

A review on Urine Analysis: Decoding Conventional & Recent Techniques in Diagnosing Urinary Tract Infection

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Abstract:

Urinary tract infections (UTIs) are the most common bacterial infections worldwide and account for a significant part in diagnosing at clinical microbiology laboratories. This type of infections can be healthcare-associated or community-acquired and affects millions of people every year. Enteric bacteria remain the most frequent cause of UTIs, although the distribution of pathogens that cause UTIs is changing. Different diagnostic procedures are available but a complete urinalysis including physical, chemical, and microscopic examinations and Culture and sensitivity testing can detect UTI. Midstream sterile collection is acceptable in most situations, but the specimen should be examined within 2-4 hours of collection. Cloudy urine and strong odor may be the result of a urinary tract infection. Dipstick urinalysis is convenient, but not for UTI detection. Uncomplicated urinary tract infection, diagnosed by positive leukocyte esterase and nitrite tests, can be treated without culture. Urine culture may not be necessary as part of the evaluation of outpatients with uncomplicated UTIs, but it is necessary for outpatients who have recurrent UTIs, experience treatment failures, or have complicated UTIs, as well as for inpatients who develop UTIs. This review highlights the advantages and disadvantages of the traditional and currently most used detection methods and which would be suitable to be adapted to UTI diagnosis.

Keywords: Culture and sensitivity, Dipstick, Enteric bacteria, Midstream, Urinary tract infection

Introduction:

Urinary tract infections (UTIs) are among the most prevalent bacterial infections, accounting for 150–250 million cases annually throughout the world. Urinary tract infections (UTIs) constitute one of the most common infections caused by bacteria. While some of these patients return from the outpatient department, while some require urgent emergency care and a small number of them need hospitalization, many of them come back from the outpatient clinic. [1, 2]. These infections are usually caused by bacteria that are part of the host's endogenous microorganisms including *Escherichia coli*, *Enterobacter* species, *Klebsiella pneumoniae*, and *Proteus* species are among the bacteria that typically cause these illnesses as part of the host's endogenous microorganisms [2, 3]. In both hospitalized and immunocompromised individuals, *E. Coli* is the primary cause of nosocomial infections and UTIs in both hospitalized and immunocompromised people. The *K. pneumoniae* is the second cause of UTIs is *K. pneumoniae* [1]. In addition to the patient's health, the costs of hospitalization and treatment for acquired infections of the urinary tract are very significant, in addition to the patient's health status substantial [2, 4].

The purpose of this review is to summarize the laboratory diagnosis of routine UTI using current diagnostic methods and also highlights the advantages and disadvantages of the traditional and currently most used detection methods and which would be suitable to be adapted to UTI diagnosis.

Due to both the enormous number of infections that occur annually and the fact that diagnosing UTIs is not always simple, the annual cost to the health care system for treating UTIs is also significant. The "gold standard" techniques for identifying and detecting pathogenic bacteria in urine include cultural enrichment, bacterial isolation and growth to raise cell counts to levels that can be detected, biochemical and serological testing, and antibiotic susceptibility testing [5]. These tests have lengthy turnaround periods, usually between 48 and 72 hours [6].

When clinical diagnoses are clear, treatment for serious infections must frequently begin without test findings because they are time-sensitive. Delaying treatment while awaiting these results can result in the spread of infectious diseases or related problems in the case of less serious infections. Nanotechnologies and sophisticated molecular-level assays have been developed during the past 20 years as ways to reduce the length of time-consuming procedures. These methods, which rely on molecular and proteomic technologies instead of waiting for bacteria to proliferate, can shorten the time needed for analysis from days to hours, which can affect how well infectious diseases are managed [6].

The goal of this study is to provide an overview of routine UTI laboratory diagnosis utilizing current diagnostic techniques. It also highlights the positive and negative aspects of the most popular and conventional detection techniques, as well as which would be most suited for UTI diagnosis.

Common Causative Agent of UTI:

Enteric bacteria, specifically *Escherichia coli*, are the causative agents of both community-based and hospital-acquired UTIs. Although there is some evidence that the percentage of UTIs caused by *E. coli* is declining, it has been and continues to be the most common cause of UTIs [6]. Numerous findings indicate that while the percentage of UTIs caused by yeasts, group B streptococci, and *Klebsiella pneumoniae* has greatly grown, the percentage of UTIs caused by *E. coli*, *Proteus* species, and *Pseudomonas* species has dropped. [6] *Pseudomonas aeruginosa*, *Enterobacter* species, and *Acinetobacter* species are the main causes of UTIs these days. The most frequent cause of funguria is *Candida albicans*, which is followed by *Candida tropicalis*, *Candida glabrata*, and other yeasts.

Susceptibility to acquire UTI for Hospitalized Patient:

Urinary catheters are crucial tools in different clinical cases, although the UTIs associated with other cases with hospitalization. Urinary catheterization is a very common procedure in which a long tube (catheter) is inserted from the urethra to the bladder to drain or collect urine [7]. Catheter-associated urinary tract infections are very common among

patients with indwelling urinary catheters, with an incidence of around 80% and are responsible for the deterioration of the health status of already debilitated patients, increasing the length of hospital stay, cost of treatment, morbidity and mortality [1,8]. The catheterization period is associated with the clinical context, varies from patient to patient and can go up to several months, in long-term situations. However, it has been reported that most catheters have to be removed earlier than expected due to the occurrence of bacterial colonization that cause catheter obstruction and medical complications [7]. The longer the catheter remains in the patient, the more likely it is to cause this type of infections: the risk of infection is 1–2% for a single day catheterization, with this percentage increasing by approximately 10% each additional day in women, and approximately 3–4% in men [9]. Although necessary and extremely useful in treatment and recovery of patients, urinary catheters weaken the barriers that prevent the colonization of bacteria naturally existent in the urinary tract, leading to biofilm formation. Thus, catheterized patients are more susceptible to pathogenic bacteria, increasing their predisposition to acquire UTIs [10]. The percutaneous nephrostomy catheters are a specific type of catheters that are inserted directly into the kidneys and are indicated for urinary tract obstructions [11]. The occurrence of infections in these situations (with incidence up to 19%) is even more serious due to the risk of pyelonephritis, kidney damage and loss of renal function [12].

Although UTIs are linked to hospitalization in other cases, urinary catheters are essential tools in various clinical situations. In order to drain or collect urine, a lengthy tube (catheter) is introduced from the urethra to the bladder in a technique known as urinary catheterization. [7]

The incidence of catheter-associated urinary tract infections is approximately 80% among patients with indwelling urinary catheters. These infections worsen the health status of already compromised patients and increase hospital stays, treatment costs, morbidity, and mortality [1,8]. The duration of catheterization is related to the clinical context, varies from patient to patient, and can reach several months in long-term

situations. However, it has been reported that most catheters must be removed earlier than anticipated due to bacterial colonization, which causes catheter obstruction and other medical complications [7].

This type of infection is more likely to occur the longer the catheter is in the patient: the risk of infection is 1-2% for a single day of catheterization, and it rises by roughly 10% for every extra day in women and roughly 3-4% in males [9]. Urinary catheters decrease the barriers that prevent naturally occurring bacteria from colonizing the urinary tract, resulting in the creation of biofilms, while being essential and very helpful in patient treatment and recovery. Patients with catheterization are therefore more vulnerable to harmful germs, which increases their risk of developing UTIs [10].

Urinary tract congestion can be treated with percutaneous nephrostomy catheters, a particular kind of catheter that is put straight into the kidneys [11]. The risk of pyelonephritis, kidney injury, and loss of renal function makes the incidence of infections in these circumstances – which can reach 19% – even more dangerous [12].

Importance of Early Diagnosis of UTI more Precisely:

Antibiotics are the most successful therapy for UTIs, thus early detection is essential. Antibiotic-resistant bacteria are becoming more common as a result of antibiotic abuse and overuse, which is a serious worry for the World Health Organization [7]. Despite the presence of worldwide guidelines, abuse of antibiotic prescriptions is rather common, accounting for around 30% of all primary care prescriptions since they are frequently written before a laboratory diagnosis. [2, 8]. As a result, hospital procedures are not appropriately impacted by or therapeutically relevant to clinical practice guidelines.

Severe discomfort in the back, burning or inflammation during urination, murky, dark, crimson, or foul-smelling urine, and fever, which can eventually lead to pyelonephritis, are common signs of UTIs [3]. However, if these signs are identified, the infection can no longer be prevented, and the only course of action is to start treatment, which may be more or less harsh depending on the severity of the infection. This

information is crucial to comprehending the necessity of early UTI detection, as is the emergence of bacterial resistance as a result of drug exposure.

Conventional Techniques of Diagnosing UTIs:

Detection of UTIs by urine microscopy.

Gram staining of uncentrifuged urine specimens, Gram staining of centrifuged urine specimens, or direct examination of bacteria in urine specimens can all be used to diagnose bacteriuria under a microscope. Gram staining urine specimens that haven't been centrifuged is a straightforward and traditional technique. Urine is placed on a glass microscope slide, left to air dry, stained with Gram stain, and then inspected under a microscope. Because numerous criteria have been used to determine a positive test result, the test's performance characteristics are not clearly defined. The test was often found to be insensitive for the detection of lesser numbers of bacteria but sensitive for the detection of 10^5 cfu/mL [12]. The test's limited sensitivity for UTI identification has been reported by other researchers [13–14].

The urine Gram stain test offers the significant benefit of instantly identifying the type of bacteria or yeast causing the infection, which helps the doctor choose an empirical antibiotic treatment. This is not always significant because the Gram stain test has three drawbacks that restrict its applicability in the majority of clinical contexts. First of all, it is an insensitive test that is only consistently positive if the urine contains 10^5 cfu/mL of bacteria; illnesses with bacterial concentrations of 10^2 – 10^3 cfu/mL might not be picked up by this test.

The test may not detect bacteria at concentrations of 10^2 – 10^3 cfu/mL, so it should not be used in the outpatient setting for patients with uncomplicated UTIs. Due to these limitations, its use should be restricted to patients with cases of acute pyelonephritis, patients with invasive UTIs, or other patients for whom it is crucial to have immediate information about the nature of the infecting pathogen. Secondly, the test is too labor-intensive for the majority of clinical microbiology laboratories to offer it.

Detection of bacteriuria by nitrite test.

Chemical detection of bacteriuria is possible when bacteria convert nitrate to nitrite. Because nitrite production is not linked to urinary tract pathogens like *S. saprophyticus*, *Pseudomonas* species, or enterococci, the test's utility is restricted. However, the biochemical reaction that the nitrite test detects is associated with members of the family Enterobacteriaceae, the pathogens most frequently responsible for UTIs [15]. The test's requirement to analyze a sample of the first pee generated in the morning is another drawback because it takes four hours for bacteria to convert nitrate to nitrite at levels that are consistently detectable.

Detection of pyuria by urine microscopy.

By counting leukocytes with a hemocytometer, assessing the urinary leukocyte excretion rate, and counting leukocytes in urine specimens using Gram staining, pyuria can be identified and measured under a microscope. The direct observation of leukocytes, leukocyte casts, and other biological components is one of the benefits of urine microscopy. The rapid deterioration of leukocytes in urine that is not fresh or has not been sufficiently stored is one drawback of urine microscopy. Furthermore, each of these techniques has drawbacks that restrict its applicability as a standard test [12]. Urine microscopy should only be performed on patients who are suspected of having pyelonephritis or other more serious diseases due to these limitations.

Urine culture and Sensitivity (C/S)

When assessing outpatients with simple UTIs, urine cultures might not be required [17, 18]. Urine cultures, however, are required for outpatients with complicated UTIs, therapy failures, or recurrent UTIs. For inpatients who get UTIs, urine cultures are also required. In addition to aiding in the documentation of infection, the bacterial culture is still a crucial test in the diagnosis of UTIs since it is essential for identifying the infecting bacterium or microorganisms and testing for antibiotic susceptibility. The rising prevalence of antibiotic resistance makes this especially true.

Recent & Advance Techniques of Diagnosing UTIs:

Immunoassay using lateral flow. Because the sample and reagents are combined on a paper substrate with liquid transport powered by capillary action and a colorimetric readout, lateral flow assays offer a cost-effective and user-friendly option for point-of-care screening tests. Although dipstick tests for leukocyte esterase and urine nitrite are popular lateral flow assays, their limitations include low sensitivity [6,39]. A human investigation assessed the effectiveness of an antibody-based lateral flow assay for the quick identification of bacteriuria [21]. Rare bacteria and fungus would not be detected by this test, which consists of two monoclonal antibodies: one specific for Enterobacteriaceae and a broader-spectrum antibody against Gram-negative and numerous Gram-positive species, including Staphylococcus, Enterococcus, and Actinomyces spp.

When tested in 966 human urine samples, this lateral flow immunoassay had a sensitivity of 86% for samples containing $\geq 10^3$ cfu/ml bacteria and a specificity of 94% when compared to standard culture (set at 100% sensitivity and specificity), and a sensitivity of 96% for Gram-negative bacteria present at $\geq 10^4$ cfu/ml. These results are encouraging, but more assay testing in a multicenter prospective trial is required to validate the test's accuracy.

Flow cytometry:

This fast screening method, which uses light scattering to identify cells in solution, has been used in numerous devices and can identify the majority of bacterial species as well as fungi [22, 23]. To quickly check for the presence of bacteria in urine, flow cytometry techniques combine light scattering and fluorescence [24]. Flow cytometry has been used to detect pathogen-positive urine for more advanced testing, including mass spectrometry analysis, and is a useful method for choosing samples for additional analysis. Although flow cytometry is simply a screen for bacteriuria because it does not offer species identification or AST for a conclusive diagnosis, it may enhance clinical laboratory workflow by lowering the amount of urine samples submitted for

additional analysis [25, 26]. Differential lysis of Gram-positive and Gram-negative bacteria with sodium dodecyl sulfate and algorithms to differentiate the light-scattering patterns of bacilli from cocci are two more attempts to incorporate some speciation information into light scattering techniques, but these methods are still in the experimental stage.

Molecular and proteomic techniques.

This includes PCR, fluorescence in situ hybridization (FISH), and mass spectrometry (such as matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry), which have been approved in the last 20 years and enhance the diagnosis of bacterial infections [27]. These technologies are currently carried out in a clinical laboratory and necessitate either significant sample processing or initial bacterial separation in order to separate the cells of the bacteria from the urine structure prior to analysis [28].

MALDI-TOF mass spectrometry:

This method uses the mass:charge ratio to identify charged molecules that are produced by ionization. Regulatory bodies have specifically authorized matrix-MALDI-TOF mass spectrometry for the detection of pathogens from culture. The method creates an organism-specific peptide-mass fingerprint that can be matched to a database of reference spectra [29]. A colony from the culture plate is examined after the urine sample has been cultivated to separate the bacteria for use in UTI detection.

Fluorescence in situ hybridization

The basis of fluorescence in situ hybridization (FISH) assays is the microscopic identification of fluorescently labeled nucleic acid probes that have hybridized to complementary targets [30]. FISH is frequently employed in research labs and has been applied to the field of infectious illness clinical diagnostics. 16S ribosomal (r)RNA, an essential part of the bacterial ribosome that comprises both evolutionarily conserved sequences and areas specific to each bacterial species, is a common target for bacterial detection by nucleic acid hybridization techniques like FISH [31]. Moreover, there are more than 10,000 copies

of 16S rRNA in every cell. Although the development of particular probes is necessary for detection, the prevalence of these species-specific sequences makes it easier to detect pathogens using molecular techniques [32].

Multiplex PCR

Since its development in the late 1980s, PCR-based nucleic acid amplification has become a staple of molecular biology and genetic research [33]. The use of PCR in clinical diagnosis applications has been aided by its sensitivity and specificity, which allow the identification of uncommon targets. Several businesses that have created technologies for PCR-based pathogen identification are looking into a role for PCR in direct-from-urine UTI diagnoses.

Real-time microscopy systems for AST

While determining the right antibiotic treatment for each patient depends on determining the organism's antimicrobial susceptibility, accurate pathogen identification is essential to diagnosis. PCR techniques can only identify pathogens and detect known resistance genes; they cannot evaluate all possible combinations of pathogens and resistance mechanisms. Phenotypic AST is still the preferred method, especially for UTI.

Biosensors, microfluidics, and lab-on-a-chip technology

With improved screening, molecular pathogen identification, and quick AST, emerging diagnostic platforms such as biosensors, microfluidics, and lab-on-a-chip technologies show promise for accelerated UTI diagnosis. Since urine is the most common clinical sample, the majority of advancements to date have focused on improving automated processing in the clinical laboratory and reducing turnaround times. This has been done either to increase the yield of screening assays, which lessens the workload associated with processing negative urine samples, or to increase batch processing throughput [34].

Despite their high sensitivity, molecular technologies like MALDI-TOF are mainly restricted to very resource-rich clinical laboratories. Point-of-care testing is possible with

integrated multiplex-PCR technologies (such as GeneXpert Omni and Cepheid), but they are constrained by the absence of integrated phenotypic AST and quantitative pathogen identification. In difficult clinical situations (like encephalopathy [35]), where infectious agents (such as bacteria, viruses, fungi, and parasites) and non-infectious aetiologies are among the differential diagnoses and a conventional culture-based approach has mostly failed, next-generation sequencing platforms are emerging as promising tools.

It is very desirable to have integrated technology platforms that can be used in a clinical laboratory or at the point of care and that can deliver quick diagnostic data (within three hours) to guide individualized antibiotic treatment.

Conclusion:

In order to identify pathogenic bacteria and diagnose UTI, quicker and more accurate methods are required as alternatives to the clinical history and routine examination alone. There is a significant demand for more accurate and effective UTI diagnosis. Rapid profile of bacterial infections and antibiotic susceptibility can guide the initiation of evidence-based treatment, which can enhance patient care and slow the spread of multidrug-resistant pathogens. Finding solutions that can take the place of conventional diagnostic techniques is still a work in progress.

For individuals with complex UTIs, early detection through laboratory testing is essential for diagnosis, specific information about pathogen identity and antibiotic susceptibility patterns, control, and spread. The ideal initial identification is compromised by the fact that all current or planned methods and technologies rely on the patient's history of symptoms. Some needs that are currently unmet were revealed by compiling various approaches and tools and aligning the related benefits and drawbacks. The next generation of diagnostic tools should be based on new technologies that enable the monitoring and prediction of a UTI before the CFU reaches infection levels. In this way, it should be possible to keep track of the amount of bacteria in a patient's urine

and take prompt action to detect asymptomatic bacteriuria, reduce complicated UTIs and antibiotic administration, and shorten hospital stays and treatment-related expenses. Treatment based on objective microbiological analysis would be made possible by the development and use of quick, easy, and accurate UTI diagnostics. The next generation of point-of-care diagnostics may be improved to analyze the host response biomarkers in order to further determine the best course of treatment when host-pathogen interactions increase. Improved antibiotic stewardship could be achieved in addition to the patient's benefit from an early, tailored course of treatment. Precision treatment for this frequent bacterial infection could be made possible by advances in UTI diagnostics, which would allow the proper medication to be administered to the right patients at the right time and dose.

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