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CONTENTS

CHAPTER 2

Diagnostic Evaluation of Renal Disease

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INTRODUCTION

The clinical presentation of renal diseases may be nonspecific with paucity of symptoms and signs even in advanced chronic kidney disease (CKD). In neonates and young infants, the clinical presentation may be related to other systems like the central nervous system or gastrointestinal, presenting as febrile convulsions, vomiting, diarrhea, or meningismus. Hence, a high index of suspicion and a sound knowledge of clues which may lead to a clinical diagnosis are essential requirements for the early detection and effective management of a renal patient. This chapter begins with discussion of the clinical clues followed by laboratory manifestations of kidney disease, with principal focus on urine analysis and kidney biopsy.

CLINICAL FEATURES OF RENAL DISEASE

History

Edema

It is the most striking feature of many renal diseases. Periorbital puffiness in the morning suggests glomerulonephritis or early stages of nephrotic syndrome. Generalized edema with ascites suggests nephrotic syndrome. Edema may occur due to hypoproteinemia or fluid overload.

Oligoanuria

Absent or reduced urine output. It may be due to dehydration, prerenal failure, acute tubular necrosis, or obstructive uropathy.

Polyuria

It suggests diabetes insipidus, chronic renal insufficiency, renal tubular acidosis, Bartter syndrome, or other tubulopathies.

Abnormal Color of Urine

- Cola-colored urine is seen typically in acute poststreptococcal glomerulonephritis, other causes being Henoch-Schonlein purpura, immunoglobulin A (IgA) nephropathy, membranoproliferative glomerulonephritis
- Bright red urine may be seen in urolithiasis, hypercalciuria, tumors of the kidney or bladder, polycystic kidney disease, sickle cell anemia, renal vein thrombosis, trauma, bleeding, or coagulation disorders, and rarely, urinary tract infections (UTIs)
- Red urine which tests positive for blood but reveals no red blood cells (RBCs) on microscopy is due to hemoglobinuria or

myoglobinuria. Ingestion of beetroot or colored sweets gives negative result for blood in urine although it may appear red

- Cloudy or whitish urine with offensive smell suggests UTI.

Painful micturition associated with dysuria, frequency, and urgency is common with lower UTI.

Dribbling, poor stream, and straining while passing urine in male infants suggest posterior urethral valves. Persistent distension of bladder after voiding supports the diagnosis of posterior urethral valves or functional obstruction due to neurogenic bladder dysfunction in meningomyelocele, lipomeningocele, transverse myelitis, or sacral agenesis.

Family History

Family history can give early clues to inherited diseases, such as deafness in Alport's syndrome and bony deformities in renal tubular acidosis. Other inherited diseases include polycystic kidney disease and congenital nephrotic syndrome. Familial focal glomerulosclerosis and vesicoureteral reflux can affect the siblings and parents of the patient.

ACUTE CLINICAL PRESENTATIONS

Breathlessness

It may be due to pulmonary edema or left ventricular failure with hypertension and may be seen as complication of acute post-streptococcal glomerulonephritis or hemolytic uremic syndrome (HUS).

Tachypnea may be due to metabolic acidosis of renal failure or renal tubular acidosis.

Seizures

These may be due to hypertensive encephalopathy, hypocalcemia, hyponatremia, or rarely uremia. Other manifestations of severe hypertension are headache, vomiting, hemiparesis, aphasia, blindness, and facial palsy.

High Fever with Rigors

It is commonly seen with acute pyelonephritis. Fever, malar rash, and joint pains are common presentations of lupus.

Abdominal Pain

Colicky loin to groin pain suggests ureteric stone. Renal angle pain with fever suggests UTI.

PHYSICAL EXAMINATION

Failure to Thrive

It is seen in CKD, chronic pyelonephritis, renal tubulopathies, congenital anomalies of the kidneys, and urinary tracts like posterior urethral valves, renal hypoplasia, and dysplasia.[1]

Short Stature

Height below 5th percentile for age and gender is short stature. Along with bony deformities and rickets, it is common in CKD due to renal osteodystrophy, renal tubulopathies.

Sexual developmental delay and delayed puberty may also be seen in CKD.

Pallor

It may be present due to anemia of CKD or chronic pyelonephritis. Sudden pallor may be seen in HUS or glucose-6-phosphate dehydrogenase (G6PD) deficiency with hemoglobinuria.

Hypertension

Blood pressure above the 95th percentile for age and gender, measured according to the height percentile, is often seen in acute glomerulonephritis, acute kidney injury,

CKD, lupus nephritis, membranoproliferative glomerulonephritis, or renovascular hypertension.[1]

Rash

Photosensitive rash on the cheeks in a butterfly distribution is seen in systemic lupus erythematosus (SLE). Purpuric rash on the lower limbs and gluteal region is seen in Henoch-Schonlein purpura. Pyoderma marks is seen in poststreptococcal glomerulonephritis. Maculopapular rash is seen in vasculitis. Neurofibromas may be seen in tuberous sclerosis.

Eyes

Cataracts and glaucoma occur in steroid toxicity, lenticonus in Alport's syndrome, cystine crystals in cystinosis, Kayser-Fleischer rings in Wilson's disease.

Ears

Branchial fistulae in branchiootorenal syndrome. Sensorineural deafness in Alport's syndrome and type 4 Bartter syndrome.

RENAL FUNCTION TESTS

The purpose of performing renal function tests in a child is to establish the presence of renal disease and to define its extent.

These can be discussed under the following three headings:

1. Laboratory manifestations of renal disease
2. Laboratory evaluation of glomerular function by glomerular filtration rate (GFR) estimation
3. Laboratory evaluation of tubular function.

Laboratory Manifestations of Renal Disease

Renal disorders may sometimes manifest with obvious symptoms and signs. The majority of cases, however, are clinically silent or have very subtle manifestations. A high index of suspicion coupled with the use of appropriate laboratory tests is vital for the recognition of renal disorders.

Laboratory evaluation of glomerular function by GFR estimation and laboratory evaluation of tubular function are discussed in another chapter.

URINALYSIS

This is one of the most important tests that should be performed while evaluating renal function. It has been discussed in detail in the chapter.

Urine Examination

Urine is also known as the "golden elixir of life." If properly evaluated with an open mind, it reveals details regarding the health of the kidney. Screening of urine is easily achieved by using a paper or plastic dipstick. The results of any urinalysis depend upon proper collection, preservation and careful examination. The three parts of routine urinalysis are as follows—gross visual or physical examination, chemical/dipstick analysis followed by detailed microscopic evaluation.[2]

Methods of Urine Collection

- Random specimen: Collected at any time of the day with no prior precautions. The sample may contain white blood cell (WBC), bacteria, and epithelial cells, and RBC in females during menstruation
- Early morning: First fasting sample collected before ingestion of any fluid. Early morning urine is usually hypertonic
- Mid-stream clean catch: Prior cleaning of the external urethral meatus to be done using benzalkonium hydrochloride before collection. After discarding the initial urine during flow, a sterile container is used to collect the midstream sample.

Culture of urine is done from this sample. The discarded first part of the urine stream contains the unwanted microbes and contaminants existing around the outer urethra

- Catheterization of the bladder: It is carried out in neurologically compromised patients and in perioperative states.[3] The possible complications of the procedure include iatrogenic infection and risk of trauma to the lower urinary tract
- Suprapubic transabdominal needle aspiration of the bladder: It is the method of choice for neonates and infants, providing the least contaminated urine sample.

Quantities of urine required for urinalysis, reagent strip testing, and urine culture testing are 10 mL, 2.5 mL, and 1 mL, respectively. Twenty-four hour urine collection is recommended for the quantitation of many substances such as protein, calcium, oxalates, and uric acid. For accurate results, urine should be refrigerated during the collection.

Physical Examination

Appearance and color

Normal urine is light to dark yellow or amber in color. Red or brown color urine could be due to eating fresh beets, drugs, or the presence of either hemoglobin or myoglobin. Cola-colored urine is more likely due to distorted RBC in urine, suggestive of glomerular hematuria, unlike bright red colored urine in renal calculus disease.

Turbid, cloudy urine may denote WBC, RBC, epithelial cells or bacteria, and crystals. Yellow-orange color of urine may be due to urobilin following hyperbilirubinemia, rifampicin, or concentrated urine. Brown-black urine may be due to methemoglobinemia, alkaptonuria, tyrosinosis, and phenol poisoning.

Odor

Freshly voided normal urine has an aromatic odor which changes to a characteristic ammoniacal odor on standing resulting from degradation of urea. Urine in children with diabetes mellitus have a fruity odor due to acetonuria. Maple syrup disease derives its name from the characteristic scent of the urine. Phenylketonuria, isovaleric academia, and methioninemia can be detected by the musty, sweaty foot, and fishy odor, respectively.

Specific gravity

It is directly proportional to urine osmolality which measures solute concentration. Specific gravity helps us to predict the ability of the kidney to concentrate urine. Neonatal kidneys with a limited ability to concentrate urine have a low specific gravity whereas early morning urine samples have high specific gravity due to overnight dehydration. Specific gravity is measured in laboratories with a refractometer. Normal values of specific gravity in a random urine sample range between 1.002 and 1.035. Specific gravity increases above 1.022 on water deprivation of more than 12 hours. Failure of the above indicates presence of intrinsic renal failure or diabetes insipidus. Isosthenuria or fixed specific gravity of 1.007–1.010 is seen in advanced stages of CKD. Specific gravity value over 1.035 is indicative of contamination, or presence of high glucose levels, following intravenous contrast radiographic studies or low molecular weight dextran solutions.

Urine osmolality

It is a measure of the number of particles in a solution. It is not affected by the weight of the solutes, and hence, it reflects the renal tubular concentrating capacity. It is measured by freezing point depression or by vapor pressure depression. Urine osmolality ranges from 300 to 900 mOsm/kg in children.

Neonates have a low concentrating ability with a maximum osmolality of 900 mOsm/kg. The concentrating ability after dehydration approaches the adult range (1,200 mOsm/kg) by 2 years of age. In prerenal failure, urine osmolality rises above the plasma osmolality, whereas in acute tubular necrosis, they are similar.

Chemical Examination

Reagent strips consisting of a plastic with multiple pads, each impregnated with specific reagents, indicators, and buffers are most commonly used for chemical screening in most laboratories.[4] After immersion of the reagent portion of the strip into fresh urine and immediate removal, the color change is compared under adequate light and at the appropriate reading time, with the color chart standards provided. The reagent strips should be stored and handled properly. They should not be exposed to direct sunlight or moisture.

pH

Precise measurement of urine pH, especially in suspected cases of renal tubular acidosis, can be done using freshly voided urine using a pH meter with a glass electrode. Normal urine pH ranges from 4.5 to 8.5; however, the urine is normally acidic resulting from continuous acid production from normal metabolism. The kidney excretes 1–2 mEq/kg/day of hydrogen ions as net titrable acid in infants, and 50–100 mEq of hydrogen ions per day in adults.

Apart from respiratory or metabolic acidosis, acidic urine is also seen in diseases such as phenylketonuria, alkaptonuria, renal tuberculosis, and methanol intoxication.

Urine becomes alkaline on prolonged standing. Alkaline urine is also seen in infections with urea splitting organisms—*Proteus*, *Pseudomonas*, *Klebsiella*, and *Staphylococcus*. Respiratory or metabolic alkalosis, hyperaldosteronism, Cushing's syndrome, renal tubular acidosis, and ingestion of citrus fruits also give an alkaline urine.

Protein

Normal total protein excretion does not usually exceed 150 mg/24 hours. The small quantities of protein normally found in urine include the Tamm-Horsfall protein produced by renal tubular cells, and a few filtered plasma proteins. More than 150 mg/day in adults and more than 4 mg/m^2 body surface area (BSA) per hour in children is defined as proteinuria. Proteinuria more than 2 g/24 hours and more than 40 mg/m^2 BSA per hour in children is severe and known as nephrotic syndrome.

Semi quantitative tests

Heat and acetic acid test: Appearance of cloudiness in the upper boiled portion of test tube containing 10 mL of filtered urine is diagnostic of proteinuria especially albuminuria. Addition of 1–2 drops of 3% acetic acid rules out phosphates and carbonates (both dissolve in the acid) as the cause of cloudiness. If an alkaline urine containing protein is boiled, the protein may be converted into "alkaline metaprotein," which is not coagulated by heat.

Sulfosalicylic acid test: On mixing equal volumes of urine and 3% sulfosalicylic acid, a white precipitate is obtained in the presence of protein. In both the above tests, the amount of precipitate is used to give a semiquantitative report of albumin:

- Negative: No cloudiness
- Trace: Faint cloudiness, seen only if the tube is held against a black background
- 1+: Slight turbidity through which print can be read clearly
- 2+: Turbidity through print is blurred
- 3+: White cloudiness with fine precipitate through which print is not visible

- 4+: Very heavy curdy flocculation.

Reagent strips: Details are given below:

- Spot urine albumin/creatinine ratio (mg/mg)
  - Normal: Less than 0.2
  - Abnormal: 0.2–2.0
  - Nephrotic range: More than 2.0.

Quantitative protein determination

Twenty-four hour urine collection is done with proper storage beginning from the second urine sample of the first day till the first urine sample of the second day. Protein estimation is done by the sensitive heat and acetic acid precipitation methods. Less sensitive methods include use of sulfosalicylic acid or concentrated nitric acid.

- Normal: Less than 4 mg/m^2/h
- Abnormal: 4–40 mg/m^2/h
- Nephrotic: More than 40 mg/m^2/h.

Glucose and other reducing substances

Very small quantities of glucose normally filtered by the glomerulus appear in urine (<130 mg/24 h). Glycosuria (excess sugar in urine) is seen in diabetes mellitus, lowered renal glucose threshold (normal threshold is 160–180 mg/dL), endocrinopathies, thiazide diuretics, and steroids.

Most newborn and infant urines are routinely screened for reducing sugars by modified Benedict's copper reduction test. This is because dipsticks which are routinely employed for sugar testing, use the glucose oxidase reaction which is specific for glucose but can miss other reducing sugars such as galactose and fructose (Table 1).[4]

Benedict's test

Take 5 mL of Benedict's qualitative reagent in a test tube. Add 8 drops of protein-free urine and boil the mixture for 3–5 minutes. The results are then noted and quantitated as follows:

- Negative: No change in color
- Trace: Solution turns pale green and slightly cloudy
- 1+: Solution turns definite cloudy green
- 2+: Yellow to orange precipitate, supernatant after precipitate settles is blue
- 3+: Orange to red precipitate, supernatant after precipitate settles is pale blue
- 4+: Black-red precipitate, supernatant after precipitate settles is discolored.

Benedict's test being very sensitive, results in a large number of false positives. Patients taking drugs such as salicylates, penicillin, and streptomycin may be tested false positive for glycosuria.

Ketones

They are easily detected using either dipsticks or test tablets containing sodium nitroprusside. Acetone, aceotacetic acid, and ß-hydroxybutyric acid are ketones resulting from diabetic ketosis or, more commonly, starvation (calorie deprivation).

Ketosis may also develop in glycogen storage disease. Normal urine levels less than 2 mg/dL of acetoacetic acid and less than 20 mg of total ketones.

Bilirubin

Bilirubin and urobilinogen are normally excreted in the urine in miniscule quantities (<0.02 mg/dL of bilirubin and <4 mg/dL or 0.1–1.0 Ehrlich units/dL of urobilinogen). Increased levels are seen in parenchymal liver disease and obstructive jaundice. Dipsticks detect 0.2 Ehrlich units/dL of uobilinogen based on aldehyde reaction method.

Blood

Bleeding may be gross or microscopic. Hematuria or RBCs in the urine should be differentiated from hemoglobinuria and myoglobinuria by simultaneous chemical and microscopic examination on a freshly voided sample of urine.

TABLE 1: Urine examination by reagent strip testing[4]

Tests	Results	Drawbacks
pH	Ranges from 5 to 8.5	–
Proteins	Indicator dye bromphenol blue is most sensitive to albumin but detects globulins and Bence-Jones protein poorly. Trace positive results (slightly hazy urine) corresponds to 150 mg/24 h (the upper limit of normal). • 1+: 200–500 mg/24 h • 2+: 0.5–1.5 g/24 h • 3+: 2–5 g/24 h • 4+: >6 g/24 h	False positive with highly alkaline urine, phenazopyridine, antiseptics. False negative with proteins other than albumin, dilute urine, urine pH <4.5
Glucose	Glucose oxidase reaction is employed for screening which is specific for glucose. However, they can miss other reducing sugars such as galactose and fructose	False positive with peroxide, oxidizing cleaning agents. False negative with high specific gravity, ketones >40 mg/dL
Ketones	Ketones easily detected by sodium nitroprusside. Acetone, aceotacetic acid, β-hydroxybutyric acid are ketones resulting from diabetic ketosis or more commonly, starvation (calorie deprivation)	False positive with phenolphthalein, phenylketones
Blood	Detects free hemoglobin and myoglobin. It can detect a hemoglobin concentration of 0.015–0.0162 mg/dL, equivalent to 5–20 intact red blood cells per high power field	False positive with myoglobin, bacterial peroxidases. False negative with ascorbic acid, high specific gravity
Nitrite	A positive nitrite test indicates presence of bacteria in urine. Gram negative bacilli such as *E. coli* are more likely to give a positive test	False positive with substances coloring urine red
Leukocyte esterase	A positive leukocyte esterase test indicates presence of white blood cells either as whole cells or as damaged or lysed cells. A negative leukocyte esterase test means that an infection is unlikely and, that, without additional evidence of urinary tract infection, further testing by microscopic exam and/or urine culture need not be done	False positive with nitrofurantoin, oxidizing cleaning agents

Hemoglobinuria without hematuria occurs due to excess free hemoglobin in the blood. It is seen with transfusion reactions, paroxysmal nocturnal hemoglobinuria, paroxysmal cold hemoglobinuria, HUS, G6PD deficiency, and black water fever. Myoglobin is derived from skeletal muscle and is a small and easily filtered molecule seen in the urine from muscle injury. Myoglobinuria is seen in crush injuries, prolonged convulsions, prolonged severe exercise, and electric shock.

Benzidine test: Add 2 mL of glacial acetic acid to a small quantity of benzidine powder in a test tube. Add an equal amount of urine, followed by 1 mL of hydrogen peroxide. Appearance of a blue color indicates the presence of blood.

Dipstick examination: Principle used is the peroxidase-like activity of hemoglobin and

myoglobin which catalyzes the oxidation of orthotoluidene on the strip to a blue color (Table 1).

Perform a microscopic examination of freshly voided urine if a positive dipstick test for blood is obtained.

Myoglobin can be differentiated from hemoglobin by cellulose acetate electrophoresis or immunoassays.

Electrolytes

Flame photometry is used to measure electrolytes in urine without interference by other substances.

- Sodium: Sodium excretion is useful to assess the volume status which is essential during treatment of acute kidney injury. Urinary sodium is also used to calculate the fractional excretion of sodium, the most accurate renal failure index
- Chloride: Chloride excretion is not very useful for clinical assessment. High levels of urinary chloride are seen in Bartter syndrome
- Potassium: Potassium excretion reflects dietary intake. Urine potassium is inappropriately low in renal failure and hyperkalemia results. Urine potassium is high in the presence of low plasma levels are seen in renal tubular disorders
- Urinary anion gap: The urinary anion gap is calculated as the difference in the positive and negative ions (Na + K – Cl) in urine. It gives a fair estimation of urinary ammonium (NH_4) excretion. Normally, urinary anion gap is positive about 30–35 mEq/L. In acidosis, the excretion of NH_4 increases and the anion gap becomes progressively negative. In distal renal tubular acidosis (RTA), the urinary anion gap is positive.
- Miscellaneous
  - Urine creatinine levels for estimation of GFR
  - Urine spot calcium/creatinine ratio (mg/mg) is used as a screening test for hypercalciuria.

Microscopic Examination

Ten milliliter of freshly voided urine after centrifugation at 3,000 rpm for 3–5 minutes is carefully examined for its sediment. Cells and casts and crystals are visualized under low power and high power fields, and sometimes special stains are used.

Cells

Normal urine contains epithelial cells, WBCs, and RBCs.

Red blood cells

Hematuria is the presence of abnormal numbers of RBC in urine. It may occur due to glomerular injury leading to red cells passing through the glomerular barrier, malignancy, kidney trauma, urinary tract calculi, renal infarcts, acute tubular necrosis, UTI, nephrotoxins, and physical stress.

Normal urine in healthy individuals has less than 2 RBC per high power field in a centrifuged sample of urine. More than five RBCs in a specimen is probably abnormal. Concentrated urine may cause RBCs to become crenated, and a dilute urine may cause RBCs to swell such that at times, only RBC ghosts and free hemoglobin may remain. Both swollen, partly hemolyzed RBCs and crenated RBCs are sometimes difficult to distinguish from WBCs in the urine. Also, red cell ghosts may simulate yeast. As RBCs pass through the abnormal glomerular structure, they can assume various shapes and these are called dysmorphic RBCs. Dysmorphic RBCs in urine suggests a glomerular hematuria.

White blood cells

More than 5 leukocytes per high power field in a centrifuged sample or more than

10 leukocytes/mm^3 in an uncentrifuged sample are suggestive of UTI (Table 1).

Leucocytes in the urine or pyuria are seen in either upper or lower UTI or acute glomerulonephritis. Usually, the WBCs are granulocytes. White cells in urine may be contaminants from vagina in females or external urethral meatus in males.

Epithelial cells

Cells containing a large round or oval nucleus normally slough off from renal tubular epithelium into the urine in small numbers. Renal tubular epithelial cells are found in large numbers in nephritic syndrome and nephritic syndrome. During lipiduria endogenous fats get deposited in these cells, these are called oval fat bodies. When visualized under polarized light microscopy, they exhibit a "Maltese cross" configuration.

Renal tubular epithelial cells are smaller and rounder than transitional epithelium, and they have larger nuclei.

Squamous epithelial cells in urine are possible contaminants from the skin surface or from the external urethral meatus.

Yeasts

Candida and other yeast forms are occasionally seen in urine.

Bacteria

Bacteriuria or presence of few bacteria in urine suggests a UTI but is not diagnostic (Table 1). Urine culture may be required to define the specific organism and its sensitivity to antibiotics.

Ova and parasites

Ova and parasites such as *Enterobius vermicularis* are found in urine because of fecal contamination.

Casts

Urinary casts are best seen in unspun sample of urine as centrifugation may damage casts. Location for formation of casts is typically in the distal convoluted tubule or the collecting duct (distal nephron).

Hyaline casts are seen in proteinuric states, and also in concentrated urine samples of normal individuals. They are an aggregate of Tamm-Horsfall protein with cells or cellular debris.

Cast formation occurs in low urine flow rates, high salt concentration, and low pH, all of which favor protein denaturation and precipitation. Cylindrical protein casts formed at the junction of Henle's loop and the distal convoluted tubule are called cylindroids.

Cellular casts

Red blood cell casts are indicative of glomerulonephritis, presence of these casts in urine is always abnormal.

White blood cell casts indicate inflammatory changes resulting from acute or chronic pyelonephritis or autoimmune diseases like SLE.

Cellular casts may be seen under the microscope as coarsely granular, finely granular, or waxy casts, depending upon the length of time they remain in the nephron.

Broad casts are seen in end-stage chronic renal disease.

A telescoped urinary sediment is one in which red cells, white cells, oval fat bodies, and all types of casts are found in more or less equal profusion. Telescoped sediments may be seen in SLE, malignant hypertension, and crescentic glomerulonephritis. In end-stage kidney disease, the urinary sediment often becomes very scant due to the isosthenuria.

Crystals

Few of the crystals like calcium oxalate, triple phosphate, and amorphous phosphates are seen in the urine of healthy individuals.

Uric acid crystals, amorphous urates, calcium oxalate crystals, and calcium sulfate or hippuric acid crystals are seen in acidic urine.

Calcium phosphate and calcium carbonate crystals are seen in alkaline urine.

Uncommon crystals

Cystine crystals, tyrosine crystals, or leucine crystals in urine are found in congenital cystinuria or severe liver disease, congenital tyrosinosis, and maple syrup urine disease, respectively. Cholesterol crystals are seen in nephrotic syndrome or lymphatic obstruction. Abnormal crystals may also be formed due to radiographic dyes and antibiotics like sulfonamides.

Routine Biochemical Tests

Blood urea is the predominant end-product of protein nitrogen catabolism. Urea is freely filtered at the glomerulus and reabsorbed by the tubule. The urea concentration of the blood, plasma, or serum is usually measured colorimetrically using automated techniques.[2] The concentration of urea in whole blood is 14% less than that in plasma.

Plasma urea × 2.8 = Plasma urea nitrogen

Plasma urea nitrogen × 0.86 = Blood urea nitrogen

The interpretation of blood urea nitrogen (BUN) values must take into account factors that influence the metabolism of urea including liver function (which influences production), urine flow rate, nonrenal clearance, and changes in the protein content of the diet. Protein load and urea generation is increased with increased protein intake or when there is internal bleeding, while creatinine level is not affected in these circumstances. Similarly, urea production is enhanced in patients who are severely catabolic as in fever, sepsis, and following extensive trauma or in patients receiving medications such as steroids or tetracyclines.

The relation between BUN and GFR is hyperbolic, and as a result, only a small absolute increase in the urea concentration occurs when GFR is substantially reduced from a normal level, whereas large increments can be noted with minor decreases in a severely compromised filtration rate.

Creatinine

Creatinine results from the enzymatic degradation of creatine found in the skeletal muscle. Muscle mass is directly proportional to body mass. Creatinine is normally present in plasma at a concentration of 25–50 μmol/L (0.3–0.6 mg/dL) in children. Creatinine concentration used to be measured by the alkaline picrate method described by Jaffe. However, the values are overestimated due to the presence of other substances that react with alkaline picrate.

Methods required to remove the noncreatinine chromogens are very cumbersome. The Ektachem slide assay does not entail prior chromogen absorption, needs only 20 μL of plasma, and is widely accepted. Drugs such as trimethoprim, probenecid, and cimetidine may raise the plasma creatinine concentration appreciably.

Electrolytes

Electrolytes are measured by various methods such as emission flame photometry, dry slide potentiometric methods, and the most sensitive and ion selective electrodes.

Sodium

The normal plasma sodium is 135–145 mmol/L. The changes in plasma sodium levels reflect the ratio of sodium to water in the extracellular fluid (ECF) and provide no information on the total body sodium content.

Hyponatremia

It is seen when there is an increase in water relative to sodium in the ECF, caused by either water retention or sodium loss. Pseudohyponatremia is seen in hyperlipidemic and hyperproteinemic samples when emission flame photometry is used for the

measurement of sodium, not seen with ion selective electrodes. An increase in the triglyceride level by 1 g/dL falsely decreases serum sodium by 2 mEq/L.

Hypernatremia

It can occur when the balance of solute and water is disrupted, either through increased solute intake, excessive loss of water, or decreased water intake. The clinical symptoms and signs resulting from hypernatremia are primarily those of central nervous system dysfunction. It may occur in diabetes insipidus.

Potassium

Normal plasma potassium ranges from 3.5 to 4.5 mmol/L.

Hypokalemia

It generally indicates a deficit in total body potassium but may also simply represent a transcellular shift of the cation. Increased gastrointestinal and renal tubular losses result in hypokalemia. Renal potassium loss is seen in Fanconi syndrome, RTA, and hyperaldosteronism. The main cause of hypokalemia can be determined by measuring urinary potassium on a spot urine sample. If urinary potassium is more than 20 mmol/L in the presence of hypokalemia, it indicates renal loss of potassium.

Hyperkalemia

It is seen in renal failure, acidosis, catabolism, and primary hypoaldosteronism. Artifactual increases are seen in hemolysis, delay in plasma separation, refrigeration of blood before plasma separation, forearm exercise after tourniquet application, and use of potassium ethylenediaminetetraacetic acid specimen collection tubes.

Chloride

Normal range for plasma chloride is 100–107 mmol/L.

Hypochloremia

Hyponatremia or bicarbonate retention associated with metabolic alkalosis leads to low plasma chloride. It occurs classically in Bartter syndrome.

Hyperchloremia

Hypernatremia, metabolic acidosis secondary to bicarbonate loss, and acid retention lead to high serum chloride.

Bicarbonate

Actual bicarbonate concentration in plasma estimated from arterial blood taken anaerobically is always derived from blood pH and pCO_2. The normal plasma standard bicarbonate concentration in infants is 18–22 mmol/L and in children 20–26 mmol/L.

Hypobicarbonatemia

Plasma bicarbonate losses (renal and gastrointestinal) increased acid production (lactic acidosis and other organic acidemias) and decreased removal of acids (other than carbonic acid) all deplete plasma bicarbonate. Respiratory loss of carbon dioxide and water during hyperventilation leads to hypobicarbonatemia.

Hyperbicarbonatemia

Plasma bicarbonate concentration increases in respiratory failure and in prolonged vomiting with acid and chloride loss.

Anion gap

The cations and the anions in the plasma are equivalent to maintain electroneutrality. Plasma bicarbonate and chloride balance plasma sodium and potassium but other unmeasured anions (phosphates, sulfates, organic acids and proteins) represent anion gap. The anion gap is calculated as:

$$\text{Anion gap} = (\text{Na} + \text{K}) - (\text{Cl} + \text{HCO}_3)$$

Normal anion gap is 9–13 mmol/L. The causes of an increased anion gap are lactic

acidosis, diabetic ketoacidosis, organic academia, and chronic renal failure.

Calcium

Calcium uptake is an actively regulated process. The physiologically important fraction of plasma calcium (PCa) is the unbound ionized calcium concentration (PiCa). Normal range for PiCa is 1.15–1.3 mmol/L. Calcium reabsorption is increased by parathyroid hormone (released in response to hypocalcemia), calcitonin, vitamin D, thiazide diuretics, and volume depletion. Calcium excretion is increased by intravenous fluid therapy, increased sodium intake, and diuretics such as mannitol and furosemide.

Hypocalcemia

Decreased PCa and PiCa are seen in hypoparathyroidism, hypocalcemia in disorders of calcium absorption and vitamin D deficiency.

Hypercalcemia

Hyperparathyroidism and vitamin D toxicity are the main causes of hypercalcemia.

Phosphate

The term hypophosphatemia refers to a circulating level of inorganic phosphate below an age related normal range. Excessive renal losses as in primary hypophosphatemic rickets, vitamin D dependent rickets, renal tubular acidosis; breastfed premature infants or use of phosphate binding antacids are the leading causes of hypophosphatemia.

Plasma phosphorus is high during infancy and decreases in childhood. High serum phosphorus levels are seen in acute kidney injury as well as in CKD.

Proteins

Total proteins and serum albumin levels are important for the diagnosis of nephrotic syndrome. Urinary albumin is increased in both glomerular injury and tubular disorders and is a good screening test for proteinuria.

Glomerular proteinuria

Urinary albumin is measured immunometrically and albumin excretion rates can be calculated in timed urine samples.

Tubular proteinuria

Measurement of urinary excretion of low molecular weight proteins (LMWP), defined as molecular weight less than 40,000 Da is suggestive of renal tubular pathology. The various LMWPs measured are lysozyme, retinol binding protein (RBP), β2-microglobulin, and α1-microglobulin. These are usually measured on spot samples and then factored by urinary creatinine to account for variations in urine dilution.

In summary, timely and appropriate tests to assess specific renal functions in a good well-equipped laboratory is essential for a complete diagnosis and subsequent management.

KIDNEY BIOPSY

The gold standard in the diagnosis and confirmation of any illness of the kidney or otherwise is visualizing the exact pathology under a microscope.[5] The biopsy of the kidney can be performed percutaneously under ultrasound guidance.

If done by an expert, it is a very safe procedure with the risk of complications being minimal. The biopsy can be subjected to a variety of tests depending on the suspected clinical illness. It also helps predict the course, prognosis, and treatment benefits.

The first reported open renal biopsy was by Gwyn in 1923 and closed needle biopsy was by Ball in 1934.

INDICATIONS

Nephrotic Syndrome

- Age less than 1 year or more than 10 years
- Gross hematuria or persistent microscopic hematuria

IAP Specialty Series on

PEDIATRIC NEPHROLOGY

This is an official publication of the Indian Academy of Pediatrics. Several luminaries in the field of Pediatric Nephrology, from home and abroad, have contributed their might in bringing out this book. The book has been designed with a practical approach to renal problems in children, faced by treating clinicians in their routine pediatric practice. The book has been kept concise with simple language, making it more reader friendly.

The book has 29 chapters, dealing with basic renal functions, common renal conditions in day to day pediatric practice and some of the more complex renal problems in children. Drug dosing guidelines for commonly used drugs in renal failure and a few useful appendices are also incorporated.

The two color format will be pleasing to the eye and will facilitate easy reading by highlighting boxes, tables and key messages.

The book is ideally suited to the needs of pediatricians, pediatric nephrologists, post graduate students, nephrologists and urologists interested in pediatric aspects of the discipline.

Queries and suggestions may be sent to Dr Anand S Vasudev at asvasudev@yahoo.com and asvasudev@gmail.com

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