CONTINUING MEDICAL EDUCATION

Urinalysis in Children and Adolescents

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SUMMARY

Background: Urinalysis is the most commonly performed biochemical test in infancy and early childhood. The urine sample should be correctly obtained, age-specific aspects should be considered, and age-dependent reference values should be used.

Method: This review is based on a selective literature search in electronic databases, textbooks, and guidelines from Germany and abroad on the acquisition of urine samples and the performance of urinalysis in infancy and early childhood.

Results: The timing and mode of acquisition of the urine sample affect the assessment of hematuria, proteinuria, leukocyturia, nitrituria, and the uropathogenic bacterial colony count in the urine culture. Dipstick tests can be used for targeted screening for these features. The test results should be interpreted together with the findings of urine microscopy, the medical history, and the physical examination. Proteinuria should be quantified and differentiated; both of these things can be done either from collected urine or (especially in infants and young children) from a spontaneously voided urine sample, by determination of the protein/creatinine quotient. Orthostatic proteinuria in an adolescent requires no further evaluation or treatment. Hematuria should be characterized as either glomerular or non-glomerular erythrocyturia. Asymptomatic, isolated microhematuria in childhood is not uncommon and often transient; in the absence of a family history, it usually does not require an extensive work-up. Proteinuria combined with hematuria should arouse the suspicion of glomerulonephritis.

Conclusion: Urinalysis in infancy and early childhood is a simple and informative diagnostic test as long as the urine sample has been obtained properly and the results are interpreted appropriately for this age group.

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Diagnostic assessment of the urine is a basic component of the evaluation of diseases of the kidneys and urinary tract, along with the history, physical examination, and other tests. Urinalysis is most commonly performed to diagnose a urinary tract infection or to rule out renal disease. Abnormal findings in urinalysis can be seen in 1–14% of healthy schoolchildren (1, 2, e1, e2).

We selectively searched the PubMed database for articles from the last ten years containing the key words “dipstick urine analysis,” “leukocyturia,” “bacteriuria,” “nitrituria,” “hematuria,” “proteinuria,” and “pediatric.” We also considered older publications cited in these articles, textbooks and current guidelines from Germany and abroad on urinary diagnosis in infancy and childhood.

Learning objectives

After reading this article, the reader should be able to list the main principles of urine sample acquisition in infancy and childhood and critically assess dipstick test findings. The reader will also learn the basic principles of the age-appropriate interpretation of hematuria, proteinuria, and leukocyturia.

Urine sample acquisition

Single urine samples

Midstream urine – Midstream urine can be obtained from any child that has achieved urinary continence. Cleaning the genitals and perineum with soap and water before voiding has been shown to lessen contamination of the urine with periurethral organisms and leukocytes (3, 4).

Acquisition of urine samples from infants and toddlers – There are four ways to obtain urine samples from small children who cannot yet control their voiding:

- **Bag urine:** The genitals are inspected, thoroughly cleaned, and dried, and a self-adhesive urine

Urine acquisition for reliable biochemical testing

- the first voiding of the day is most suitable for biochemical testing
- the second voiding of the day is more practical in the outpatient clinic

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TABLE 1

Measurement of proteinuria in collected urine and determination of the protein/creatinine quotient in spontaneously voided urine (10, 28–30, e4)

	24-hour urine collection	Protein/creatinine quotient in spontaneous urine	Albumin/creatinine quotient in spontaneous urine
Physiological	$\leq 4 \text{ mg/m}^2 \text{ BSA/hr}$ ($\leq 100 \text{ mg/m}^2 \text{ BSA/d}$)	$\leq 0.2 \text{ mg/mg}$ (children 6–24 mo $\leq 0.5 \text{ mg/mg}$)	$\leq 30 \text{ mg/g}$
Proteinuria	$> 4 \text{ mg/m}^2 \text{ BSA/hr}$ ($> 100 \text{ mg/m}^2 \text{ BSA/d}$)	$> 0.2 \text{ mg/mg}$ (children 6–24 mo $> 0.5 \text{ mg/mg}$)	30 – 299 mg/g, microalbuminuria
Marked proteinuria	$> 40 \text{ mg/m}^2 \text{ BSA/hr}$ ($> 1 \text{ g/m}^2 \text{ BSA/d}$)	$> 2.0 \text{ mg/mg}$	$> 300 \text{ mg/g}$, macroalbuminuria

BSA, body surface area

collection bag is securely attached. Ideally, the child should void after being given fluids, and the urine sample should be processed immediately. Bag urine is unsuitable for culture, because contamination frequently causes false-positive findings (5–7).

- **Clean-catch urine:** For the acquisition of a fresh vesical urine sample, the child is held on an adult's lap with the genitals exposed; urine that is spontaneously voided after drinking is caught in a sterile vessel. This method yields false-positive findings in 5–26% of cases (7, 8).
- **Catheter urine:** A suitable urine sample for culture can be obtained from a female infant or toddler by one-time catheterization (i.e., not from an indwelling bladder catheter). In boys, suprapubic bladder puncture should be performed instead of transurethral catheterization (9).
- **Suprapubic bladder puncture:** This is a simple (though rarely performed), relatively noninvasive means of acquiring a urine sample if pyelonephritis is suspected, particularly when the patient is an infant. Vesical puncture is indicated whenever bag urine can be expected to be contaminated, e.g., in patients with vulvovaginitis, anogenital dermatitis, or phimosis. The puncture is most likely to be successful if the degree of filling of the bladder is assessed beforehand by ultrasonography: in neonates and infants, ultrasonography increases the likelihood of an adequate urine sample from 60% to nearly 97% (e3, e4).

A sample from the first voiding of the morning is most suitable for biochemical testing (10, 11), but the second voiding is more practical in the outpatient clinic (10). Urine should always be obtained at the same time of day from each patient, so that the findings will be comparable across tests. Spontaneously voided urine should not be kept before testing for any longer than 1–2 hours at room temperature, or 4 hours in a refrigerator (at 4 °C), or else the cells will disintegrate, the bacterial count will increase, and the pH will rise (e5).

Collected urine

Common indications for urine collection include the determination of endogenous creatinine clearance, the quantification and differentiation of proteinuria (Table 1), and the measurement of fluid and electrolyte excretion. The most important determinant of test validity is the accuracy, rather than the overall duration, of urine collection (10, 12, e6). Urine should be collected in a clean vessel that is stored in a cool place. The starting point of collection is considered to be the time of the last spontaneous voiding before collection, and its endpoint is the time of the last collected voiding. The duration and total volume of urine collection are documented, and 10–20 mL of the mixed urine are analyzed.

Accurate urine collection in infants or incontinent children is possible only through an indwelling bladder catheter. In such cases, the single-void urine samples should be reported as a quotient of the parameter in question and the creatinine concentration and compared with age-specific norms (13, e7–e10).

Leukocyturia

Leukocyturia makes a urinary tract infection likely; as an isolated finding, it is highly sensitive (83%), but not very specific (Table 2, [14]). The authors recommend microscopic analysis of a freshly obtained, native urine sample, because, in our opinion, the leukocyte esterase reaction of urinary dipsticks is not a fully adequate substitute for microscopy, although there is some debate on this point in the literature (14, 15, e11). The leukocyte esterase test can be made positive by lysed leukocytes or subpreputial material even when microscopy does not reveal any leukocytes; it can also be negative despite positive microscopic findings if the urine is highly concentrated or contains “collapsed” leukocytes (e6).

Whatever is being tested, the instructions for use of the dipstick should be followed conscientiously. The leukocyte count per unit volume is affected by

Urine acquisition for reliable microbiological testing

In infants and toddlers, urine must be obtained by clean catch, catheterization, or bladder puncture; spontaneously voided urine is likely to be contaminated.

Isolated leukocyturia or bacteriuria

Isolated leukocyturia does not imply a urinary tract infection.

the variable amount of urine in each voiding. This can alter the findings not only of dipstick tests, but also of counting chambers and other cell-counting methods. A leukocyte count of 5–10/μL is considered abnormal in boys over age 3; in girls, counts in the range of 20–50/μL are suspect for a urinary tract infection, and counts above 50/μL are considered clearly abnormal (*Table 3*).

The microscopic demonstration of leukocyte cylinders in the urine sediment, together with marked bacteriuria, is pathognomonic for pyelonephritis.

Nitrite test

Most urinary pathogens (with the important exception of enterococci) can reduce nitrate to nitrite; thus, nitrite in the urine indicates bacteriuria. The nitrite dipstick test may be falsely negative if the urine is held for too short a time in the bladder (less than 4 hours). As a result, the sensitivity of nitrite dipstick testing for clinically significant bacteriuria is no higher than 30–50% in infants, who generally urinate every 1–4 hours. On the other hand, its sensitivity in girls at least 3 years of age is 98% (9, 14, 16). The simultaneous demonstration of nitrituria and leukocyturia is 93% sensitive for a urinary tract infection (*Table 2*, [14]).

Bacteriuria

For urine culture, a fresh urine sample should be obtained and kept at 4–8°C until and during its transport to the laboratory. Alternatively, the sample can be pre-incubated in culture media and sent directly at 36°C. The bacterial count per milliliter is determined; its interpretation depends on the mode of acquisition of the sample. The diagnosis of a urinary tract infection requires the demonstration of at least 10⁵ organisms/mL (17); more recent studies call for a minimal count of 10⁶ or 10⁷/mL (18). Lower counts in catheterized urine may be pathological, and any number of demonstrated organisms is pathological in urine obtained by bladder puncture (*Table 3*). Depending on the mode of acquisition, urine culture often has false-positive rates up to 25%, and the false-positive rate of bag urine culture ranges from 30% to 63%. Bladder puncture is superior to clean catch and thus provides a far more suitable sample than bag collection of the urine (5, 6, 17, 18).

In children of school age, the typical clinical manifestations of urinary tract infection are pain on

TABLE 2

**Sensitivity and specificity of urine tests
(14, 20, 22, 23, 38, e2, e17)**

	Sensitivity (range), %	Specificity (range), %
Leukocyte esterase test	83 (67–94)	78 (64–92)
Nitrite test	53 (15–82)	98 (90–100)
Leukocyte esterase or nitrite test positive	93 (90–100)	72 (58–91)
Microscopy, leukocytes	73 (32–100)	81 (45–98)
Microscopy, bacteria	81 (16–99)	83 (11–100)
Leukocyte esterase or nitrite test or microscopy positive	99.8 (99–100)	70 (60–92)
Hematuria (peroxidase test)	86.1 (73–89)	85 (81–93)

urination, increased voiding frequency, and difficulty voiding; pyelonephritis is characterized by flank pain and fever. Whenever there are discrepant findings, urinalysis should be repeated before any further, possibly inappropriate diagnostic or therapeutic measures are taken. A recurrent or complicated urinary tract infection or a history of recent treatment with antibiotics should arouse the suspicion of a fungal or viral infection or of a pathogen whose detection requires special culture media (*Chlamydia*, *Trichomonas*, *Ureaplasma*).

One should ask critically whether the demonstrated organism is typical for the patient's age and sex. At any age, and in both sexes, the most common pathogen is *Escherichia coli*. In boys at least 1 year of age, *Proteus* species account for up to 30% of urinary tract infections, while *Staphylococcus* species are found in about 30% of urinary tract infections in girls aged 9 to 15 (1, 19–24). Indications of possible contamination include a low cell count, mixed flora in a single culture, different pathogens in serial studies, and organisms that are not usually found in urinary tract infections.

Routine screening occasionally reveals significant bacteriuria without leukocyturia in apparently healthy children (0.2–2%). This is called asymptomatic bacteriuria (25, 26, e12) and does not require antibiotic treatment. Urethritis is common in sexually active adolescents (e13, e14).

Urinary tract infections are classified as either asymptomatic (bacteriuria and leukocyturia without

The diagnosis of urinary tract infection

The way urine is obtained is very important for the diagnosis. Bacteriuria (single pathogen) and significant leukocyturia are required; nitrite tests are often falsely negative, in infants.

Complicated urinary tract infections

These arise in the setting of urinary tract anomalies, urine transport disorders, or immune compromise.

TABLE 3

Reference ranges for leukocyte and bacteria counts (per μL and mL , respectively) in uncentrifuged urine (14, 22, e30)

	Spontaneously voided urine	Midstream or catheterized urine		Urine obtained by bladder puncture
		Girls; boys under age 3	Boys age 3 and above	
Leukocyte count				
physiological	< 20	< 15	< 5	< 5
suspect	20–50	15–50	5–10	5–10
pathological	> 50	> 50	> 10	> 10
Bacteria count				
physiological	< 10 ⁴	< 10 ³	< 10 ³	sterile
suspect	10 ⁴	10 ³ to 5 × 10 ⁴	10 ³ to 5 × 10 ³	sterile
pathological	> 10 ⁵	> 5 × 10 ⁴	> 5 × 10 ³	any detection of bacteria

clinical symptoms) or symptomatic (with symptoms, possibly but not necessarily including fever). They can also be classified as uncomplicated or complicated on the basis of the patient's urinary tract anatomy (malformations of the urinary tract), vesical and renal function, and immune competence. In complicated urinary tract infections, culture often reveals multiple pathogens. Colony counts and resistance testing should be obtained for each pathogen.

Leukocyturia without bacteriuria may represent sterile leukocyturia; its differential diagnosis includes urolithiasis, renal tubular acidosis, interstitial nephritis, cystic renal diseases, glomerulonephritis, febrile diseases, tuberculosis, appendicitis, vaginitis, irritation of the meatus/urethra, and dehydration (14).

Proteinuria

Proteinuria—excessive elimination of protein in the urine—is a feature of tubular or glomerular dysfunction. It is assessed on the basis of a midstream urine sample in school-age children or a bagged urine sample in infants and toddlers. The second voiding of the day is often used; the first voiding of the day is the most concentrated, but often cannot be obtained in outpatients (e7–e9).

Dipstick tests provide only semiquantitative findings because they do not take the renal filtration rate into account. The degree of blue staining in the test

field is correlated, in particular, with the strength of the albumin reaction with tetrabromophenol. False positive findings can arise because of mucus, pus, blood, or highly alkaline ($\text{pH} > 8$) and highly concentrated urine; false negative ones, because of diluted urine (27). Proteinuria is present by definition when the protein concentration is at least 30 mg/dL (e6). Microalbuminuria at lower concentrations is present in as many as 5–12% of asymptomatic children (e7).

Ideally, urinary protein should be quantified on the basis of a 24-hour urine collection (*Table 1*). Collected urine samples are considered the gold standard of diagnosis. For infants and toddlers, in whom the collection of urine samples over time is especially problematic, the protein/creatinine and albumin/creatinine quotients in spontaneously voided urine can be measured instead. These values are independent of the urine volume, because the amount of creatinine excreted per day is stable. For the quotient to be reliable, the urinary creatinine concentration should be no lower than 10 mg/dL ; lower values in neonates (including premature ones) and in children with polyuria may lead to misinterpretation. A low albumin fraction in the total amount of excreted protein may indicate an extrarenal cause of proteinuria, e.g., hemoglobin, myoglobin, light chains (very rare in children), amyloid, and other causes.

Utility of dipstick tests for proteinuria

The extent and type of proteinuria cannot be judged from a dipstick test alone. Further tests are needed so that proteinuria can be quantified and categorized.

Orthostatic proteinuria

Orthostatic proteinuria is diagnosed on the basis of a daytime urine sample and the first voided urine of the morning.

The protein/creatinine quotient in single, spontaneously voided urine samples is closely correlated with the amount of protein in 24-hour urine collections and is therefore suitable for the quantification of proteinuria, including for follow-up over time (*Table 1* [10, 28–30, e4]). Just as in the determination of the glomerular filtration rate, the amount of proteinuria may be under- or overestimated if the urinary creatinine concentration is very high (> 2.5 g/L, e.g., among adolescent body-builders) or very low (< 0.2 g/L, e.g., in muscular dystrophy). A 24-hour urine collection is needed if proteinuria is to be assessed precisely without any interference from circadian fluctuations (11). These fluctuations are due, in part, to changes in body position over the 24-hour period.

Large protein molecules, such as immunoglobulins, do not cross the glomerulus, while smaller ones do. In addition to this selectivity with respect to size, there is also selectivity with respect to charge: strongly negatively charged proteins are retained, including more than 99% of albumin. Neutral or positively charged molecules the size of albumin pass more freely through the glomerular filter. Low-molecular-weight proteins normally cross the basal membrane but are then reabsorbed by endocytosis in the proximal tubule in amounts up to 96% (e15).

The above considerations account for the typical patterns of abnormal urinary protein findings. In selective glomerular proteinuria, medium-sized protein molecules—mainly albumin—cross the basal membrane. If the IgG/albumin quotient exceeds 3%, nonselective glomerular proteinuria is present. In tubular proteinuria (e.g., after chemotherapy or in hereditary or acquired tubulopathy), low-molecular-weight proteins are reabsorbed from the urine in the proximal tubule in less than normal amounts.

Urinary dipstick tests mainly disclose the presence of albumin, in semiquantitative fashion, and thus cannot reveal tubular proteinuria. In contrast, the Biuret reaction gives a quantitative measure of all urinary proteins. To quantify further proteins in the urine, other methods are needed, e.g., SDS-PAGE (sodium dodecyl sulfate—polyacrylamide gel electrophoresis).

Asymptomatic proteinuria is present as an isolated finding in 0.6% to 6.3% of children. In a cohort of 9000 children, significant proteinuria was found in a single sample in 10.7%, but was present in two

TABLE 4

Causes of dark urine (e5)

Endogenous	
erythrocytes	
hemoglobin	
myoglobin	
metabolic products	homogentisic acid (alcaptonuria), porphyrins
amorphous urates (brick-dust sediment)	
Exogenous	
foods	red beets (betanidine), rhubarb (anthrone derivatives), blackberries, food coloring (e.g., aniline)
drugs	chloroquine, deferoxamine, ibuprofen, metronidazole, nitrofurantoin, rifampicin, phenolphthalein, phenothiazines, phenytoin, imipenem/cilastatin
bacteria	<i>Serratia marcescens</i>

samples from the same child in only 2.5% and in four samples in only 0.1% (31). Clearly, urinalysis should always be repeated if proteinuria is found before any further testing is done for renal or systemic disease.

Proteinuria can be transient or functional. In general, proteinuria is not indicative of renal disease in the following situations (32, e8):

- hyperthermia
- fever
- physical exertion
- emotional stress
- congestive heart failure
- seizures
- hyperthyroidism.

Orthostatic proteinuria is characterized by moderate, nonselective proteinuria of up to 1.0 mg/mg creatinine in the daylight hours, and physiologic protein excretion during nighttime sleep. It is diagnosed by separate analysis of daytime and nighttime urine samples. It mainly affects obese adolescents and accounts for 20–60% of all cases of asymptomatic proteinuria. Its overall prognosis is favorable, as it does not seem to be associated with renal disease of any kind (11, e16).

If an isolated finding of mild proteinuria persists (< 1 g/m²/day, or an albumin/creatinine quotient of 0.17–2 mg/mg [exception: orthostatic proteinuria]), a

Marked proteinuria

Marked proteinuria may already be present before a child has any clinical signs of nephrotic syndrome (edema, oliguria).

Proteinuria combined with hematuria

A finding of proteinuria combined with hematuria necessitates consultation with a pediatric nephrologist, particularly if there are signs of nephritic syndrome or of a systemic disease.

TABLE 5

Charakteristic findings in erythrocyturia of glomerular and non-glomerular origin (29, 40, e18)

	Non-glomerular	Glomerular
Erythrocyte morphology	normal/eumorphic	dysmorphic
Erythrocyte cylinders	none	many
Proteinuria	≤ 500 mg/d ≤ 300 mg/m ² ·d	> 500 mg/d > 300 mg/m ² ·d
Color	bright red	dark brown, "like Coca-Cola"
Blood clots	possible	absent

glomerular and/or tubular disease such as glomerulonephritis or tubulointerstitial nephritis should be ruled out (e6). Proteinuria can also be the sole manifestation of a malformation of the urinary tract.

Marked proteinuria (> 1 g/m²/day, or an albumin/creatinine quotient above 2 mg/mg) with or without edema in the setting of idiopathic nephrotic syndrome is found mainly in children aged 2 to 8 (or 10) years as the result of minimal change glomerulonephropathy. The incidence of nephrotic syndrome has been estimated at 1.52 per 100 000 children per year (33). In infants and toddlers, marked proteinuria often reflects a congenital nephrotic syndrome traceable to a genetic abnormality of podocyte function; in older children, the main elements of the differential diagnosis are focal-segmental glomerulosclerosis, membranoproliferative glomerulonephritis, immune disorders, and connective-tissue diseases (e6).

Hematuria

Serial studies reveal hematuria in 1.5–2% of all children and adolescents (34). Macrohematuria arises in 1.3/1000 children (35). The prevalence of microhematuria in routine school medical examinations was found to be 41/1000 in a sample of 8954 children aged 8–15. In another study, girls were found to have microhematuria more commonly than boys (incidence 32/1000 versus 14/1000 in a sample of 12 000 children) [36, 37].

Hematuria is the abnormal excretion of blood or erythrocytes in the urine (34). It is subcategorized as erythrocyturia (red blood cells in the urine) or hemo-

globinuria (hemoglobin in the urine). Microhematuria is diagnosed either indirectly with a dipstick test (1 to 2 times positive testing, due to the peroxidase-like activity of hemoglobin) or directly by light microscopy (> 5[–10] RBC/μL) in a counting chamber; macrohematuria (> 1000 RBC/μL) is grossly visible as a reddish discoloration of the urine (34). Even 1 mL of blood in a liter of urine produces macrohematuria (ca. 25 000 RBC/μL). Microhematuria is usually an incidental finding, while macrohematuria often leads patients to consult a physician. Microhematuria should always be confirmed by multiple urinalyses. A positive urinary dipstick test is 73–89% sensitive and 81–93% specific for hematuria (Table 1 [38, e17]). Hematuria combined with proteinuria indicates renal disease and calls for further diagnostic evaluation.

Reddish discoloration of the urine is not, however, synonymous with macrohematuria, as it may also be due to hemoglobinuria, myoglobinuria (dipstick test positive, microscopy negative), or medications or foods (dipstick test and microscopy both negative) (Table 4, [e5]). The basic diagnostic evaluation of macrohematuria for its further differentiation always includes microscopic analysis of the urine.

Erythrocyturia can be of either glomerular or post-glomerular (non-glomerular) origin. Postrenal sources of bleeding may be located anywhere in the urinary pathway, from the calyces to the urethral opening. Macrohematuria of postrenal origin causes bright red discoloration of the urine, while macrohematuria of glomerular origin is rusty brown. Centrifugation of fresh blood-tinged urine yields a clear fluid if hematuria is postrenal, a brownish fluid if hematuria is renal, and an unchanged reddish fluid in case of hemoglobinuria or myo-globinuria. This test alone is insufficient for clinical evaluation; microscopy is essential for diagnostic purposes, ideally phase-contrast microscopy of the urine sediment, as the demonstration of dysmorphic erythrocytes (acanthocytes or "Mickey Mouse" cells) or of erythrocyte cylinders may indicate glomerular damage. A fraction of dysmorphic erythrocytes above 5% is 52% sensitive and 98% specific for a glomerular source of erythrocyturia, such as glomerulonephritis or congenital glomerulopathy [29]. The sensitivity can be increased to 80% by repeated microscopy of at least three different urine samples (40). The demonstration of erythrocyte cylinders proves that the source of the erythrocytes is glomerular, as the cylinders arise by compaction of glomerular-derived

Determining the cause of hematuria

The evaluation of hematuria should not end with a positive dipstick test. Urine microscopy is obligatory in all cases.

Glomerular vs. non-glomerular causes

Phase-contrast microscopy of the urine sediment is suitable for distinguishing glomerular from non-glomerular causes of hematuria.

erythrocytes in the renal tubules and collecting ducts (e18). Blood clots are not found in glomerular hematuria (Table 5).

Transient hematuria

Transient hematuria is often not of any pathological significance. It can accompany fever or arise with exercise (“jogger’s hematuria” [e19]), but it may also be due to a urinary tract infection, urolithiasis, a renal tumor (Wilms tumor), or interventions in the urinary tract. In girls, the urine sample may contain blood from vaginal secretions (menstruation) or after sexual intercourse.

Persistent hematuria

Rare but serious causes of glomerular hematuria include hereditary defects of the glomerular basal membrane, as in Alport syndrome (e20, e21) and the thin basement membrane disease (benign familial microhematuria) (e22). These diseases are due to defects in the synthesis of type 4 collagen; they have different inheritance patterns and overlapping clinical manifestations. They are often associated with sensorineural hearing impairment and ocular changes. Isolated asymptomatic microhematuria requires long-term follow-up, as it may indicate the presymptomatic stage of a renal disease (e23). Glomerular (micro-)hematuria needs further evaluation if other family members also have this finding, or if there is a family history of chronic renal disease or hearing impairment. The evaluation should include audiometry, ophthalmologic and molecular-genetic testing, and/or renal biopsy.

Tubulointerstitial causes of erythrocyturia include the following:

- cystic renal diseases
- pyelonephritis (of bacterial or, rarely, other origin, e.g., adenovirus [e24], malaria, toxoplasmosis)
- nephrocalcinosis
- medications
- toxins or tumors (e25).

As these diseases do not involve the glomerulus, the erythrocytes in the urine are eumorphic.

The same holds for hematuria of vascular origin, e.g., microthrombosis in sickle-cell anemia, renal venous thrombosis, or renal artery embolism (e25, e26).

Postrenal causes of hematuria include trauma, urinary tract infections, urolithiasis, hypercalciuria, and

anatomical lesions (obstruction, hydronephrosis, tumor). A tumor causing postrenal hematuria in childhood is almost always a nephroblastoma (Wilms tumor); such tumors can be visualized by ultrasonography (e27, e28). In some of the cohorts studied, 30–35% of children with isolated microhematuria were found to have hypercalciuria (i.e., a calcium excretion of more than 4 mg/kg BW/24 hours; age-dependent calcium/creatinine ratio in spontaneously voided urine, [e29]).

As findings such as proteinuria, hematuria, leukocyturia, and bacteriuria/nitrituria can arise either in isolation or in combination, they should always be interpreted in the light of the history and physical examination, and a differential diagnosis should be generated. In this article, which focuses on basic nephrologic testing, we cannot provide a complete diagnostic algorithm and instead give only a rough guide to the relevant clinical situations.

A thorough history, physical examination including blood pressure measurement (obligatory), ultrasonography of the kidneys and urinary tract, and the urinary evaluation described above may need to be supplemented by further laboratory tests depending on the clinical situation (complete blood count, C-reactive protein [CRP], creatinine, and, if indicated, cystatin C, electrolytes, blood-gas analysis, albumin, IgA, C3 complement, anti-neutrophil cytoplasmic antibodies [ANA], p-/c-ANCA, anti-streptococcal antibodies, clotting tests). Other diagnostic tests that may be indicated in the further evaluation of hematuria/proteinuria include threshold audiometry, ophthalmologic examination for retinal changes (fundus hypertonicus), echocardiography (to evaluate possible hypertrophy), chest x-ray (infiltrates, hemorrhage, pleural effusion); in patients with urinary tract infections, a reflux study (micturition cystourethrography); and, in patients with hydronephrosis, dynamic (MAG3) renal scintigraphy.

Overview

The basic prerequisites for the interpretation of urinalysis findings are the correct acquisition of the sample and the correct performance of the tests in question. Dipstick tests can be used to detect leukocyturia, nitrituria, proteinuria, and hematuria; their findings are best interpreted together with the findings of urine microscopy and in view of the

Localizing the source of erythrocyturia

In children and adolescents with hematuria, an underlying nephrologic disease should be ruled out. The erythrocyte morphology should be evaluated early to localize the source of erythrocyturia.

Isolated erythrocyturia

Although isolated erythrocyturia may be a clinically irrelevant finding, it nonetheless requires comprehensive nephrologic evaluation and follow-up.

clinical situation, sometimes with targeted further testing.

Leukocyturia should be evaluated in connection with the presence or absence of any clinical signs of a urinary tract infection, a systemic inflammatory reaction, and a clearly identified pathogen.

Proteinuria should be quantified and subcategorized by type. Orthostatic proteinuria is of no pathological significance. Proteinuria combined with hematuria and/or edema calls for a nephrological evaluation for possible glomerulonephritis and/or glomerulopathy (respectively).

The detection of erythrocyturia should be followed by urine microscopy to determine whether its origin is glomerular or non-glomerular. The further diagnostic evaluation depends on which of these is the case. Microhematuria, if it is an isolated finding, may be of no pathological significance. Hematuria accompanied by other abnormal urinary findings or clinical manifestations may be a sign of nephritis or of a systemic disease with renal involvement.

Conflict of interest statement

Prof. Klaus and PD Dr. Utsch declare that they have no conflict of interest.

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REFERENCES

- Kaplan RE, Springate JE, Feld LG: Screening dipstick urinalysis: a time to change. *Pediatrics* 1997; 100: 919–21.
- Chandar J, Gómez-Marín O, del Pozo R, et al.: Role of routine urinalysis in asymptomatic pediatric patients. *Clin Pediatr* 2005; 44: 43–8.
- Koch VH, Zuccolotto SM: Urinary tract infection: a search for evidence. *J Pediatr (Rio J)* 2003; 79: 97–106.
- Vaillancourt S, McGillivray D, Zhang X, Kramer MS: To clean or not to clean: effect on contamination rates in midstream urine collections in toilet-trained children. *Pediatrics* 2007; 119: 1288–93.
- Hardy JD, Furnell PM, Brumfitt W: Comparison of sterile bag, clean catch and suprapubic aspiration in the diagnosis of urinary infection in early childhood. *Br J Urol* 1976; 48: 279–83.
- Al-Orifi F, McGillivray D, Tange S, Kramer MS: Urine culture from bag specimens in young children: are the risks too high? *J Pediatr* 2000; 137: 221–6.
- Tosif S, Baker A, Oakley E, Donath S, Babl FE: Contamination rates of different urine collection methods for the diagnosis of urinary tract infections in young children: an observational cohort study. *J Paediatr Child Health*. 2012;48: 659–64.
- Ramage IJ, Chapman JP, Hollman AS, Elabassi M, McColl JH, Beat-tie TJ: Accuracy of clean-catch urine collection in infancy. *J Pediatr* 1999; 135: 765–67.
- Finnell SM, Carroll AE, Downs SM: Subcommittee on Urinary Tract Infection. Technical report—Diagnosis and management of an initial UTI in febrile infants and young children. *Pediatrics* 2011; 128: e749–70.
- Price CP, Newall RG, Boyd JC: Use of protein:creatinine ratio measurements on random urine samples for prediction of significant proteinuria: a systematic review. *Clin Chem* 2005; 51: 1577–86.
- Brandt JR, Jacobs A, Raissy HH, et al.: Orthostatic proteinuria and the spectrum of diurnal variability of urinary protein excretion in healthy children. *Pediatr Nephrol* 2010; 25: 1131–7.
- Wiegmann TB, Chonko AM, Barnard MJ, MacDougall ML, Folscroft J, Stephenson J, Kyner JL, Moore WV: Comparison of albumin excretion rate obtained with different times of collection. *Diabetes Care* 1990; 13: 864–71.
- Abitbol C, Zilleruelo G, Freundlich M, Strauss J: Quantitation of proteinuria with urinary protein/creatinine ratios and random testing with dipsticks in nephrotic children. *J Pediatr* 1990; 116:243–7.
- Roberts KB, Downs SM, Finnell SM, et al.: Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management, Roberts KB. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics* 2011; 128: 595–610.
- Glissmeyer EW, Korgenski EK, Wilkes J, et al.: Dipstick Screening for Urinary Tract Infection in Febrile Infants. *Pediatrics* 2014; (Epub ahead of print)
- Downs SM. Technical report: urinary tract infections in febrile infants and young children. The Urinary Tract Subcommittee of the American Academy of Pediatrics committee on Quality Improvement. *Pediatrics* 1999; 103: e54. 464
- Kass EH. Bacteriuria and the diagnosis of infections of the urinary tract. *Arch Int Med* 1957; 100: 709–14.
- Coulthard MG, Kalra M, Lambert HJ, Nelson A, Smith T, Perry JD: Redefining urinary tract infections by bacterial colony counts. *Pediatrics* 2010; 125: 335–41.
- Zorc JJ, Levine DA, Platt SL, et al.: Multicenter RSV-SBI Study Group of the Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. Clinical and demographic factors associated with urinary tract infection in young febrile infants. *Pediatrics* 2005; 116: 644–8.
- McGillivray D, Mok E, Mulrooney E, Kramer MS. A head-to-head comparison: "clean-void" bag versus catheter urinalysis in the diagnosis of urinary tract infection in young children. *J Pediatr* 2005; 147: 451–6.
- Armengol CE, Hendley JO, Schlager TA: Should we abandon standard microscopy when screening for urinary tract infections in young children? *Pediatr Infect Dis J* 2001; 20: 1176–7.
- Hoberman A, Wald ER, Reynolds EA, Penchansky L, Charron M: Pyuria and bacteriuria in urine specimens obtained by catheter from young children with fever. *J Pediatr* 1994; 124: 513–5.

Red discoloration of the urine

Even a small amount of blood can cause macro-hematuria. The finding of red discoloration of the urine provides no information about its cause (glomerular or non-glomerular hematuria, other).

23. Craver RD, Abermanis JG: Dipstick only urinalysis screen for the pediatric emergency room. *Pediatr Nephrol* 1997; 11: 331–3.
24. Winberg J, Andersen HJ, Bergström T, Jacobsson B, Larson H, Lincoln K: Epidemiology of symptomatic urinary tract infection in childhood. *Acta Paediatr Scand Suppl* 1974; 252: 1–20.
25. Jodal U: The natural history of bacteriuria in childhood. *Infect Dis Clin North Am* 1987; 1: 713–9.
26. Kunin CM: Urinary tract infections in females. *Clin Infect Dis* 1994; 19: 1–12.
27. Moxey-Mims M: Hematuria and proteinuria. In: Kher KK, Schnaper HW, Makker SP (eds.): *Clinical Pediatric Nephrology*. 2nd edition Abingdon, United Kingdom: Informa Healthcare; 2007: 129–39.
28. Kaneko K, Someya T, Nishizaki N, Shimajima T, Ohtaki R, Kaneko K: Simplified quantification of urinary protein excretion using a novel dipstick in children. *Pediatr Nephrol* 2005; 20: 834–6.
29. Bisaz E, Bianchetti MG, Donati R, Peheim E, Colombo JP, Oetliker OH: Simplified determination of proteinuria in children using a single urine sample. *Klin Padiatr* 1994; 206: 387–91.
30. Ruggenti P, Gaspari F, Perna A, Remuzzi G. Cross sectional longitudinal study of spot morning urine protein:creatinine ratio, 24 hour urine:protein excretion rate, glomerular filtration rate, and end stage renal failure in chronic renal disease in patients without diabetes. *BMJ* 1998; 316: 504–9.
31. Vehaskari VM, Rapola J. Isolated proteinuria: analysis of a school-age population. *J Pediatr* 1982; 101: 661–8.
32. Bangstad HJ, Dahl-Jørgensen K, Kjaersgaard P, Mevold K, Hanssen KF: Urinary albumin excretion rate and puberty in non-diabetic children and adolescents. *Acta Paediatr* 1993; 82: 857–62.
33. El Bakkali L, Rodrigues Pereira R, Kuik DJ, Ket JC, van Wijk JA: Nephrotic syndrome in The Netherlands: a population-based cohort study and a review of the literature. *Pediatr Nephrol* 2011; 26: 1241–6.
34. Vehaskari VM, Rapola J, Koskimies O, Savilahti E, Vilks J, Hallman N: Microscopic hematuria in school children: epidemiology and clinicopathologic evaluation. *J Pediatr* 1979; 95: 676–84.
35. Vehaskari VM. What is the prevalence of asymptomatic microscopic haematuria and how should such children be managed? *Pediatr Nephrol* 1989; 3: 32.
36. Ingelfinger JR, Davis AE, Grupe WE: Frequency and etiology of gross hematuria in a general pediatric setting. *Pediatrics* 1977; 59: 557–61.
37. Dodge WF, West EF, Smith EH, Bruce Harvey 3rd. Proteinuria and hematuria in schoolchildren: epidemiology and early natural history. *J Pediatr* 1976; 88: 327–47.

38. Bank CM, Codrington JF, van Diejen-Visser MP, Brombacher PJ: Screening urine specimen populations for normality using different dipsticks: evaluation of parameters influencing sensitivity and specificity. *J Clin Chem Clin Biochem* 1987; 25: 299–307.
39. Köhler H, Wandel E, Brunck B: Acanthocyturia – a characteristic marker for glomerular bleeding. *Kidney Int* 1991; 40: 115–20.
40. Wandel E, Köhler H: Acanthocytes in urinary sediment – a pathognomonic marker? *Nephrol Dial Transplant* 1998; 13: 206–7.

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Question 1

What method of obtaining a urine sample is most suitable for reliable biochemical testing?

- a) the first voided urine of the day
- b) the second voided urine of the day
- c) a 12-hour urine collection
- d) a 24-hour urine collection
- e) the nocturnal portion of collected urine

Question 2

Which of the following statements about the interpretation of findings of urinary dipstick tests is true?

- a) The time the urine spent in the bladder does not affect the result of the nitrite dipstick test.
- b) Fluctuations of urine volume do not affect the leukocyte count per unit volume.
- c) The sensitivity of dipstick testing for clinically significant bacteriuria in an infant is roughly 90%.
- d) In infants, the nitrite dipstick test is rarely falsely negative.
- e) The nitrite dipstick test can be falsely negative if the voided urine has been in the bladder for too short a time (less than 4 hours).

Question 3

What symptoms and signs are characteristic of pyelonephritis in school-aged children?

- a) insomnia and hematuria
- b) pleuritic pain and dysuria
- c) arthritis and pain on urination
- d) flank pain and fever
- e) vomiting and sepsis

Question 4

Which of the following is the most likely underlying cause of a bacterial urinary tract infection in an infant?

- a) an anatomical malformation of the urinary tract
- b) nephroblastoma
- c) diaper dermatitis
- d) a virus or fungus
- e) neoplasia

Question 5

Which of the following testing methods in urinalysis in childhood has the highest specificity?

- a) the peroxidase test
- b) the leukocyte esterase test
- c) the nitrite test
- d) microscopy for bacteria
- e) microscopy for leukocytes

Question 6

Which of the following foods can darken the urine?

- a) potatoes
- b) strawberries
- c) asparagus
- d) carrots
- e) rhubarb

Question 7

What is the reference range for an abnormal leukocyte count in midstream urine from a girl under 3 years of age?

- a) 1 – 10/ μ L
- b) 10 – 20/ μ L
- c) 20 – 30/ μ L
- d) 30 – 40/ μ L
- e) > 50/ μ L

Question 8

Which of the following is a tubulo-interstitial cause of erythrocyturia?

- a) surgery on the urinary tract
- b) hepatitis
- c) urolithiasis
- d) toxoplasmosis
- e) Alport syndrome

Question 9

What type of malignant tumor is the cause of nearly all cases of postrenal hematuria in childhood?

- a) adenocarcinoma
- b) nephroblastoma
- c) choroid plexus carcinoma
- d) myelodysplastic lymphoma
- e) osteosarcoma

Question 10

What conditions are often associated with type 4 collagen mutations?

- a) sensorineural hearing impairment and ocular changes
- b) rheumatoid arthritis and Crohn's disease
- c) varicocele and hepatitis
- d) reflux esophagitis and arrhythmia
- e) atopic dermatitis and dysphagia

CONTINUING MEDICAL EDUCATION

Urinalysis in Children and Adolescents

Boris Utsch, Günter Klaus

REFERENCES

- e1. Yanagihara T, Kuroda N, Hayakawa M et al.: Epidemiology of school urinary screening over a 30 year period in Tokyo. *Pediatr Int* 2007; 49: 570–6.
- e2. Sekhar DL, Wang L, Hollenbeak CS, Widome MD, Paul IM: A cost-effectiveness analysis of screening urine dipsticks in well-child care. *Pediatrics* 2010; 125: 660–3.
- e3. Buys H, Pead L, Hallett R, Maskell R: Suprapubic aspiration under ultrasound guidance in children with fever of undiagnosed cause. *BMJ* 1994; 308: 690–92.
- e4. Kiernan SC, Pinckert TL, Keszler M: Ultrasound guidance of suprapubic bladder aspiration in neonates. *J Pediatr* 1993; 123: 789–91.
- e5. Thomas L: Niere und Harnwege – Labordiagnostik von Erkrankungen der Niere und ableitenden Harnwege. In: Thomas L (ed.): *Labor und Diagnose – Indikation und Bewertung von Laborbefunden für die medizinische Diagnostik*. 5th edition, Frankfurt: TH Books 1998; 372–410.
- e6. Hogg RJ: Adolescents with proteinuria and/or the nephrotic syndrome. *Adolesc Med Clin* 2005; 16: 163–72.
- e7. Jones CA, Francis ME, Eberhardt MS et al.: Microalbuminuria in the US population: third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 2002; 39: 445–59.
- e8. Tsioufis C, Mazaraki A, Dimitriadis K, et al.: Microalbuminuria in the paediatric age: current knowledge and emerging questions. *Acta Paediatr* 2011; 100: 1180–4.
- e9. Ozkaya O, Buyan N, Erol I, Atalay Y, Beyazova U, Sahin F, Söylemezözü O: The relationship between urinary calcium, sodium, and potassium excretion in full-term healthy newborns. *Turk J Pediatr* 2005; 47: 39–45.
- e10. Erol I, Buyan N, Ozkaya O, et al.: Reference values for urinary calcium, sodium and potassium in healthy newborns, infants and children. *Turk J Pediatr* 2009; 51: 6–13.
- e11. Armengol CE, Hendley JO, Schlager TA: Should we abandon standard microscopy when screening for urinary tract infections in young children? *Pediatr Infect Dis J* 2001; 20: 1176–7.
- e12. Wiswell TE, Smith FR, Bass JW: Decreased incidence of urinary tract infections in circumcised male infants. *J Pediatr* 1985; 75: 901–3.
- e13. Bavastrelli M, Midulla M, Rossi D et al.: Sexually active adolescents and young adults: a high-risk group for Chlamydia trachomatis infection. *J Travel Med* 1998; 5: 57–60.
- e14. Orr DP, Johnston K, Brizendine E, Katz B, Fortenberry JD: Subsequent sexually transmitted infection in urban adolescents and young adults. *Arch Pediatr Adolesc Med* 2001; 155: 947–53.
- e15. Christensen EI, Nielsen R: Role of megalin and cubilin in renal physiology and pathophysiology. *Rev Physiol Biochem Pharmacol* 2007; 158: 1–22.
- e16. Ryttand DA, Spreiter S: Prognosis in postural (orthostatic) proteinuria: forty to fifty-year follow-up of six patients after diagnosis. *New Engl J Med* 1981; 305: 618–21.
- e17. Marx AM, Kropf J, Gressner AM: On the performance and reliability of mechanized urine teststrip measurement in comparison with visual reading. *J Clin Chem Clin Biochem* 1989; 27: 433–43.
- e18. Thiel G, Biemann D, Wegmann W, Brunner FP: Erythrozyten im Urin: Erkennung und Bedeutung. *Schweiz Med Wschr* 1986; 116: 790–7.
- e19. McInnis MD, Newhouse IJ, von Duvillard SP, Thayer R: The effect of exercise intensity on hematuria in healthy male runners. *Eur J Appl Physiol Occup Physiol* 1998; 79: 99–105.
- e20. Longo I, Scala E, Mari F et al.: Autosomal recessive Alport syndrome: an in-depth clinical and molecular analysis of five families. *Nephrol Dial Transplant* 2006; 21: 665–71.
- e21. Jais JP, Knebelmann B, Giatras I et al.: X-linked Alport syndrome: natural history and genotype-phenotype correlations in girls and women belonging to 195 families: a „European Community Alport Syndrome Concerted Action“ study. *J Am Soc Nephrol* 2003; 14: 2603–10.
- e22. Carasi C, Van't Hoff WG, Rees L, Risdon RA, Trompeter RS, Dillon MJ: Childhood thin GBM disease: review of 22 children with family studies and long-term follow-up. *Pediatr Nephrol* 2005; 20: 1098–105.
- e23. Zhai Y, Xu H, Shen Q et al.: Renal histological features of school-age children with asymptomatic haematuria and/or proteinuria: A multicenter study. *Nephrology (Carlton)* 2014; 19: 426–31.
- e24. Allen CW, Alexander SI: Adenovirus associated haematuria. *Arch Dis Child* 2005; 90: 305–6.
- e25. Kirschstein M: Hämaturie 2011 In: *Differentialdiagnose Pädiatrie*, Michalk D, Schönau E (eds.), 3. Auflage, Urban & Fischer, Elsevier GmbH, S. 389–95.
- e26. Kuhle S, Massicotte P, Chan A, Mitchell L: A case series of 72 neonates with renal vein thrombosis. Data from the 1–800-NO-CLOTS Registry. *Thromb Haemost* 2004; 92: 729–33.
- e27. Greenwood MF, Holland P: Clinical and biochemical manifestation of Wilms'tumor. In: Pochedly C, Baum S (eds.) *Wilms Tumor: Clinical and Biochemical manifestations*. New York, Elsevier 1984, S. 11.
- e28. Gutjahr P, Kaatsch P, Spaar HJ et al.: Klinik, Therapie und Prognose bei 373 Kindern mit Wilms-Tumoren – Ergebnisse der bundesweiten Studie 1980–1988. *Acta Urol* 1990; 21: 132–41.
- e29. Stapleton FB: Hematuria associated with hypercalciuria and hyperuricosuria: A practical approach. *Pediatr Nephrol* 1994; 8: 756–61.
- e30. Kirschstein M: Leukozyturie/Bakteriurie 2011 In: *Differentialdiagnose Pädiatrie*, Michalk D, Schönau E (eds.), 3rd edition, München: Urban & Fischer, Elsevier GmbH, 396–403.