The Abnormal Urinalysis

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The urinalysis is one of the most commonly ordered clinical tests in pediatrics. This frequency is partly due to the ease of urine collection and testing. Urine testing has been a part of medicine for many centuries, with Hippocrates having written about urine examination as early as 400 bc [1,2]. Advances in chemistry allowed significant progress in urine testing during the nineteenth century, and the modern era of reagent strip (dipstick) testing began in 1956 [3]. Urine testing can be used to screen for a number of disorders. Because it is most commonly used in the primary care office setting, the components of the urine dipstick test are emphasized in this article. In addition to the basic urinalysis, this article reviews urine microscopic analysis and the urine quantification tests that are more commonly being used.

Urine screening

The merits of mass screening of asymptomatic healthy children have been debated for some time [4–6]. The American Academy of Pediatrics previously recommended a screening urinalysis at four time points during childhood, but the current recommendation is to obtain a screening urinalysis only at the preschool physical and yearly in sexually active adolescents to look for leukocyte esterase (LE) [7]. Many pediatricians obtain screening urinalyses more frequently. It is common to find abnormalities on urine screening tests, but in most cases, these are transient or due to a false positive reading [8]. Screening can also identify individuals who have subclinical chronic kidney disease who may potentially
benefit from early identification. Mass urine screening is thought to be of benefit in a number of Asian countries [9–11], although it is not clear whether it is cost effective. In the United States, mass screening of asymptomatic individuals has not been shown to be cost effective. Differences in the effectiveness of mass urine screening between populations may be due to different incidence rates of renal diseases or to different approaches to an abnormal urine screening test.

Urine dipstick testing

Urine dipstick analysis remains one of the few tests commonly performed in the primary pediatrician’s clinic. It is used to screen asymptomatic patients and to test for specific indications. Likewise, abnormal findings are sometimes expected and sometimes incidental. It must be remembered that not all abnormal results are clinically significant. Abnormal results can result from pathologic or non-pathologic causes (Table 1). In addition, false positive and false negative results are common (Table 2).

Following certain precautions limits the number of false positive and false negative readings [12]. Reagent strips should be stored in their original container and the lid should be kept tightly closed. Strips should not be used if expired or discolored. Strips should not be exposed to sunlight, moisture, heat, or cold. The specific reagents should be read at the appropriate time after dipping in urine, as recommended by the manufacturer. The strip should not be dipped for more

<table>
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<th>Urine dipstick test</th>
<th>Nonpathologic causes</th>
<th>Pathologic causes</th>
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</thead>
<tbody>
<tr>
<td>SG</td>
<td>Low SG: polydipsia</td>
<td>Low SG: DI, renal tubular dysfunction</td>
</tr>
<tr>
<td></td>
<td>High SG: inadequate volume intake</td>
<td>High SG: volume depletion</td>
</tr>
<tr>
<td>pH</td>
<td>Low pH: high protein diet</td>
<td>Low pH: acidosis</td>
</tr>
<tr>
<td></td>
<td>High pH: low protein diet, recent meal</td>
<td>High pH: renal tubular acidosis (inappropriate renal response), UTI</td>
</tr>
<tr>
<td>Blood</td>
<td>Menses, traumatic catheterization, exercise</td>
<td>Glomerular disorders, tubular disorders, UTI, stones, hypercalciuria, urinary tract trauma, tumor</td>
</tr>
<tr>
<td>Protein</td>
<td>Orthostatic proteinuria, fever, exercise</td>
<td>Glomerular disorders, tubular disorders, UTI</td>
</tr>
<tr>
<td>Glucose</td>
<td>Renal glycosuria</td>
<td>Diabetes mellitus, Fanconi syndrome</td>
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<tr>
<td>Ketones</td>
<td>Restricted carbohydrate intake</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>None</td>
<td>Hepatitis, biliary obstruction</td>
</tr>
<tr>
<td>Urobilinogen</td>
<td>Low: systemic antibiotic therapy</td>
<td>Hepatitis, intravascular hemolysis</td>
</tr>
<tr>
<td>Nitrite</td>
<td>None</td>
<td>UTI</td>
</tr>
<tr>
<td>LE</td>
<td>Fever</td>
<td>UTI, glomerulonephritis, pelvic inflammation</td>
</tr>
</tbody>
</table>

Table 1
Pathologic and nonpathologic causes of abnormal urine dipstick findings

False positive and false negative causes of abnormal results are not included.

Abbreviations: DI, diabetes insipidus; SG, specific gravity; UTI, urinary tract infection.
than a second in the urine, and excess urine should be blotted off on the edge of absorbent paper to prevent mixing of reagents. A midstream urine specimen reduces contamination. When the urine will not be tested for more than an hour, it should be refrigerated. When the urine has been refrigerated, it should be allowed to warm to room temperature before performing the urinalysis.

**Color and appearance**

The normal appearance of a freshly voided urine sample is clear and pale to dark yellow. A number of medications and foods can alter the appearance of urine [2]. Substances that cause abnormal urine color may affect the readability of all reagent strip tests, which could result in false positive or false negative readings. Urine may have a cloudy appearance from sitting at room temperature for a pro-

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**Table 2**

<table>
<thead>
<tr>
<th>Urine dipstick test</th>
<th>False positives</th>
<th>False negatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>SG</td>
<td>Contamination during collection/storage</td>
<td>None</td>
</tr>
<tr>
<td>pH</td>
<td>High pH from urease producing organisms (eg, <em>Proteus mirabilis</em>), prolonged standing of urine</td>
<td>Low pH from mixing of reagents from adjacent test pads</td>
</tr>
<tr>
<td>Blood</td>
<td>Oxidizing contaminants (eg, hypochlorite), microbial peroxidase associated with UTI</td>
<td>High ascorbic acid, large nitrites, high SG</td>
</tr>
<tr>
<td>Protein</td>
<td>Fever, exercise, alkaline urine, concentrated urine, presence of cells/bacteria in urine</td>
<td>Dilute urine, low molecular weight proteins</td>
</tr>
<tr>
<td>Glucose</td>
<td>Strong oxidizing agents in urine container</td>
<td>Ascorbic acid, high SG, exposure to humid environment</td>
</tr>
<tr>
<td>Ketones</td>
<td>Captopril, methyldopa</td>
<td>Prolonged standing of urine, moisture on test pad</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>Rifampin, chlorpromazine</td>
<td>Ascorbic acid, prolonged standing in light</td>
</tr>
<tr>
<td>Urobilinogen</td>
<td>Alkaline urine, sulfonamides&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Broad-spectrum antibiotics, discolored urine, prolonged standing in light</td>
</tr>
<tr>
<td>Nitrite</td>
<td>Urine contamination, medications that turn urine color to red, gross hematuria</td>
<td>Inadequate dietary nitrate intake (vegetables), non–nitrate-reducing bacteria, insufficient incubation time for conversion of nitrate to nitrite, ascorbic acid, high urobilinogen</td>
</tr>
<tr>
<td>LE</td>
<td>Contamination with vaginal fluid, oxidizing agents, <em>Trichomonas</em></td>
<td>Ascorbic acid, high protein, high glucose, high SG, cephalosporins, tetracycline, nitrofurantoin</td>
</tr>
</tbody>
</table>

*Abbreviations:* SG, specific gravity; UTI, urinary tract infection.

<sup>a</sup> For Multistix (Bayer Corporation, Elkhart, Indiana).
longed period (>1 hour), triphosphate crystals (seen in alkaline urine), increased urates, urinary tract infection (UTI), pyuria, or high concentration. If cloudy urine is obtained and there is no suspicion for UTI based on clinical presentation or urinalysis, then a repeat urinalysis with microscopy should be performed on a freshly voided specimen after instructing the family to increase the patient’s fluid intake. If the repeat urine is clear and the patient is asymptomatic, then the patient can be observed without further work-up.

Specific gravity

The specific gravity (SG) reagent on the dipstick is sensitive to the number of ions in the urine specimen and is a measure of urine concentration. Usually, it simply reflects recent fluid intake but should be interpreted with the clinical situation in mind. A urine SG of 1.010 approximates a urine osmolality of 300 mOsm/L. A low urine SG in a patient clinically euvoletic is likely nonsignificant. Low urine SG in someone who appears dehydrated can result from a renal concentrating defect. A high urine SG may reflect lack of recent fluid intake in an otherwise healthy-appearing child or dehydration in someone who has been ill. Glycosuria and recent intravenous contrast can result in a false elevation of urine SG when calculated in the laboratory by a refractometer or urinometer but not on the urine dipstick.

pH

Urine pH varies with acid–base balance and can range from 5 to 8 in healthy individuals. On a typical Western diet, the urine pH is usually around 6. The urine pH is primarily of interest in limited clinical situations such as metabolic acidosis and with certain types of kidney stones. A low urine pH promotes the formation of uric acid and cystine stones, whereas high urine pH promotes calcium-phosphate precipitation. Urine pH is reliable only on a freshly voided specimen.

Hemoglobin

The urine dipstick is very sensitive to intact red blood cells (RBCs) and even more so to free hemoglobin. In dilute urine, the dipstick may react more strongly positive than the degree of actual hematuria due to lysis of RBCs and release of free hemoglobin. Because the reagent strips are so sensitive, the finding of transient hematuria is common. In a large screening study of school-aged children, 4% of children had a urine dipstick positive for blood on at least one of four urine specimens taken over a 2-day period. Of the subjects who had at least one positive urine test for blood, however, 74% had only one of four specimens positive and only 6% had blood detected in all four samples [13]. Therefore, in asymptomatic patients who had urine dipstick positive for blood and an otherwise normal urinalysis, the initial step in management should be to obtain at least two repeat urinalyses on different occasions to rule out transient hematuria.
When a dipstick is persistently positive for blood, a microscopic examination of the urine should be performed (see later discussion). The differential diagnosis of hematuria is extensive and the work-up should be tailored to the patient’s presentation [14,15]. Recent data favor a more limited work-up for isolated microscopic hematuria [16,17].

**Protein**

Under normal circumstances, low molecular weight proteins and a small amount of albumin are filtered through the glomerular capillary wall. Most of the low molecular weight proteins are reabsorbed in the tubules, whereas Tamm-Horsfall protein is secreted. As a result, up to 150 mg/d (in adults) or 4 mg/m²/h (in children) of protein in the urine is considered to be within normal limits. In glomerular disease, the primary protein excreted is albumin, whereas in tubular disease, low molecular weight proteins, which would usually be reabsorbed, are excreted in the urine. One limitation of the urine dipstick is that it primarily detects albumin but not low molecular weight proteins. In addition, it is possible to have elevated albuminuria that is still below the threshold of detection by the standard urine dipstick (see later discussion).

Negative or trace protein on the dipstick is considered normal, whereas a protein value of 1+ should at least be monitored. The presence of increased protein in the urine can signify underlying renal disease, although there are a number of false positives/negatives. When there is a concern for a false positive or false negative reading, the amount of proteinuria can be quantified by the urine protein/creatinine ratio on a random urine specimen (see later discussion). The reader is referred elsewhere for the evaluation of proteinuria [18,19]. A common cause of proteinuria in asymptomatic patients is orthostatic proteinuria, a benign diagnosis, which should be ruled out using a first morning void specimen before pursuing further evaluation.

**Glucose**

Glucose is freely filtered at the glomerulus but is almost completely reabsorbed in the proximal tubule. The appearance of glucose in the urine may reflect high plasma glucose, resulting in a glucose load in the filtrate that exceeds the proximal tubule’s ability to reabsorb glucose. Typically, glucose does not appear in the urine until the plasma level exceeds 180 to 200 mg/dL. Alternatively, glycosuria may reflect a defect in the proximal tubule cells’ ability to reabsorb a normal filtered glucose load. When this defect is an isolated one, it is termed renal glycosuria and is due to a mutation in the SGLT2 transporter [20]. The glucose wasting that occurs is not clinically significant. More commonly, the defect is part of a generalized proximal tubule cell dysfunction referred to as Fanconi syndrome. Other manifestations of Fanconi syndrome include phosphorus wasting resulting in hypophosphatemia, bicarbonate wasting resulting in a proximal renal tubular acidosis, sodium wasting resulting in polyuria, and
aminoaciduria. Although the loss of glucose may not be clinically significant, the loss of phosphorus and bicarbonate often requires replacement therapy. Fanconi syndrome should be considered in any patient who has glycosuria and normal serum glucose.

**Ketones**

Ketone production is increased when there is altered glucose metabolism. The increased breakdown of fatty acids generates ketones. Ketones in the urine are most commonly seen in patients whose nutritional intake has been compromised by illness or starvation. Ketones can also be seen with uncontrolled diabetes mellitus, a high-fat/low-carbohydrate diet (eg, ketogenic diet), liver disease, and certain forms of glycogen storage disease [12].

**Bilirubin and urobilinogen**

Bilirubin is a breakdown product of hemoglobin formed in the reticuloendothelial cells. Unconjugated bilirubin such as that observed with hemolysis is not water soluble, remains tightly bound to albumin, and is not filtered at the glomerulus. After bilirubin is conjugated to bilirubin glucuronide by the liver, it is water soluble and can appear in the urine. In the normal individual, the amount of bilirubin in the urine is below the threshold of detection of most reagent test strips. Most conjugated bilirubin is eliminated in bile into the gastrointestinal tract. The appearance of bilirubin in the urine suggests obstruction to bile outflow or hepatitis. The presence of bilirubin in the urine can be confirmed with the diazo test method (eg, Ictotest [Bayer Corporation, Elkhart, Indiana]), which is more sensitive and less affected by the color of the urine.

Urobilinogen is formed in the colon when bacterial glucuronidases hydrolyze conjugated bilirubin followed by reduction of free bilirubin to urobilinogen. Most urobilinogen is excreted in the feces, but up to 20% is reabsorbed and enters the portal circulation. The liver then re-excretes most of this urobilinogen into the bile, and a small amount of urobilinogen is usually seen in the urine. Patients who have liver dysfunction may have decreased hepatic uptake with resulting increased urobilinogen in the urine. With biliary obstruction, the amount of urobilinogen is more variable, but with severe obstruction, urobilinogen can be negative due to the absence of bilirubin in the intestines. Unlike bilirubin, urobilinogen is increased in the urine following hemolysis.

**Nitrite and leukocyte esterase**

Members of the gram-negative, rod-shaped Enterobacteriaceae family are able to reduce dietary nitrate to nitrite. Positive nitrites in the urine are strongly suggestive of the presence of a significant number of bacteria, and a urine culture should be performed. Because the bacteria require 4 hours to convert nitrate to nitrite, a false negative can occur if the urine has not been incubating in the
urinary tract for sufficient time. Therefore, the test is best done from a first morning specimen.

The presence of LE in the urine suggests the presence of neutrophils, whether due to infection or some other inflammatory process. Neutrophils can be labile in urine; thus, the presence of LE may detect the enzyme remnants of cells that are no longer visible on microscopic examination.

In a meta-analysis study, urine dipsticks performed nearly as well as Gram stain for predicting UTI. The sensitivity for detecting UTI using the presence of LE or nitrite was 0.88; when LE and nitrite were present, the false positive rate was 0.04 [21]; however, it is still recommended that UTI be confirmed with a urine culture [22]. A reasonable and cost-effective strategy is to obtain urine culture on children suspected to have UTI and start empiric antibiotic therapy on those who have at least moderate LE or positive nitrites on urine dipstick [23] or have symptoms strongly suggestive of UTI until the culture results are available.

**Urine microscopy**

Microscopic examination of the urine primarily consists of examining the urine for the presence of cells, casts, crystals, and bacteria. Urine microscopy should be performed on any patient who has persistent hematuria or proteinurias and may be useful if the urine dipstick is suggestive of UTI. To examine urine sediment to further evaluate hematuria/proteinuria, approximately 10 mL of urine should be centrifuged for 5 minutes, the supernatant decanted, and the remaining drop examined on a clean slide.

**Cells**

*Red blood cells*

In most cases, two or less RBCs per high-power field is considered normal, although some laboratories may have a slightly different reference range. When a patient has persistent urine dipsticks positive for blood, it is important to confirm the presence of increased RBCs by microscopy. In dilute urine of normal color, a heme-positive dipstick and little or no RBCs seen on microscopic examination is more likely due to lysis of RBCs. In a patient who has urine that appears grossly bloody, however, a strongly positive dipstick with minimal RBCs visualized on microscopic examination is suggestive of rhabdomyolysis or intravascular hemolysis.

In addition to confirming hematuria, urine microscopy may be useful in determining the etiology of hematuria. The presence of dysmorphic RBCs and RBC casts suggests a renal source of the hematuria, most likely glomerular disease. Normal-appearing RBCs and the lack of casts suggest lower–urinary tract bleeding. Dysmorphic RBCs may have membrane blebs, an irregular surface, or other membrane defects. Using a cutoff of 10% to 20% as the upper limit of normal has good sensitivity and specificity for defining glomerular hematuria.
When examining concentrated urine, it must be remembered that RBCs can appear crenated.

**White blood cells**

Greater than five white blood cells per high-power field is generally considered abnormal. Pyuria usually signifies UTI, although it is not specific for UTI. Other conditions that can result in pyuria include fever, glomerulonephritis, and other inflammatory processes, whether in the bladder or pelvic region (eg, appendicitis). The presence of pyuria does not add to and may not be as good a screen for UTI as LE and nitrites from the urine dipstick [21]; the urine should still be cultured to confirm UTI. White blood cells from the vagina can contaminate urine specimens and give a false positive reading. Prolonged standing of hypotonic urine results in lysis of white blood cells and a false negative reading.

**Epithelial cells**

Epithelial cells that may be observed on microscopic examination include renal tubular cells, transitional cells, and squamous epithelial cells. All three cell types may be observed in normal urine. Increased numbers of renal tubular cells may be seen with acute tubular necrosis and exposure to nephrotoxic agents. Squamous epithelial cells line the distal third of the urethra. In female patients, squamous cells may originate from the vagina or vulva. Large amounts of squamous epithelial cells in the urine suggest a contaminated urine sample.

**Bacteria**

The presence of bacteria in an asymptomatic patient is most likely due to contamination with normal flora from the external urethral meatus or vagina. When the urine has been centrifuged, the bacteria clump and are more easily seen. When bacteria are observed in unspun urine, the patient may have significant bacteriuria. It is generally recommended, however, that asymptomatic bacteriuria not be treated because it has not been shown to have benefit and may increase the risk for pyelonephritis [27].

**Casts**

Casts are formed in the lumen of distal convoluted tubules and collecting ducts and consist of an organic matrix composed of Tamm-Horsfall mucoprotein with or without additional elements. There are many different types of urinary casts that may be observed on urine microscopy (Table 3). Hyaline casts are the most common and can be seen in normal individuals. They consist primarily of mucopolysaccharides and may be increased with concentrated urine, diuretics, renal disease, fever, and exercise. The presence of cellular casts is of greater significance. Because cellular casts can dissolve within 30 minutes in acidic urine and within 10 minutes in alkaline dilute urine, they can be missed if the microscopic examination is not performed soon after voiding.
Crystals

It is common to find crystals on microscopic examination of the urine. Crystal formation depends on a number of factors, and the presence of crystals may or may not be pathologic. Usually, the presence of crystals in the urine is of limited clinical significance [28]. Supersaturation of the solute components of the crystals must occur for crystallization to initiate. A number of factors affect supersaturation, including solute concentration, ionic strength, urine pH, and the presence of promoters or inhibitors. These factors vary during the day depending on fluid intake, dietary intake, and body metabolism. Urine in normal individuals is often supersaturated with calcium oxalate, calcium phosphate, and sodium urate [29]. Calcium oxalate, uric acid, and amorphous urate crystals are typically found in acidic urine. Calcium phosphate, amorphous phosphate, and ammonium magnesium phosphate (struvite) crystals form in alkaline urine. Cystine crystals are always abnormal and are found in people who have cystinuria and who often have kidney stones. Tyrosine and leucine crystals are also abnormal and suggest liver disease. Certain medications such as sulfonamides and ampicillin may crystallize in the urine. Prolonged standing of the urine may result in increased crystallization.

Quantitative urine measurements

Although 24-hour urine collections can provide useful information, they are cumbersome and difficult to obtain accurately, especially in younger children. Some data that had traditionally been assessed with 24-hour urine collections can now be obtained with reasonable accuracy from a random urine specimen, making it more convenient for patients and their families. Three of the more

<table>
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<tr>
<th>Type of cast</th>
<th>Component</th>
<th>Common clinical situations</th>
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<tbody>
<tr>
<td>Hyaline</td>
<td>Mucoprotein</td>
<td>Normal health, fever, exercise, diuretics, renal disease</td>
</tr>
<tr>
<td>Granular</td>
<td>Degenerating cellular casts or aggregated proteins</td>
<td>Glomerular disease, tubular disease, pyelonephritis, viral infections</td>
</tr>
<tr>
<td>Waxy</td>
<td>Last stages of granular cast degeneration</td>
<td>Advanced renal failure or other conditions with dilated tubules with diminished flow</td>
</tr>
<tr>
<td>Fatty</td>
<td>Lipid-containing renal tubular cells</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Red blood cell</td>
<td>Red blood cells</td>
<td>Glomerulonephritis, tubulointerstitial nephritis, acute tubular injury/necrosis</td>
</tr>
<tr>
<td>White blood cell</td>
<td>White blood cells</td>
<td>Pyelonephritis, glomerulonephritis, tubulointerstitial nephritis</td>
</tr>
<tr>
<td>Epithelial cell</td>
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useful quantification tests are the urine protein/creatinine ratio, the urine albumin/creatinine ratio, and the urine calcium/creatinine ratio. In addition to being useful for the initial evaluation, these tests can be used for monitoring of therapy.

Urine protein/creatinine ratio

Quantification of proteinuria can be useful in the work-up of a patient who has a urine dipstick positive for protein. Quantification using a 24-hour urine collection for protein is being replaced by the urine protein/creatinine ratio from a random urine specimen, ideally from the first morning void. The urine protein-to-creatinine ratio closely correlates with daily protein excretion that is based on grams per 1.73 m² body surface area [30–33]. This measurement provides a more accurate quantification of proteinuria compared with the urine dipstick and is much less subject to false negative and false positive readings. Because creatinine excretion is based on muscle mass, the ratio may overestimate proteinuria in a cachetic child. A normal ratio is less than 0.2 mg of protein per milligram of creatinine.

Urine albumin/creatinine ratio

Normal albumin excretion is less than 20 mg/d. Albumin excretion of 30 to 300 mg/d (approximately 20–200 μg/min) is abnormal but not detected by standard urine dipsticks and is termed microalbuminuria. Microalbuminuria is the earliest clinical finding of diabetic nephropathy, and children who have diabetes should be screened for microalbuminuria [34,35]. As with protein, the urine albumin/creatinine ratio correlates well with albumin excretion in a timed urine sample [36,37]. A ratio of greater than 0.03 mg of albumin per milligram of creatinine is considered abnormal. There is increasing evidence that microalbuminuria predicts cardiovascular disease in nondiabetic adults [38,39]. Its significance in nondiabetic children is not yet known.

Urine calcium/creatinine ratio

Hypercalciuria is a relatively common finding in a child who has hematuria [16,40]. Although a 24-hour urine collection for calcium excretion is the “gold standard,” a more commonly used test that correlates with this value is the calcium/creatinine ratio from a random urine specimen. The normal value for the ratio depends on age but should be less than 0.22 in the school-aged child and adolescent [41,42].

Additional urine testing

Other urine tests that are commonly performed but not discussed in detail here are the urine culture, gonorrhea/chlamydia testing, the urine pregnancy test,
and urine toxicology. The reader is referred to recent recommendations [22] on the use of urine culture and a review of urine collection techniques [2]. Follow-up urine cultures are of limited utility [43]. A number of additional tests can be performed on urine but are less commonly used in primary care. Some of these include urine collections for stone risk profiles, catecholamines, steroids, and testing for inherited metabolic disorders. Finally, with the advancement of molecular biology applications, the future holds promise for the development of additional urine tests [44].

Summary

The urinalysis is a frequently used tool in primary care, and abnormal findings are common. The utility of mass urinalysis screening remains to be determined. Although urine dipstick analysis can be very helpful, the pediatrician must remain mindful of the number of false positives and false negatives that can affect urine testing. The interpretation of abnormal urine dipstick results and the need for further evaluation should be guided by the clinical situation. Further evaluation can include simply retesting the urine to check for persistence of abnormal findings or additional testing for underlying conditions. In certain settings, urine microscopic analysis and quantification tests are useful follow-up studies to urine dipstick testing.

References