LABORATORY DIAGNOSIS OF URINARY TRACT INFECTIONS: A REVIEW

1Biswajit Batabyal, 2Bappa Mandal and 3Sukanta Chakraborty

1Department of Microbiology, Gurunanak Institute of Dental Science & Research, Panihati, Kolkata-700114, North 24 parganas, West Bengal, India.
2Department of Pathology, Bankura Sammilani Medical College & Hospital, Bankura, West Bengal, India.
3Consultant pathologist, Theism ultrasound centre, Department of pathology, Dum Dum, Kolkata, West Bengal, India.

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ABSTRACT

Urinary tract infections (UTIs) are among the most common bacterial infections and account for a significant part of the workload in clinical microbiology laboratories. Enteric bacteria (in particular, Escherichia coli) remain the most frequent cause of UTIs, although the distribution of pathogens that cause UTIs is changing. The purpose of this review is to summarize the laboratory diagnosis of routine UTI using current diagnostic methods. The review will not cover the diagnosis of UTI in special patient populations, a topic that merits a separate review.

INTRODUCTION

A urinary tract infection (UTI) is an infection that affects part of the urinary tract. When it affects the lower urinary tract it is known as a simple cystitis (a bladder infection) and when it affects the upper urinary tract it is known as pyelonephritis (a kidney infection). Symptoms from a lower urinary tract include painful urination and either frequent urination or urge to urinate (or both), while those of pyelonephritis include fever and flank pain in addition to the symptoms of a lower UTI. In the elderly and the very young, symptoms may be vague or non specific. The main causal agent of both types is Escherichia coli, however other bacteria, viruses or fungi may rarely be the cause.

Urinary tract infections occur more commonly in women than men, with half of women having at least one infection at some point in their lives. Recurrences are common. Risk factors include female anatomy, sexual intercourse and family history. Pyelonephritis, if it occurs, usually follows a bladder infection but may also result from a blood borne infection. Diagnosis in young healthy women can be based on symptoms alone. In those with vague symptoms, diagnosis can be difficult because bacteria may be present without there being an infection. In complicated cases or if treatment has failed, a urine culture may be useful. In those with frequent infections, low dose antibiotics may be taken as a preventative measure.

In uncomplicated cases, urinary tract infections are easily treated with a short course of antibiotics, although resistance to many of the antibiotics used to treat this condition is increasing. In complicated cases, longer course or intravenous antibiotics may be needed, and if symptoms have not improved in two or three days, further diagnostic testing is needed. In women, urinary tract infections are the most common form of bacterial infection with 10% developing urinary tract infections yearly.

UTIs are challenging, not only because of the large number of infections that occur each year, but also because the diagnosis of UTI is not always straightforward. Physicians must distinguish UTI from other diseases that have a similar clinical presentation, some UTIs are asymptomatic or present with atypical signs and symptoms, and the diagnosis of UTIs in neutropenic patients (who do not typically have pyuria) may require different diagnostic criteria than those used for the general patient population. Because of these factors, physicians frequently rely on a small number of imperfect laboratory tests to augment clinical impressions; even when clinical diagnoses are unequivocal, physicians may order laboratory tests to identify the cause of the infection and/or to provide isolates for antimicrobial susceptibility testing. It therefore comes as no surprise that the laboratory examination of urine specimens accounts for a large part of the workload in many hospital-based laboratories. In fact, in many clinical laboratories, urine cultures are the most common type of culture, accounting for 24%-40% of submitted cultures; as many as 80% of these urine cultures are submitted from the outpatient setting.

The purpose of this review is to summarize the laboratory diagnosis of routine UTI using current diagnostic methods. The review will not cover the diagnosis of UTI in special patient populations, a topic that merits a separate review.
Causes of UTIs

*E. coli* is the cause of 80–85% of urinary tract infections, with *Staphylococcus saprophyticus* being the cause in 5–10% [Nicolle LE; 2008]. Rarely they may be due to viral or fungal infections [Amdekar, S et al.; 2011]. Other bacterial causes include: *Klebsiella*, *Proteus*, *Pseudomonas*, and *Enterobacter*. These are uncommon and typically related to abnormalities of the urinary system or urinary catheterization [Salvatore, S et al.; 2011]. Urinary tract infections due to *Staphylococcus aureus* typically occur secondary to blood-borne infections [Lane, DR & Takhar, SS; 2011].

Sex

In young sexually active women, sexual activity is the cause of 75–90% of bladder infections, with the risk of infection related to the frequency of sex. The term "honeymoon cystitis" has been applied to this phenomenon of frequent UTIs during early marriage. In post-menopausal women, sexual activity does not affect the risk of developing a UTI. Spermicide use, independent of sexual frequency, increases the risk of UTIs [Nicolle LE; 2008].

Women are more prone to UTIs than men because, in females, the urethra is much shorter and closer to the anus [Dielubanza, EJ & Schaeffer, AJ; 2011]. As a woman's estrogen levels decrease with menopause, her risk of urinary tract infections increases due to the loss of protective vaginal flora [Dielubanza, EJ & Schaeffer, AJ; 2011].

Urinary catheters

Urinary catheterization increases the risk for urinary tract infections. The risk of bacteriuria (bacteria in the urine) is between three to six percent per day and prophylactic antibiotics are not effective in decreasing symptomatic infections [Dielubanza, EJ & Schaeffer, AJ; 2011].

The risk of an associated infection can be decreased by catheterizing only when necessary, using aseptic technique for insertion, and maintaining unobstructed closed drainage of the catheter [Nicolle LE; 2001; Phipps S et al.; 2006; & Gould CV et al.; 2010].

Others

A predisposition for bladder infections may run in families. Other risk factors include diabetes [Nicolle LE; 2008], being uncircumcised, and having a large prostate [Lane, DR & Takhar, SS; 2011]. Complicating factors are rather vague and include predisposing anatomic, functional, or metabolic abnormalities. A complicated UTI is more difficult to treat and usually requires more aggressive evaluation, treatment and follow-up [Charles Bryan MD; 2011]. In children UTIs are associated with vesicoureteral reflux (an abnormal movement of urine from the bladder into ureters or kidneys) and constipation [Bhat, RG et al.; 2011].

Persons with spinal cord injury are at increased risk for urinary tract infection in part because of chronic use of catheter, and in part because of voiding dysfunction [Eves, FJ & Rivera, N; 2010]. It is the most common cause of infection in this population, as well as the most common cause of hospitalization [Eves, FJ & Rivera, N; 2010]. Additionally, use of cranberry juice or cranberry supplement appears to be ineffective in prevention and treatment in this population [Opperman, EA; 2010].

Laboratory Diagnosis

Routine urine cultures should be plated using calibrated loops for the semi quantitative method. This method has the advantage of providing information regarding the number of cfu/mL, as well as providing isolated colonies for identification and susceptibility testing. The types of media used for routine cultures should be limited to blood agar and MacConkey's agar. For urine specimens obtained from outpatients, it is not necessary to routinely inoculate a medium that is selective for gram-positive bacteria, because nearly all UTIs in outpatients are caused by aerobic and facultative gram-negative bacteria [Bale MJ, Matsen JM; 1981 & Carroll KC; 1994]. Even in patient populations in which *Staphylococcus saprophyticus* is a common cause of UTIs, it is not necessary to use selective media. In contrast, urine specimens obtained from hospitalized patients are likely to contain enterococci, which have emerged as the second most common cause of nosocomial infections. Laboratories may want to consider inoculating urine specimens obtained from hospitalized patients, or from patients in whom gram-positive bacterial infection is suspected but not documented, to a medium that is selective for gram-positive cocci. A medium such as phenylethyl alcohol suppresses the growth of swarming *Proteus* species and other gram-negative bacilli that can overgrow gram-positive cocci in the specimen. Urine cultures should be incubated overnight at 35°C–37°C in ambient air before being read. There is no added benefit to incubating routine urine cultures for 48 h, provided that specimens are incubated for a full 24 h and that urine specimens containing <10⁴ uropathogens or specimens from patients with suspected funguria are incubated for 48 h [Joho KL et al.; 1995; Murray P et al.; 1992 & Aspevall O et al.; 2002].

Most pathogenic yeasts grow well on blood agar plates, so it is unnecessary to use selective fungal media for urine cultures, even for samples obtained from patients with suspected funguria. Selective fungal media can be used in those rare instances in which there is a high clinical probability that a UTI is caused by a more fastidious yeast or mold. Urine specimens obtained from patients with suspected mycobacterial UTIs should be processed and plated to the appropriate mycobacterial media [Metchock BG et al.; 1999].

Nonculture Methods for the Laboratory Diagnosis of UTI

**Detection of bacteriuria by urine microscopy**

Bacteriuria can be detected microscopically using Gram staining of uncentrifuged urine specimens, Gram staining of centrifuged specimens, or direct observation of bacteria in urine specimens. Gram stain of uncentrifuged urine specimens is a simple method. A volume of urine is applied to a glass microscope slide, allowed to air dry, stained with Gram stain, and examined microscopically. The performance characteristics of the test are not well-defined, because different criteria have been used to define a positive test result. In one study, the test was found to be sensitive for the detection of $10^5$ cfu/mL but insensitive for the detection of lower numbers of bacteria [Carroll KC; 1994].

**Detection of bacteriuria by nitrite test**

Bacteriuria can be detected chemically when bacteria produce nitrite from nitrate. The biochemical reaction that is detected
by the nitrite test is associated with members of the family Enterobacteriaceae (the pathogens most commonly responsible for UTIs), but the usefulness of the test is limited because nitrite production is not associated with urinary-tract pathogens such as S. saprophyticus, Pseudomonas species, or enterococci [Pappas PG; 1991] Another limitation to the test is that it requires testing a specimen of the first urine produced in the morning, as $\geq 4$ h are required for bacteria to convert nitrate to nitrite at levels that are reliably detectable.

Detection of pyuria by urine microscopy

Pyuria can be detected and quantified microscopically by measuring the urinary leukocyte excretion rate, counting leukocytes with a hemocytometer, counting leukocytes in urine specimens using Gram staining, or counting leukocytes in a centrifuged specimen. The advantages to urine microscopy are that leukocytes, leukocyte casts, and other cellular elements are observed directly. One disadvantage to urine microscopy is that leukocytes deteriorate quickly in urine that is not fresh or that has not been adequately preserved. In addition, each of these methods has disadvantages that limit its usefulness as a routine test [Carroll KC; 1994]. Because of these disadvantages, urine microscopy should be limited to patients in whom pyelonephritis or other more serious infections are suspected.

Simultaneous detection of bacteriuria and pyuria.

Commercial urinalysis products include tests for both nitrite and leukocyte esterase, thus providing tests for both bacteriuria and pyuria. The evaluations are not directly comparable because the studies occurred over a 20-year period in a number of different laboratories and health care settings, there were a multiplicity of study designs, and various commercial products were used in the studies. Nonetheless, the tests are sufficiently consistent to allow some conclusions to be made. First, the 2 tests, when used together, perform better than either test performs when used alone. Second, the tests have better performance characteristics for detecting bacteriuria at high colony counts than at low colony counts [Pezzlo MT; 1985]. Third, these tests have low sensitivity, high specificity, low positive-predictive values, and high negative-predictive values. Taken together, the performance characteristics of these tests make them useful as a way to rule out bacteriuria on the basis of a negative test result.

A number of drugs can change the color of urine; abnormal urine color may affect urine tests that are based on the interpretation of color changes. In some cases, this can mask color changes, and in others, it may result in false-positive interpretations [Elkhart, IN: Bayer; 1992].

Interpretation of urine culture results

Microbiologists need to interpret the microbiologic relevance of growth on culture plates to determine whether further identification and antimicrobial susceptibility testing are necessary. Most culture results can be interpreted readily; no growth and gross contamination are both unambiguous results, as are pure cultures of common pathogens growing in a quantity of $>10^8$ cfu per milliliter of urine. The interpretation of cultures that yield pure growth in lower quantities is also clear for specimens obtained via suprapubic aspiration or straight catheterization. On the other hand, interpretation of urine cultures that yield mixed flora in varying quantities can be difficult. Although a number of algorithms have been developed to guide the interpretation of urine cultures, the large number of potential combinations of microorganisms—in varying quantities—and the need to correlate these results with different types of UTIs limits the usefulness of any algorithm. Interpreting culture results for urine specimens yielding common urinary tract pathogens.

Irrespective of the algorithm used to guide interpretation, laboratories should report culture results with interpretive guidelines to help the ordering physician assess the clinical relevance of the results. Cultures that yield unambiguous culture results should be interpreted and reported as such. Test reports for cultures that yield mixed flora in varying quantities should specify the microorganisms that were recovered, the quantity of each microorganism, and the probable clinical importance of each isolate.

Antimicrobial susceptibility testing

Each laboratory should have guidelines by which pathogens are tested for antimicrobial susceptibility. These guidelines should be developed and antimicrobial susceptibility tests should be performed and reported according to the most recent version of the NCCLS guidelines. Bacterial or fungal isolates of uncertain clinical importance should not be tested for antimicrobial susceptibility for purposes of routine patient care.

CONCLUSION

Most patients with uncomplicated acute cystitis have cases that are clinically straightforward, and they may not require any laboratory testing beyond urinalysis. For a significant number of patients, however, the clinical history and physical findings alone may be insufficient to make a definitive diagnosis of UTI. For those patients and for patients with complicated UTIs, laboratory tests are necessary to make the diagnosis and to provide specific information regarding the identity and the antimicrobial susceptibility pattern of pathogens. Both the laboratory diagnosis and the clinical diagnosis of laboratory test results must be made in light of the method of collection used; clinicians should specify the method of collection on test requisition forms. Of the available laboratory tests, urinalysis is helpful primarily as a means of excluding bacteriuria, but it is not a surrogate for culture. Although cultures identify pathogens, the accurate interpretation of culture results requires clinical information that is usually available only to the clinician. We hope that infectious diseases physicians, in particular, will understand both the strengths and the limitations of the laboratory-based diagnostic studies for UTIs that have been reviewed in this article, and we hope that they will incorporate this understanding with current treatment guidelines [Warren JW;1999] to optimize patient care.

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