effect of specimen preservation on urine culture results, and the interpretation of low urine culture colony counts.

Introduction

Urinary tract infection (UTI) is one of the most common infectious diseases in both adults and children. In children, UTIs are a common cause of febrile illness in the first 2 years of life, and the majority of UTIs may remain undiagnosed if specific tests, such as urine culture, are not performed. Although most cases of uncomplicated UTI are mild and transient, sequelae of untreated UTIs can include renal scarring, hypertension, and eventually end-stage renal disease, emphasizing that correct and timely diagnosis of UTIs is imperative. Mistakes in the diagnosis of UTIs are common due to a high contamination rate with the inherent difficulty of distinguishing between genuine bacteriuria and specimen contamination (1-3).

The diagnostic approach for patients presenting with symptoms consistent with cystitis or urethritis includes a history, physical exam, and urinalysis. This algorithm should be sensitive enough to diagnose uncomplicated UTIs. However, urine culture continues to be an important diagnostic tool in patients with recurrent UTIs or with previous treatment failure (4), as well as in pediatric patients (5). In addition, with the increase in antimicrobial resistance in urinary pathogens, culture is often necessary so that antimicrobial susceptibility testing can guide therapy (6). Controversies exist regarding optimal specimen collection and preservation to ensure optimal culture recovery and relevance. There are several well-known methods of urine specimen collection and preservation, each associated with its own advantages and disadvantages.

In addition, there has been controversy regarding the significance of low-level bacteriuria. Most clinicians consider bacteriuria to be a definitive marker of UTI, with 10^5 colony-forming units (CFU)/ml of an organism being indicative of infection (7,8). However, more recent studies have suggested that lower levels of bacteriuria (10^2 to 10^4 CFU/ml) should be considered indicative of UTI (4,9,10), raising the question of how and when to follow up on low colony counts. Conversely, low colony counts in urine cultures have traditionally been regarded as a sign of contamination in most patients (11). Other criteria for the definition of contamination have included the growth of two or more isolates at $\geq 10^5$ CFU/ml (12) or the growth of one or more nonpathogens (13).

This review examines the available literature comparing specimen collection and preservation methods in regard to their associated contamination rates. In addition, we have reviewed current guidelines for the follow-up of low-colony-count urine culture results.

Current Urine Specimen Collection Methods

The appropriate collection of urine specimens is critical for the evaluation of culture results. Contamination with perineal, vaginal, or urethral flora is a common problem, even with careful

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patient instruction and specimen collection. The most commonly used methods for obtaining urine for culture are (i) clean catch; (ii) midstream collection; (iii) collection via indwelling catheters; (iv) bagged and diaper specimens, especially in non-toilet-trained children and elderly patients; (v) straight ("in-and-out") catheterization; and (vi) suprapubic aspiration (SPA). Other methods of collection, such as cystoscopy and percutaneous nephrostomy, are not discussed in this review.

Clean-catch midstream specimens

The most frequently used method for urine specimen collection is the clean-catch midstream specimen, which is non-invasive and without risk of iatrogenic UTI. This method includes cleansing of the periurethral area and perineum, spreading the labial folds apart (in women) or retracting the foreskin (in uncircumcised men), and collecting a midstream specimen after voiding the first few milliliters of urine. Appropriate patient education regarding collection is mandatory in order to minimize contamination of the specimen, and still, these specimens are among the most prone to contamination (6). Another disadvantage of the clean-catch midstream collection method is that it is difficult to obtain specimens in a standardized fashion (6). Despite the fact that there is a paucity of scientific evidence supporting clean-catch midstream urine samples as a standard, the method remains the most frequently recommended method of urine collection. Numerous studies have compared the contamination rates of clean-catch midstream specimens with non-clean-catch midstream specimens and reported that there was not a significant difference in contamination between the two collection methods (14-18), concluding that there is no benefit to cleansing the perineum before collection of a midstream urine specimen. Some studies have suggested that spreading of the labia in female patients is an important factor in decreasing the contamination rates of midstream specimens (19). Interestingly, several studies have shown that the contamination of clean-catch midstream specimens is comparable to first-void specimens in both men and women (1,20-23).

Indwelling catheters

Specimens from indwelling catheters are frequently received from hospitalized patients. In patients with any indwelling urinary catheter, the collection port should be used for collection of a specimen with a sterile needle and syringe after disinfection of the port. Specimens should never be collected from collection bags. However, it should be noted that although specimens from indwelling catheters are submitted for culture, urine obtained through an indwelling catheter is often not representative of urine in the bladder (24). Organisms colonizing indwelling catheters are often found in association with a biofilm, which often contains a greater quantity of bacteria and a higher number of bacterial species, including urease-producing organisms, *Enterococcus*, and *Pseudomonas aeruginosa.* For this reason, in the case of suspected UTI, urethral catheters should be removed and replaced, if necessary, prior to specimen collection.

Urine bag technique

In non-toilet-trained children, collection of a clean-catch midstream urine sample can be difficult, if not impossible. Therefore, adhesive urine collection bags are very often used, because they are a non-invasive alternative to catheterization. Unfortunately, they are associated with a high contamination rate, and culture results are therefore often difficult to interpret, so their usefulness and effectiveness are debatable. Most studies agree that a negative culture from a bag specimen effectively rules out a UTI, but it is recommended that positive cultures be confirmed by collection of urine by straight catheterization or SPA (25-27).

Diapers and urine collection pads

Similar to urine collection bags, diapers and urine collection pads are a non-invasive urine collection method frequently used for pediatric and elderly patients. The contamination rate of urine cultures from diapers or collection pads is comparable to that of urine bag specimens (28-31), although there have been studies suggesting that diapers and collection pads show good correlation to specimens collected by catheterization and SPA (32-34).

Straight ("in-and-out") catheterization

Straight (in-and-out) catheterization is a fairly common method of urine specimen collection in children and adults, mainly when they are unable to produce a self-collected specimen, for example, due to an inability to void, or when results from previous midstream, clean-catch specimens have been equivocal. After disinfection, a catheter is inserted into the bladder, the first few milliliters of urine are discarded to avoid contamination by urethral flora that could have collected on the catheter, and the remaining specimen is collected into a sterile container (35). A disadvantage of straight catheterization is the small risk of introducing bacteria into the bladder and inducing an infection (36). In addition, the method is obviously more invasive and potentially painful than obtaining a clean-catch midstream sample.

Suprapubic aspiration

The gold standard for obtaining bladder urine is by SPA, because it is

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associated with the lowest contamination rates. The procedure should only be performed on a full bladder and includes puncturing the bladder with a sterile needle and syringe after disinfection of the overlying skin. In infants, SPA continues to be the method of choice for specimen collection, but in older children and adults, it is rarely used, mainly because there are a variety of other, less invasive methods available. Often, specimens received from adults that are labeled SPA are actually collected from suprapubic catheters and should be considered the same as indwelling-catheter specimens rather than a true bladder aspiration.

Comparison of Specimen Collection Methods

Adults

Prior to 1958, urethral catheterization was routinely used to obtain urine specimens for culture, because the method was thought to be the most effective in avoiding contamination of the sample. In 1958, Beeson (37) published an article arguing against the use of invasive catheterization and supporting the use of clean-catch midstream specimen collection, claiming that "with proper precautions, clean-voided specimens can be used for this purpose." This revolutionary concept of a noninvasive method of urine collection became the new standard, especially in the outpatient setting.

Since the institution of the clean-catch midstream specimen as the standard for noninvasive urine collection, there has been conflicting evidence in the literature of its utility. Walter and Knopp (38) demonstrated that clean-catch midstream urine specimens had contamination rates that were comparable to those of straight catheterization specimens, so the non-invasiveness of the procedure would support clean-catch midstream collection over catheterization. However, another study (21) demonstrated that even an un-prepped void (without prior cleansing) into a nonsterile urine cup showed 95% correlation with specimens collected by cystoscopy. This raises the question of whether pre-voiding perineal cleansing is really necessary and effective in decreasing contamination rates. It is interesting that in these studies, one common factor was spreading the labial folds prior to specimen collection. This suggests that this action may contribute more than cleansing to the collection of a quality specimen. Although there is little scientific evidence supporting clean-catch midstream urine samples as a standard over non-clean-catch sampling, the clean-catch midstream method continues to be advocated as the standard.

Numerous studies conducted on young women in the ambulatory setting have compared the contamination rates of clean-catch midstream specimens with those of non-clean-catch midstream specimens and have reported that there was not a significant difference in contamination between the two collection methods (1,14-18,22,39,40) concluding that there is no benefit to cleansing the perineum before collection of a midstream urine specimen in this patient population. One study (20) included women 16 to 75 years of age and found no significant difference in the number of contaminated cultures between these two collection methods.

Of note, several studies (1,21,41) have also shown that the contamination of clean-catch midstream specimens is comparable to that of first-void specimens in young women. This raises the question of whether midstream collection is really necessary or effective in avoiding contamination of urine specimens. This may be relevant in light of the fact that first-void specimens should be collected for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* nucleic acid amplification testing.

Notably absent from the literature are similar studies in the elderly female population. Collection of midstream, let alone clean-catch midstream, specimens is particularly difficult for older women, and this is likely why they are not included in studies regarding collection methods. One study (42) that did evaluate collection methods specifically in elderly females compared cleansing of the vulva with water, followed by collection of a voided sample into a sterile collection device with SPA. While the voided collection method did detect all patients with a UTI, it also produced a significant number of contaminated specimens. Due to the inherent difficulty of self-collection in these patients, symptomatic patients may require more invasive methods of collection to establish a reliable diagnosis.

A relatively new device for midstream urine collection has been shown to reduce contamination rates in urine cultures (43). The device (Whiz UCD; JBOP Ltd., Oxford, United Kingdom) automatically collects a midstream urine sample by excluding the initial portion of the urinary stream without interruption of urine flow (43), thereby eliminating time-consuming instruction and simplifying the procedure for the patient. A study (43) performed on 2,823 specimens from antenatal women showed that the device significantly reduced contamination rates in urine samples and improved the predictive value of culture.

In males, it has been demonstrated that urethral cleansing does not significantly affect culture results (22,44). However, collection of a midstream specimen does significantly reduce contamination rates (22). Some authors have advocated the collection of voided specimens in males without specific collection instructions, and if a culture of this specimen grows a single or predominant organism at $>10^3$ CFU/ml, then a second specimen should be obtained by the clean-catch midstream method or catheterization (22).

In conclusion, contamination seen with midstream urine specimens is comparable to that seen in specimens obtained following catheterization. Cleansing prior to collection of a midstream urine sample does not appear to be effective in significantly decreasing contamination rates and is comparable to collection of a midstream urine sample without cleansing in non-elderly, ambulatory women, as well as men. Self-collected urine samples in elderly women are difficult to obtain. Culture of a midstream specimen in this population will likely be helpful if it demonstrates no growth but may be difficult to interpret if it is positive. New urine collection devices for females may simplify urine specimen collection further and assist in collection from elderly patients.

Children

SPA or straight (in-and-out) catheterization is the urine specimen collection method of choice in infants and young children who are not toilet trained, whereas clean-catch midstream collection is the most frequently recommended

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method in older, toilet-trained children. SPA is especially recommended in situations where catheterization is not feasible or is inconclusive. The frequent practice of using adhesive collection bags for urine collection has not advocated, because there are data from the older literature suggesting that up to 88% of positive cultures from bagged specimens are false positives due to contamination (45). In addition, specimens may also be obtained by using diapers, since adhesive bags may not adhere properly or may cause perineal discomfort. Specimens obtained using this method suffer from the same issues with contamination. These specimen types are only useful for ruling out UTI when the culture results are negative. However, some authors have suggested that there may be a role for bagged urine specimens as a screening tool to determine whether catheterization is necessary in children at low risk for a UTI (27,46).

More recent studies continue to support this recommendation. A study by Karacan, et al. (3), in 2010 compared four different methods of urine collection (SPA, catheterization, clean-catch midstream, and bagged collection) in 1,067 children suspected of having a UTI. The results of this study showed a contamination rate of 43.9% in bagged specimens, equivalent contamination rates of 14.3% in catheterized and clean-catch midstream specimens, and the lowest contamination rate of 9.1% in the SPA specimens (3). In spite of its high contamination rate, in this study, bagged collection was the most frequently used method of collection in infants and children younger than 2 years of age, while in older children, clean-catch midstream collection was the preferred method of collection. Contamination not only causes erroneous interpretation of urine cultures, it can also mask true infection (30% of contaminated cases in this study were truly infected). Therefore, contamination may lead to unnecessary diagnostic intervention, unnecessary treatment, or delay in diagnosis and treatment (3). Other recent studies (47,48) have compared catheterization to clean-voided, bagged specimens and demonstrated that catheterized urine specimens are superior to bagged specimens and that adverse clinical outcomes based on decisions made from culture results are significantly more common when the bag technique is used (47). Based on their results, Al-Orifi's group recommended catheterization for urine specimen collection in all febrile children younger than 3 months and older febrile children who are not toilet trained and are at high risk for UTI. Another study (25) comparing SPA to bagged urine specimens in 50 children younger than 18 months of age suspected of having UTIs showed that more than half of the bagged specimens produced a false-positive culture result. The authors concluded that SPA is superior to bagged collection and should remain the method of choice for the diagnosis of UTI in infants. In addition, a study by Alam and colleagues (28) demonstrated that pad and bagged specimen contamination were equivalent when compared to each other and that both methods were inferior to clean-catch midstream urine specimens, which had a significantly lower contamination rate.

Several older studies from the 1990s have reported high correlation between culture results from disposable diapers and bagged specimens and that these results correlated with more invasively collected specimens (32,33). However, the results of a more recent study by Farrell and colleagues (49) demonstrated poor correlation between bag and pad specimens, suggesting that pads may have a deleterious effect on bacterial counts. It should be noted, however, that the sample size of this study was very small.

In keeping with the strong evidence in the literature against the use of bagged specimens, the American Academy of Pediatrics in its recent *Clinical Practice Guideline for the Diagnosis and Management of the Initial UTI in Febrile Infants and Children* has recommended the collection of urine via catheterization or SPA in febrile children prior to the administration of antibiotics (50). These guidelines specifically state that the diagnosis of UTI cannot be reliably established using a bagged specimen.

In older, toilet-trained children, the clean-catch midstream technique continues to be the recommended method of collection. However, just as in adults, this technique requires instruction and is still frequently performed incorrectly. While multiple studies (1,11,14,16,17,22) in adults have shown no difference in the contamination rates of clean-catch and non-clean-catch midstream urine specimens, only a few studies have been conducted in toilet-trained children to evaluate the effectiveness of cleaning on the contamination rate of midstream urine specimens (44,51,52). These studies suggested that there was no difference in contamination rates. However, these studies were limited, because they were not randomized and had relatively small sample sizes and the collection techniques were not standardized. A more recent randomized study involving 350 toilet-trained children showed contamination rates of 7.8% in the cleaning group and 23.9% in the non-cleaning group, indicating that a clean-catch midstream collection is superior to a non-clean-catch midstream specimen (13).

In conclusion, SPA is the method with the lowest contamination rate but has the disadvantage of being the most invasive. Catheterization and clean-catch midstream specimens have comparable contamination rates that are slightly higher than those of SPA specimens, and bagged and diaper urine specimens have comparable contamination rates, which are the highest of all available techniques. Current guidelines recommend SPA or catheterization in febrile infants and children at high risk for UTI. Given the high rates of contamination and adverse outcomes associated with bagged and diaper urine specimens, these specimens should not be accepted for culture. In older, toilet-trained children, catheterization does not appear to decrease contamination compared to the less invasive clean-catch midstream collection provided that the patient is instructed regarding appropriate collection technique or observed during collection.

Specimen Preservation

Since urine is an excellent culture medium for bacteria, urine specimens should ideally be processed as near to the time of collection as possible to minimize the chances for an increase in the true colony count of any pathogens or contaminants that may be present. While rapid processing of urine specimens is without doubt the ideal method to avoid loss of fastidious organisms or false- positive cultures, immediate processing is often not possible. Refriger-

ation is an effective conservation method when available, but even this is not always feasible. Studies (53-57) have demonstrated that preservation with boric acid is an effective way to inhibit growth of pathogens or contaminants in urine specimens while they are being transported or waiting to be processed. They have demonstrated the ability of boric acid preservative to maintain the colony counts of most organisms in urine for 24 (53-55) to 48 (56) hours. In order to ensure growth of pathogens, the preservative tube should be filled as recommended by the manufacturer and should be greater than 3 ml; otherwise, the boric acid may inhibit the growth of some bacteria (*Escherichia coli* and *Klebsiella pneumoniae*) on culture (55). One study (55), however, has demonstrated that boric acid urine preservation does not adequately maintain the colony count of *Enterococcus* spp., with increased colony counts seen after 24 hours of preservation. In addition, a British study (58) found that overnight urine preservation with boric acid was associated with a significant alteration of culture results, with inhibition of growth in 16% of specimens and increased growth in 16.2% of specimens, leading the authors to the conclusion that rapid transportation and processing of the urine specimen remains the optimum procedure.

Commercially available urine transport systems can be useful when prolonged transport time is expected and refrigeration is not an option. However, care must be taken to preserve the specimen as quickly after collection as possible and to follow the manufacturer's directions regarding specimen volume to limit potential toxicity. While preservation with boric acid may lead to alteration of bacterial growth (58), it may still be the best available preservation method when immediate processing or refrigeration is not feasible.

Interpretation of Low Urine Culture Colony Counts

Based on the work of Kass (8), most clinicians consider bacteriuria to be a definitive marker of UTI, with $>10^5$ CFU/ml of urine being indicative of a UTI. Conversely, low CFU counts in urine cultures have long been regarded as a sign of contamination (11). Other criteria for the definition of contamination are the growth of two or more isolates at $\geq 10^5$ CFU/ml (12) and the growth of one or more non-pathogens (13). More recent literature (4,9,10) has suggested that lower levels of bacteriuria (10^2 to 10^4 CFU/ml) should be considered positive for UTI in patients with symptoms of cystitis.

It is not well understood why some women with true UTI have lower colony counts. It is possible that the low counts could reflect an early stage of infection or that they could be due to increased efficacy of bladder washout during urination in certain patients (59). When acute symptoms and pyuria are present in female patients, low colony counts in midstream urine specimens may be considered positive (59). Other settings in which a low colony count is more likely to represent true infection rather than contamination are patients already being treated with antibiotics; male patients, in whom contamination is less likely than in female patients; and when organisms other than *E. coli* and *Proteus* are present (especially *Pseudomonas*, *Klebsiella-Enterobacter-Serratia*, and *Moraxella* spp.), particularly in patients with indwelling catheters (59). In these patients, it may be advisable to obtain a repeat urine specimen and follow up low colony counts.

In pediatric patients, determining whether bacteriuria is significant depends on the method of collection and the identification of the isolated organism. In a clean-catch midstream sample, a positive culture has classically been defined as for adults (growth of $\geq 10^5$ CFU/ml of a single uropathogen) (5). In specimens obtained by catheterization or SPA, bacteriuria suggestive of UTI is defined as growth of $\geq 5 \times 10^4$ CFU/ml in the presence of a urinalysis, suggestive of infection (pyuria and/or bacteriuria) (50,60).

Conclusion

UTI is one of the most common infectious diseases in both adults and children. Although most cases of uncomplicated UTI are mild and transient, sequelae of untreated UTI can include renal scarring, hypertension, and even end-stage renal disease, emphasizing that correct and timely diagnosis of UTI is imperative. Mistakes in the diagnosis of UTI are common due to a high contamination rate with the inherent difficulty of distinguishing between genuine bacteriuria and contamination of the sample. Contaminated urine specimens have a direct impact on patient care, introducing delays and increasing costs.

As with other specimens received by the clinical microbiology laboratory, the collection of an optimal specimen is imperative for the generation of optimum culture results. There are different methods of urine specimen collection, each associated with its own advantages and disadvantages. In adults, midstream urine specimens are comparable to catheterized urine samples in terms of contamination rates. In addition, cleansing before collecting a midstream urine sample is apparently not effective in significantly decreasing culture contamination rates in comparison to collection of a midstream specimen without cleansing. Therefore, clinical microbiology laboratories should not require that urines submitted for culture be collected using the conventional clean-catch midstream method and should encourage the collection of appropriately collected midstream specimens. It is imperative that patients be provided with appropriate collection instructions (verbal and written) to ensure optimal specimen quality. Newer urine collection devices for women may simplify urine specimen collection further.

In pediatric patients, SPA or catheterization is the method of choice for collection of urine specimens in non-toilet-trained febrile children. Bagged specimens and urine obtained from diapers should not be accepted for culture because of their unacceptably high contamination rates. In older children, clean-catch midstream collection, rather than midstream collection, should be encouraged as contamination rates are no higher than those found in catheterized specimens.

Because urine is an excellent growth medium for bacteria and it is not always possible to immediately process urine specimens, preservation with boric acid has been advocated and widely practiced. While there have been data to suggest a toxic effect of boric acid on urine specimens that could possibly lead to false-negative results, preservation of urine specimens with boric acid may still be the best method available to avoid bac-

terial overgrowth of specimens.

The diagnostic approach for patients presenting with symptoms consistent with UTI includes history and physical examination, urinalysis, and often urine culture, with susceptibility testing of the resulting uropathogens when indicated. Most clinicians consider bacteriuria to be a definitive marker of UTI, with growth of $>10^5$ CFU/ml of a uropathogen being indicative of infection. However, more recent studies have suggested that lower levels of bacteriuria (10^2 to 10^4 CFU/ml) should be considered indicative of UTI in the appropriate clinical setting, including women with acute UTI symptoms and pyuria, patients already being treated with antibiotics, male patients, and growth of organisms other than *E. coli* and *Proteus*. Lowering the colony count definition of a "positive" culture increases the sensitivity of culture without an appreciable effect on specificity. In infants and young children, an appropriate threshold to consider bacteriuria significant is the presence of $\geq 5 \times 10^4$ CFU/ml. Maintaining a dialog with clinicians regarding the work-up of low numbers of potential uropathogens is imperative to ensure optimal patient care.

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