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Chapter

Urine Tests for Diagnosis of Infectious Diseases and Antibiotic-Resistant Pathogens

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Abstract

The relation between disease and urine was recognized by physicians since the earliest civilization BC. Urine is considered an ideal diagnostic specimen for its noninvasive and easy method of collection. Urinalysis encompasses a wide range of tests, which includes a variety of chemical tests, urine microscopy, bacterial cultures, and molecular tests. Importantly, urine tests can diagnose patients with antibiotic-resistant urinary tract infections (UTI), directly from urine and/or bacterial culture. This chapter summarizes the most common urine tests in the infectious disease field, with a special focus on diagnosing UTI and characterizing their antibiotic resistant. In addition to describing the advantages and limitation of these tests, the chapter explores the promising emerging technologies and methods in this field. This chapter is beneficial for scientists and healthcare workers in the field.

Keywords: urine, infectious diseases, urinalysis, bacteria, antibiotic resistance

1. Introduction

Urinalysis has been a useful diagnostic tool since thousands of years. Although urine was the first body fluid to be examined by mankind for the diagnosis of diseases [1], it is still one of the most common specimens used in clinical and diagnostic laboratories. Urine samples have been used for the diagnosis of a wide and diverse range of disorders, including but not limited to renal diseases [2, 3], metabolic disorders [4], cancer [5], infectious diseases [6], and others [7–10].

In infectious disease field, urine tests are applied in diagnosing urinary tract infections (UTI) [11–13]. Further, several other infections can be diagnosed by urine tests at different levels [14] including community-acquired pneumonia (CAP) [15], legionellosis [16], tuberculosis [17, 18], congenital cytomegalovirus (CMV) infection [19], and dengue virus [20, 21], and recently, several papers suggest the high value of urinalysis in the detection of Zika virus [22, 23]. Parasites can also be diagnosed from the urine by detection of urinary egg, for example, diagnosis of *Schistosoma haematobium* (*S. haematobium)* [24]. Furthermore, urine has been used for screening of different sexually transmitted diseases (STD) such as *Neisseria gonorrhoeae* and *Chlamydia* sp. [25, 26]. The sensitivity and accuracy of urine test vary according to the agent being detected [14], and in some cases, urinalysis is only performed to exclude other diseases [27].

Many of the aforementioned infections are treated with antimicrobial drugs [28–30], a discovery of the past century that completely changed the medical field and saved millions of lives [31]. Unfortunately, this discovery did not last unchallenged for long; soon after the discovery of penicillin by Sir Alexander Fleming in 1928 [32], the problem of penicillin resistance first emerged in 1947—19 years after its discovery and 4 years after the dug started being mass-produced and was used heavily to treat allied troops fighting in Europe during the World War II. Ever since, antimicrobial resistance (AMR) has become a fierce challenge endangering the existence of many antimicrobial agents [33].

With the emergence of pathogenic strains resistant to almost all available antimicrobial drugs [34, 35] and with only few new drugs in the development and production pipeline [36], AMR is now one of the most urgent global health threats [33]. This emphasizes on the importance of urine analysis and detection of antimicrobial resistance in the diagnostic laboratories.

Treatment of UTI is a good example of AMR impact on the medical field. Many of the antibiotics prescribed traditionally for the treatment of UTIs are now compromised and to a large extent are ineffective [37]. More alarming, recent years have recorded the emergence of bacterial strains that are resistant to even last resort antibiotics such as colistin, making the treatment of UTIs a global challenge [38].

2. Urine tests for infectious disease diagnostics and treatment

A urine specimen is one of the most frequent specimens examined in many of the clinical- and hospital-based laboratories. Urine cultures account for up to 40% of those laboratories' cultures, making it the most common type of culture in such laboratories [27]. Urine is considered an ideal diagnostic specimen for its noninvasive, easy method of collection and the sufficient amount in which it is excreted [14].

The most common infections diagnosed by urinalysis are UTIs, which are one of the most common bacterial infections that require medical intervention. Several other infections such as community-acquired pneumonia and viremia infections can also be diagnosed with the help of urinalysis.

2.1 Urinalysis for diagnosis of urinary tract infection

UTI affects about 150 million around the globe every year [28]. Urinary tract infections are common in women and to less extent in children. Many women experience multiple infections during their lifetimes. Risk factors specific to women for UTIs include female anatomy. A woman has a shorter urethra than a man does, which shortens the distance that bacteria must travel to reach the bladder [39]. UTIs are generally categorized clinically as complicated and uncomplicated based on the presence of risk factors that comprise the urinary tract or the host defense [40]. Both Gram-negative and Gram-positive bacteria can cause UTIs, with *Escherichia coli* representing about 40–70% of the cases [27].

The diagnosis of UTIs is mainly based on urinalysis and the medical history of the patient, with latter being the most essential element [27].

2.1.1 Sample collection

Avoiding contamination is a key element when collecting samples for diagnostic purposes. Bacterial contamination of the urine during collection is always a concern, and midstream urine is recommended for UTI. Clear instruction to the patient is indicated to reduce the risk of contamination with the use of clean containers.

Although methods such as suprapubic aspiration and straight catheter technique can reduce or even eliminate the chances of contamination, they are rarely performed as they are not practical for routine cases [27]. Importantly, these methods are invasive, costly, take a lot of time and effort, and are not risk free. Contamination and infection caused by the catheter used to collect the sample is one example [41]. One of the most common method used for the collection of urine is the clean-catch midstream technique [42], which is simple, noninvasive, and risk free and most importantly gives accurate enough results to be used for routine testing. Nonetheless, contamination of the sample is the main disadvantage of this method [43].

2.1.2 Sample processing

The clinical information obtained from a urine specimen is influenced by the collection method, timing, and handling. An enormous variety of collection and transport containers for urine specimens are available, depending on the type of laboratory test ordered. National Committee for Clinical Laboratory Standards (NCCLS) recommended testing urine sample within 2 hours of collection to avoid false-positive results; however refrigeration or chemical preservation of urine specimens may be utilized if testing or refrigeration within a two-hour window is not possible. A variety of urine preservatives (tartaric and boric acids being the most common) are available that allow urine to be kept at room temperature while still providing results comparable to those of refrigerated urine. Generally, the length of preservation capacity ranges from 24 to 72 hours. Metabolites which can be significantly influenced by the interaction of exposure time and temperature include arginine, glutamine, methionine, phenylalanine, and others, while metabolites which can be significantly influenced by freeze and thaw cycles are the C3 family and histones H1 [44].

2.1.3 Urine microscopy

Bacteria can be simply observed in urine specimens under the microscope, especially after Gram staining. After centrifugation of urine samples, a small amount of the pellet is applied to a glass microscopic slide and stained with the usual Gram-staining protocol. Gram staining can also be done to uncentrifuged specimen; however, there are no definitive criteria to determine positive results with this method, and it is not sensitive for detection of low number of bacteria.

Although Gram-staining test can give relatively fast results about the nature of the causative agent; however it is not practical for routine use, it is labor intensive, insensitive test for concentration of bacteria lower than 10^5 cfu/mL, and time-consuming, making it unsuitable for the patient with uncomplicated UTIs [45].

2.1.4 Urine nitrite test

Enterobacteriaceae are the main causative agent of UTI. They typically produce nitrite, thus making this bacterium chemically detectable. The urine sample for this test should be taken from the first urine produced in the morning, as a minimum of 4 hours are required for the bacteria to produce a detectable amount nitrite. Unfortunately, other bacteria such as *Staphylococcus saprophyticus* cannot produce nitrite, introducing limitation for this test [46].

2.1.5 Pyuria

The presence of pus in the urine (i.e., pyuria) can be detected by various methods. The best and most accurate method is to microscopically measure the urinary

leukocyte excretion rate. Other microscopic methods may also include counting the leukocyte in the urine. However, as the microscopic method is unpractical for routine use, other easier methods such as leukocyte esterase tests for detection of pyuria can be performed. The leukocyte esterase tests have many disadvantages as it produces false-positive results due the presence of eosinophils in the urine. Decreased positive results or false-negative results of this test are referred to other reasons including elevated level of glucose and protein in the urine or if the patient is treated with certain drugs such as cephalexin or tetracycline [47]. The commercial products are believed to be more efficient, although they have low sensitivity, but they are highly specific, and they provide information about both pyuria and bacteriuria [27].

2.1.6 Urine culture

Urine culture is the gold standard in diagnosing UTI. It is crucial not only for the diagnosis but also to guide appropriate antimicrobial prescription and treatment. Patients with complicated UTIs, those who have suffered from recurrent UTIs, or those who are not responding to the empirical treatment are the ones usually subjected for urine culture. In this regard, the most common used culture media are the blood agar and MacConkey's agar. This is especially true for specimen from outpatients, knowing that almost all UTIs in outpatients are caused by aerobic and facultative Gram-negative bacteria, making it unnecessary to use a medium that is selective for Gram-positive bacteria. However, for the hospitalized patients, inoculation of Gram-positive bacteria especially cocci should be considered as enterococci is one of the most common causative agents of UTIs in inpatients. Thus, media routinely used should support growth of both Gram-negative and Gram-positive bacteria.

On the other hand, anaerobic bacteria are rarely a cause of UTIs, and cultures of anaerobic bacteria are usually indicated only for the patient with increased risk of infection with anaerobic bacteria, and those are usually patients with anatomical abnormalities.

For the diagnosis of Candiduria, blood agar which is used for routine bacterial culture can be used perfectly for its detection and other funguria.

2.2 Urinalysis for diagnosis of other infectious diseases

Many systemic infections other than UTIs can be diagnosed utilizing urine samples. This is applied for viral and bacterial infections. Some of the viruses are directly shed in urine such as human polyomaviruses and congenital cytomegalovirus. Other infections can be detected by markers and antigen secretion in the urine. With the rapid development in diagnostic technologies, urine can be utilized to diagnose even a larger number of infectious agents.

2.2.1 Streptococcus pneumoniae

Streptococcus pneumoniae is the number one causative agent of community-acquired pneumonia both in adult and children. In addition, it is underdiagnosed because of the lack of reliable and sensitive diagnostic method. CAP can be diagnosed using various samples including blood, sputum, and urine. Recently, multiple publications [48–50] provided evidence showing that urinalysis and urine specimen can be a very helpful in the diagnosis of CAP with relatively highly sensitive results. Urine immunoassay was used by reference laboratories to determine the course of a complicated outbreak of *S. pneumoniae* complicated by influenza A; this clearly indicates the importance of urine as a diagnostic specimen for the detection of S. *pneumonia* [51].

2.2.2 Legionellosis

Legionella pneumophila is the most common cause of the life-threatening atypical pneumonia known as legionellosis or Legionnaires' disease. Rapid urinary antigen detection kits are the primary choice for the diagnosis of legionellosis. It is considered to be a reliable diagnostic method for the detection of legionellosis with acceptable sensitivity. New tests and assays such as *Legionella* fluorescence immunoassay have been developed. And they seem promising with papers showing a higher sensitivity results [52].

2.2.3 Tuberculosis

Tuberculosis is a worldwide health issue. Many factors make tuberculosis hard to control, and one of them is the lack of fast and accurate diagnostic tools. With lipo-arabinomannan (cell wall glycolipid of *Mycobacterium tuberculosis*) being secreted in the urine, several assays and tools have been developed to detect this marker of infection. However, no urine test until now is sensitive enough to be adopted for routine use [17, 18].

2.2.4 Human polyomaviruses

Infections with polyomaviruses with clinical significance occur generally only in immunocompromised patients; the virus is shed in urine in large quantities. The best way to detect the virus is by electronic microscopy, which is highly sensitive, although it is less sensitive than PCR; however, it might be more reliable clinically. That is because a large portion of the adult population are exposed to the virus, and PCR can give positive results to clinically insignificant cases [53].

2.2.5 Congenital cytomegalovirus

Congenital cytomegalovirus is the leading cause of neurological impairment and nongenetic sensorineural hearing loss. The virus can be cultured from urine and diagnosis can be made from various types of specimen which include urine, blood, and saliva [54]. PCR both quantitative and qualitative is widely used for diagnosis of CMV infection. Qualitative PCR test is intended to detect CMV DNA in urine, whereas quantitative PCR test is performed to detect quantitatively CMV DNA in urine specimens as an aid in identifying or management of CMV infections.

2.2.6 Dengue virus

Dengue virus is a mosquito-borne disease affecting more than 50 million people worldwide yearly. Urine specimen can be used for the early detection of this virus, although RT-PCR and ELISA along with other new methods all of which utilizing blood specimen are usually the way to detect dengue virus.

2.2.7 Zika virus

Zika virus is another mosquito-borne pathogen, and it is endemic to Africa and Southeast Asia. The detection of Zika virus can be achieved by ELISA, but it is usually detected by reverse transcription PCR (RT-PCR) from a serum sample. Some evidence shows that the virus can be detected from mother urine sample even after 10 days of the onset of the disease, which is not feasible with serum samples.

This suggests that detection of Zika virus by real-time RT-PCR from urine specimen can be a valuable diagnostic tool [22].

2.2.8 Sexually transmitted disease

Urine specimen is of valuable importance in the diagnosis of sexually transmitted diseases. Urinalysis can help in diagnosis of *Mycoplasma genitalium*, *Chlamydia*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, and urethritis to name but a few. For example, leukocyte esterase dipstick test as a point-of-care diagnostic tool for urogenital *Chlamydia*, can be a valuable tool to accurately exclude *Chlamydia*. However, it shows low positive predictive value. Furthermore *Chlamydia trachomatis*, *Mycoplasma genitalium*, and *Neisseria gonorrhea* can be detected with PCR and real-time duplex PCR from urine samples [55–58]. Using urine as a specimen for diagnosis of Gonococcal infections by molecular tests has eased out uncomfortable sample collection by urethral swab and hence increased the number of patients volunteering to give specimen for this disease of public health importance.

2.2.9 Parasite detection in urine

Urine microscopy and sediment test analysis help in the diagnosis of urinary parasites like *Schistosoma urinary egg detection.* However, egg detection method is below optimum and requires multiple samples; other methods for the detection of parasite in urine are being investigated. PCR shows promising results in this regards, and many papers are advocating for the clinical establishment of this method for detection of parasites such as *S. haematobium*, *Leishmania infantum*, *Trypanosoma* sp., and others [59–64].

2.3 New technologies and urinalysis

New technological advances have paved the way for significant progress in automated urinalysis [65]. Time and accuracy are the two key factors for diagnosis. In UTIs, urine dipsticks are very fast and easy to use, but it lacks the accuracy, whereas in the other hand, urine culture for antimicrobial susceptibility testing shows clinically reliable and accurate results, but it takes up to 3 days to give results. Many novel and improved diagnostic technologies and tools are introduced in the market, and some of them are already approved for clinical use and helped significantly in increasing the accuracy and decreasing the time of the test; a good example would be nucleic acid tests and mass spectrometry. Some other technologies show promising future such as the utilization of smartphone for urinalysis [65–68].

2.3.1 Flow cytometry

Recently flow cytometry is being introduced as a reliable method for fast diagnosis of UTIs by counting the bacteria in the urine specimen. With the improved counting precision over visual counting methods, highly accurate positive results can be obtained by this method. Detection of bacteriuria can be achieved with clinical standards using flow cytometry technology [69, 70].

2.3.2 Test strip technology

Major improvement in the test strip technology has been made in recent years. Not only highly sensitive test strips are being introduced, but also now, one can find strips, which give quantitative results for urinary proteins. The financial aspect is also

of great importance, especially in the third world and developing countries; inexpensive test strips for various diagnostic reasons such as the diagnosis of diabetes form urine sample are available [71, 72]. Test strip method also shows promising result in antibiotic susceptibility tests; if optimum diagnostic requirement is reached, it can reduce the test time significantly from 2 to 3 days to few hours [73–75].

2.3.3 Automated microscopy

Urine microscopy is one of the most important diagnostic methods for UTIs and other kidney diseases. Manual microscopy is time-consuming and can be labor extensive. Furthermore, with centrifugation decantation and re-suspension always lead to cell loss and cellular lysis. With the current available digital microscopy technologies, a significant time reduction can be archived with much more sample being processed in significantly short time in comparison to manual microscopy. In addition, with the ability to process uncentrifuged urine sample, issues like cell loss and lysis are of no more concern. Many automated analyzers are now available in the market with different kinds of technologies such as laminar flow digital imaging technology and pattern recognition technology [65, 76, 77].

2.3.4 MALDI-TOF

The proteomic method "Matrix-assisted laser desorption ionization–time-of-flight mass spectrometry (MALDI-TOF MS)" for identification of microorganisms directly from culture coupled with Gram stain has given new direction, saved considerable amount of time in diagnosis of UTI, and contributed greatly in the field of clinical microbiology in general. It can identify different pathogens accurately and significantly in short time. The utilization of this technology for the diagnosis of UTIs and furthermore in preforming antibiotic susceptibility tests to decrease the testing time from days to as fast as 2 hours can open wide doors [78, 79].

2.3.5 Urinalysis and smartphones

Smartphone technologies improved the quality of life in countless fronts, and it has large potential for applications in the medical field. With point-of-care testing attracting much attention in recent years, smartphone solutions can be a valuable tool in this regard. It can, for example, increase the compliance of populations with screening programs by offering easy and fast screening method [80]. Studies exploring the possibility of establishing a smartphone-based diagnostic platform for rapid detection of Zika, chikungunya, and dengue viruses showed valuable prospective [20]. Several other smartphone applications utilizing urinalysis for various diagnostic reasons had been tested, and it shows promising future prospective which can greatly help both medical practitioners and patients alike [67, 81, 82].
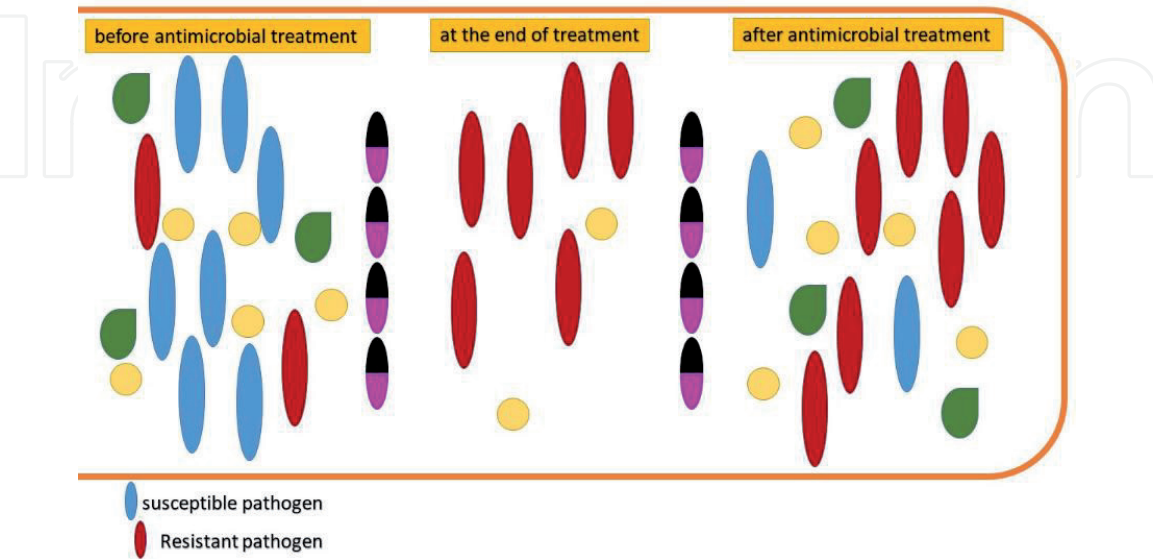
3. Urine specimen and antibiotic-resistant pathogens

The emergence of the antimicrobial resistant pathogen is worldwide issue threatening thousands if not millions of lives every year and with more and more strains developing not only a single drug resistance but also multidrug resistance (MDR) making the treatment of the disease much more complicated. Furthermore, many pathogens have developed resistance against a second-line or even last resort drugs. Recently the emergence of colistin-resistant strains attracted a lot of attention. Some of these resistant pathogens can cause serious illness or even death.

Some *Mycobacterium tuberculosis* strains developed what is called extensively drug-resistant (XDR), a rare form of MDR which shows resistance to at least one of the second-line drugs, isoniazid, rifampin, and fluoroquinolone [83, 84].

Enterobacteriaceae, the leading cause of UTIs, developed resistance to β-lactam antibiotics by producing β- Lactamases, rendering this class of antibiotic to a large extended ineffective [37]. As mentioned above, with the lack of new drug

Figure 1.
Schematic demonstrating how antibiotics can contribute to the AMR crisis and how it can change the microbiome of the patient.

	Susceptible		Resistant	
	n	**Estimated proportion [% (95% CI)]**[*]	**n**	**Estimated proportion [% (95% CI)]**[*]
Amoxicillin	215	62.0 (55.5–68.9)	116	38.0 (31.1–44.5)
Amoxicillin/clavulanate	307	91.3 (87.9–94.6)	12	3.5 (1.5–5.5)
Cefuroxime	323	98.0 (96.4–99.7)	8	2.0 (0.3–3.6)
Cefotaxime	323	98.1 (96.5–99.7)	6	1.5 (0.1–3.0)
Ceftazidime	323	98.1 (96.5–99.7)	3	0.9 (0.0–2.1)
Carbapenems	331	100.0	0	0.0
Fosfomycin	331	100.0	0	0.0
Nitrofurantoin	328	99.6 (99.0–99.9)	3	0.4 (0.0–1.0)
Nalidixic acid	311	94.6 (92.1–97.1)	17	4.6 (0.2–7.1)
Ofloxacin	312	94.9 (92.6–97.3)	11	2.8 (1.1–4.4)
Ciprofloxacin	323	98.1 (96.5–99.7)	6	1.5 (0.1–3.0)
Aminoglycoside	327	98.7 (97.0–99.9)	4	1.3 (0.0–3.0)
Trimethoprim/sulfamethoxazole	278	81.9 (75.9–88.0)	51	17.8 (11.7–24.0)

[*]*Estimated proportion with the sampling design and 95% CI.*
n size in the study population.

Table 1.
Resistance rates among 331 Escherichia coli *from urinary tract infection of women over 18 visiting a French GP in 2012–2013 [85].*

development and only few new drugs being in the production pipeline, UTIs with AMR are a major concern, and it is a leading cause of morbidity and a cause of significant financial loss in many countries. It is estimated that 50% of all women will suffer from UTI at some point in their lives.

The abuse and misuse of antimicrobial drugs are the leading causes of this worldwide issue. Controlling the prescription of antimicrobial drugs by practicing judicial drug prescription based on susceptibility testing is of paramount importance not only to control this fast-growing issue of AMR against currently used drugs in the market but to ensure lasting effectiveness of future treatment options and drugs. This cannot be achieved by the effort of the medical practitioner only, but it needs the active effort of policymakers, scientist, and the large community (**Figure 1**).

Urine specimen can play a major role in fighting against this crisis; urine cultures for the diagnosis of UTIs can be used for susceptibility testing, thus following antimicrobial stewardship program recommendation. Urine specimen has the potential to be used for the same reason in other infectious diseases where the pathogen can be found in urine (**Table 1**).

4. Conclusion

Over the ages, urine proved to be an extremely valuable diagnostic specimen; today, it constitutes one of the most common samples processed in clinical and diagnostic laboratories. Its role in the diagnosis of a wide and diverse range of disorders cannot be argued against, ranging from drugs test and metabolic diseases identification to the diagnosis of STDs and lethal infectious disease. Its importance in antimicrobial resistance tests is also of great value, contributing to achieving the antimicrobial stewardship program recommendations.

With the advances in today's technologies, urinalysis now has great potentials, and the merging of test strip technologies with smartphone technologies can lead to tremendous changes in healthcare system and can deeply integrate point-of-care testing into the health system. Furthermore, advances in mass spectrometry can lead to great achievement not only in the diagnostic field by providing a much faster and accurate results, but it can also contribute greatly in the medical and biomedical research fields.

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