Assessment of Renal Function

5

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5.1 Introduction

Core Messages

(a) Kidney and urinary tract abnormalities are common neonatal and congenital findings that warrant appropriate and timely assessment of structural and functional integrity of the kidneys.
(b) Renal dysfunction is often subtle and asymptomatic requiring reliance on various laboratory tests to identify and manage underlying conditions.
(c) Awareness of antenatal and postnatal laboratory evaluation methods is the key to timely interventions.
(d) Ability to understand the age and gestation-associated variation of certain tests might avoid unnecessary investigations.

Case Vignette

A 6-week-old male neonate, born to a 23-year-old healthy primigravida, was brought to the pediatrician's office with history of reddish discoloration noticed in the diaper for about a week. There was no associated change in urine output. He has been feeding well on breast milk. Physical examination was unremarkable with adequate anthropometric measurements (>75th percentile for weight and height). The pediatrician performed a dipstick urinalysis to asses for a possible urinary tract infection, which was negative for blood; a CBC and renal function panel were normal but a renal sonogram revealed slightly small and mildly echogenic kidneys bilaterally, which can be seen in this age group. The patient was then referred to a nephrologist for further evaluation. At the nephrologist's office, the diagnosis of uric acid crystalluria was considered as the possible cause, and urine was evaluated for urinalysis, microscopy, and urine electrolytes including creatinine. Tubular functions were assessed which were essentially normal including fractional excretion of sodium of 0.5 % {FeNa}, urinary uric acid to GFR ratio of 0.3 (<0.56 mg/dL of GFR), urine calcium to creatinine ratio of

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1 (<0.8), and tubular reabsorption of phosphorus was 96 %. These tests were done to reassure the family of completely normal neonatal renal function.

Renal disease is usually silent; the changes are usually subtle and can only be elicited if precisely sought for. Pediatricians must use the best of the clinical acumen and use the appropriate diagnostic tools, with the knowledge of the differences in the normal ranges at various ages. The diagnostic tools in the assessments of renal function have improved over the last few decades.

5.2 Urine Analysis (UA)

UA is the oldest method of diagnostic urine testing, first used more than 6,000 years ago [20]. Often neglected by the clinicians and poorly performed by laboratories, it is an inexpensive, readily available, and easy to interpret test with or without automated analyzers. It is an excellent indicator of a variety of renal functions, and some people consider it as a medical "poor man's" biopsy of the kidney.

Urinalysis has two components: (1) Dipstick urinalysis gives semiquantitative analysis of chemical and metabolic abnormalities. Most commercially available dipsticks can screen for pH, specific gravity, ketones, glucose, protein, bilirubin, white blood cells, red blood cells, and nitrites. Newer dipsticks can even detect microalbumin as well. (2) Wet urinalysis consists of macroscopic appearances and microscopic analysis of the cellular elements, crystals, and bacteria in the urine. The urine specimen has to preferably be evaluated within an hour of voiding.

Macroscopic assessment of urine is useful and informative. Color, clarity, and odor of urine can give a wealth of information. Depending on concentration, the color of urine varies from clear to dark yellow. Amber to reddish brown urine suggests presence of hemoglobin, myoglobin, and hemosiderin. Bright red color signifies fresh blood, urate crystals (pink diaper syndrome), porphyrins, food coloring, and foods like beets. Brown-black discoloring is seen in alkaptonuria. Urine normally is clear, but the presence of white blood cells, bacteria, amorphous phosphates, and urates can turn it cloudy.

Urine specific gravity is commonly measured by a reagent strip; it ranges from 1.001 to 1.035, and it is indicative of tubular function. High-specific gravity is associated with volume depletion, syndrome of inappropriate antidiuretic hormone, and in glycosuria. It is rather low with diuretic use, in diabetes insipidus, and in impaired renal function [47].

Urinary pH is also assessed by the reagent strips, but it is not very accurate; in circumstances when exact pH is desirable, it should be measured using a pH meter in freshly voided urine. Assessment of urinary pH is useful in assessing acid–base status in a variety of conditions and in the evaluation for renal tubular acidosis as well as mixed respiratory and metabolic disturbances. It is also useful for the monitoring and treatment of nephrolithiasis.

Glucose is usually not present in the urine as it is completely reabsorbed in the proximal tubule after being filtered. It can be seen in significant hyperglycemic states (serum glucose >200 mg/dL), isolated renal glycosuria due to altered SGLT −1 or GLUT 2 transport proteins and in proximal tubular injury due to Fanconi's syndrome. The reagent strips are only sensitive to the presence of glucose, so other reducing sugars have to be tested for independently.

Ketone bodies are the product of fat metabolism and consist of acetoacetic acid, beta hydroxybutyrate, and acetone. Reagents on the dipstick only detect acetoacetic acid so dipstick underestimates the burden of ketone bodies in the system. Ketones are seen in the urine in diabetic ketoacidosis, glycogen storage diseases, starvation, high-fat diets, and in hyperthyroidism.

Urinary nitrites are produced by the conversion of dietary nitrates by the action of bacteria and are indicative of urinary tract infection (UTI) [42], mostly due to gram-negative bacteria. The absence of nitrites does not rule out an infection, as the urine may not have stayed long enough (usually about 4 h) in the bladder for the chemical reaction to be completed. False-negative results

could be seen with excess of vitamin C in the urine, patients on vegan diets, and infection by yeast or gram-positive bacteria and especially in neonates in whom frequent emptying of the bladder may not allow the chemical reaction to be completed.

Crystals are seldom seen in freshly voided urine, but their presence can definitely suggest various pathologies like cystinuria and several others. Some are more readily seen in acidic urine like calcium oxalate and uric acid, while calcium phosphates, amorphous phosphates, and magnesium ammonium phosphates are readily visualized in alkaline samples.

White blood cells in the urine are seen with UTI or glomerulonephritides, which are detected by the leukocyte esterase, an enzyme present in the leukocyte granules.

Hematuria is detected by the reagent strip and confirmed by the presence of two-five red blood cells per high power field in the centrifuged urine under the microscope. The shape of RBCs can help determine the origin of these cells, as the red blood cells cross the glomerular filtration barrier, their pliable membrane gets distorted, or some part of it is pinched off giving the classic appearance of acanthocytes, and the red blood cells originating in the lower tract keep their eumorphic appearance. In addition red blood cell casts confirm glomerular etiology of hematuria.

5.3 Assessment of Proteinuria

In normal states, minimal amounts of high molecular weight proteins are filtered through the glomerular filtration; low molecular weight proteins that are filtered are mostly reabsorbed by the proximal tubules. Tamm-Horsfall protein is secreted by the tubules constituting the major component of excreted urinary proteins. In a variety of disease states, proteinuria increases either through the glomerular barrier or secreted by the diseased tubules. Albumin is the marker of glomerular proteinuria, while beta-2 microglobulin, alpha-1 microglobulin, and retinol-binding protein are common markers of tubular proteinuria.

5.3.1 Glomerular Proteinuria

Dipstick reagents are highly sensitive for albuminuria. They can give false-positive results due to prolonged immersion of the dipstick in the urine, a high urinary pH (>8.0), or in the presence of pyuria or bacteriuria. Dipsticks are useful for semiquantitative estimation of protein in the urine based on the color change of the strip (trace to 4+ suggestive of 10 mg/dL up to >500 mg/dL). Standard urine dipsticks are of little to no use for assessment of low molecular weight proteins. For the assessment of tubular proteinuria, sulfosalicylic acid precipitation test can be used but that is only a qualitative assessment, and urine protein electrophoresis will be needed for confirmation and quantification.

Spot urine protein to creatinine ratios are commonly used quick and reliable tests for protein excretion. The normal value varies according to the age and gestation; in general a ratio of <0.2 and under is considered normal, and values >2 suggest nephrotic range proteinuria [23]. In premature babies, this ratio can be as high as 0.6.

A 24-h timed urine collection is the gold standard for estimation of urinary protein loss. It is always necessary to check the total amount of creatinine in the same collection to assess adequacy of the collection. Amounts of 4 mg/m^2/day or less are considered normal protein excretion, while protein of >40 mg/m^2/day is confirmatory of nephrotic range proteinuria [23].

5.3.2 Tubular Proteinuria

Impaired proximal tubular reabsorption of filtered low molecular weight proteins leads to tubular proteinuria. Alpha-1 microglobulin (MW 30 kDa), retinol-binding protein (21.4 kDa), and beta-2 microglobulin (11.8 kDa) are the main markers of tubular injury. These proteins are much higher in diseased preterm babies in comparison to healthy preterm and healthy term babies; in addition all babies show decline in their urinary excretion within a few days in postnatal life suggesting tubular maturity happens rather quickly [2].

5.4 Assessment of Glomerular Function

Knowledge of the glomerular filtration rate (GFR) is critical in the management of newborn, infants, and children, not only to assess the renal function itself but also to help with function-based dosing of various medications that might be necessary in the premature infants and neonates, assessing potential risk of radiocontrast materials and in early detection of acute kidney injury.

Glomerular filtration is the commonly used measure of renal function. GFR changes significantly from early fetal life until 2 years of age when it reaches adult levels (Table 5.1). Neonates at term are born with minimal measureable GFR, but it is sufficient for the metabolic needs of the neonate. Glomerular filtration starts between 10 and 12 weeks of gestation; after birth, the GFR in term infants doubles by 2 weeks, triples by 3 months, and quadruples by 6 months of age. In premature babies born at 26 weeks of gestation, average GFR is 6 mL/min/1.732 m^2. A minimal increase in GFR occurs by 34 weeks of gestation (Table 5.1).

GFR increases rather quickly in first few weeks of postnatal life. GFR estimation is done using endogenous substances like creatinine and cystatin C or exogenous markers like inulin and iohexol or radioisotopic agents like DMSA or DTPA.

Table 5.1 Glomerular filtration in infants and children as assessed by the inulin clearance

Age	GFR ± SD mL/min/1.732 m^2
Preterm babies	
1–3 days	14+/−5
1–7 days	18.7+/−5.5
4–8 days	44+/−9.3
3–13 days	47.8+/−10.7
8–14 days	35.4+/−13.4
1.5–4 months	67.4+/−16.6
Term babies	
1–3 days	20.8+/−5
3–4 days	39+/−15.1
4–14 days	36.8+/−7.2
6–14 days	54.6+/−7.6
15–19 days	46.9+/−12.5
1–3 months	60.4+/−17.4
4–6 months	87.4+/−22.3
7–12 months	96.2+/−12.2
1–2 years	105.2+/−17.3

Modified with kind permission Springer: Schwartz and Furth [45]

Table 5.2 Normal serum creatinine levels

Age	Creatinine mg/dL {mmol/L}
<34 weeks of gestation	
<2 weeks old	0.7–1.4 {62–123}
>2 weeks old	0.7–0.9 {62–80}
>34 weeks of gestation	
<2 weeks old	0.4–0.6 {35–53}
>2 weeks old	0.3–0.5 {26–44}
1 month to 2 years	0.2–0.5 {18–44}

Modified from Chan et al. [8]

5.4.1 Creatinine-Based GFR Estimation

Creatinine-based GFR estimation methods are most commonly employed as it correlates well with inulin clearance within normal GFR ranges [45]. Creatinine as a by-product of muscle breakdown, hence it is not an ideal marker of GFR as there is some degree of reabsorption by the renal tubular cells. It is also secreted in the tubules and therefore overestimates the GFR at higher serum creatinine concentrations. Nevertheless it is overall the easiest and most commonly used test to assess GFR (Table 5.2).

The Schwartz formula [46] is quick and easy, utilizing height or length and serum creatinine concentration to calculate GFR; it has been recently modified in 2009, now recommending a fixed K of 0.413:

$$\text{GFR} = 0.413 \times \text{Length or Height}\,(\text{cm}) \,/\text{S. Creatinine}\,(\text{mg/dL})$$

Another commonly used formula is by Counahan [10] for serum creatinine measured in mg/dL or mmol/L, respectively:

$$\text{GFR} = 0.43 \times \text{Length or Height (cm)} / \text{S.Creatinine (mg/dL)}$$

$$\text{GFR} = 0.43 \times \text{Length or Height (cm)} / \text{S.Creatinine (micromol/L)}$$

Estimated GFR formulae have an intrinsic limitation, and they cannot be used in cases of severe obesity, malnutrition, and at the extremes of serum creatinine, where the secretory component of the creatinine can result in overestimation of GFR. In addition these cannot be used in critically ill patients with rapidly changing serum creatinine and in acute kidney injury.

Table 5.3 Normal serum cystatin C and creatinine levels

Age	Cystatin C mg/L (range)	Creatinine mmol/L (range)
24–28 weeks GA	1.48 (0.65–3.37)	78 (35–136)
29–36 weeks GA	1.65 (0.62–4.42)	75 (27–175)
0–3 months	1.37 (0.81–2.32)	47 (23–127)
4–11 months	0.98 (0.65–1.49)	42 (32–100)
1–3 years	0.79 (0.5–1.25)	45 (33–60)
1–17 years	0.8 (0.5–1.27)	56 (33–88)

Adapted from Finney et al. [14]. Copyright (2000) with permission from BMJ Publishing Group Ltd.

5.4.2 Cystatin C-Based GFR Estimation

Cystatin C is an endogenous low molecular weight protein (13.4 kD) and a member of cysteine protease inhibitor protein. It is produced by all the nucleated cells at a constant rate, completely filtered by the glomeruli, and almost 100 % metabolized by the renal tubular cells. Cystatin C is not affected much by age (the serum level decreases from birth to age 1 year and remain stable thereafter), gender, body composition, inflammatory conditions, and muscle mass. It can be affected by steroid use, thyroid disorders, and cigarette smoking. Multiple adult studies [18, 48] and a large pediatric study [14] suggest that cystatin C measurements correlate better with measured GFR and are more sensitive to subtle changes in GFR in comparison to creatinine (Table 5.3).

There are multiple cystatin C-based GFR formulae *without* measurement of serum creatinine:

Filler	$91.62 \times \text{Cystatin C}^{-1.123}$	{mL/min/1.732 m^2} [13]
Zappitelli	$75.94 \times \text{Cystatin C}^{-1.17}$	{mL/min/1.732 m^2} [55]
Grubb	$83.93 \times \text{Cystatin C}^{-1.676}$	{mL/min/1.732 m^2} [19]
Larsson	$77.24 \times \text{Cystatin C}^{-1.2623}$	{mL/min} [25]

Some calculations include the serum creatinine:

Zappitelli

$$\frac{\left(507.76 \times e^{0.0003\text{Ht}}\right)}{\text{CystC}^{0.634} \quad \text{Cr}^{0.547} \quad 1.165^{\text{Tx}}}$$

{Crmmol/L and Cystatin C mg/L}

$$43.82\left[1/\text{CystC}\right]^{0.635}\left[1/\text{Cr}\right]^{0.547}\left[1.35\right]^{\text{Ht}}$$

{Crmg/dL and Cystatin C mg/L}

Zappitelli et al. [55].

Bouvet

$$63.2 \times (\text{Cr}/96)^{-0.35} \times (\text{Cyst C}/1.2)^{-0.56} \times (\text{Wt}/45)^{0.3} \times (\text{age}/14)^{0.4}$$

{Crmmol/L and Cystatin C mg/L}

Bouvet et al. [7].

$$63.2\left[1.2/\text{CystC}\right]^{0.56}\left[(96/88.4)/\text{S.Cr}\right]^{0.35} \times (\text{Wt}/45)^{0.3} \times (\text{age}/14)^{0.4}$$

{Crmg/dL and Cystatin C mg/L}

Schwartz CKiDs

$39.1 \times (\text{HT/S.Cr})^{0.516} \times (1.8/\text{Cyst C})^{0.294} \times (30/\text{BUN})^{0.169} \times (1.099)^{\text{Male}} \times (\text{HT}/1.4)^{0.188}$ (Schwartz et al. [46]).

5.4.3 Exogenous Substrate-Based GFR Estimation

Multiple substrates like inulin [1], iothalmate [37], iohexol [3], ethylenediaminetetraacetic acid {EDTA} [41], and diethylenetriaminepentaacetic acid {DTPA} [41] are used for GFR estimation. Some use radioactivity and others use plasma clearance/disappearance curves. The limitation of inulin, iohexol, and iothalmate is their availability and difficulty in collecting timed urine samples from neonates and infants. Tc-DTPA is a very useful radiotracer as it allows assessment of differential renal function of either kidney, but its limitation is the exposure to radiation. A detailed discussion of these methods is beyond the scope of this chapter.

5.5 Assessment of Tubular Function

Renal tubular cells along all nephron segments are responsible for the processing of glomerular filtrate until it is ready to be excreted as final urine. Tubular cells have a remarkable ability to reabsorb or secrete substances according to the bodily needs; their functions are measured by absolute values of various solutes and proteins excreted along with various determinants like fractional excretion of sodium, fractional excretion of urea nitrogen, trans-tubular potassium gradient, and tubular reabsorption of phosphorus.

5.5.1 Fractional Excretion of Sodium and Urea (FeNa)

It is one of the most sensitive indicators of volume status and tubular integrity.

$$\text{FeNa} = \left\{ \begin{matrix} \text{Urine Na/Plasma Na} \times \\ \text{Plasma Creatinine/} \\ \text{Urine Creatinine} \end{matrix} \right\} \times 100$$

In older children, the FeNa usually is <1 % in prerenal states and >1 % in acute tubular injury, but in neonates, the threshold raises to 2.5–3.0 % due to inability to concentrate the urine [26, 50]. The value is dependent upon the gestational age as well; at 28 weeks, this could be as high as 12–15 % which gradually drops to 2–5 % by term and continues to fall postnatal even in premature infants [16]. It is also important to note that in face of diuretic use, FeNa cannot be used reliably due to increased sodium excretion caused by the diuretic. Under those circumstances, fractional excretion of urea can be substituted to assess intravascular volume or tubular integrity with a value of <35 % suggesting intravascular volume depletion and >35 % being suggestive of acute tubular injury [12].

$$\text{FeUrea} = \left\{ \begin{matrix} \text{Urine Urea/Plasma Urea} \times \\ \text{Plasma Creatinine/} \\ \text{Urine Creatinine} \end{matrix} \right\} \times 100$$

5.5.2 Fractional Excretion of Magnesium (FeMg)

Mg is primarily reabsorbed in the proximal tubule and thick ascending limb of the loop of Henle. Mg handling is assessed by FeMg, which is normally 2–4 %.

$$\text{FeMg} = \left\{ \begin{matrix} \text{Urine Mg} \times \text{Plasma Creatinine} \times 100/ \\ \text{Plasma Mg} \times \text{Urine Creatinine} \times 0.7 \end{matrix} \right\}$$

A factor of 0.7 is used to estimate the free serum Mg concentration, as only the free unbound Mg is available to be filtered by the glomeruli.

5.5.3 Trans-tubular Potassium Gradient (TTKG)

It is an indicator of action of aldosterone on distal tubules and collecting ducts [43]. It is very useful in the differential diagnosis of hypo-/hyperkalemia. Its prerequisite is that the urinary osmolality has to be greater than the serum osmolality, or urinary sodium has to be >25 mmol/L as potassium secretion is markedly reduced in these circumstances.

$$\text{TTKG} = \left\{ \frac{\text{Urinary Potassium} \times \text{Plasma Osm}}{\text{Plasma Potassium} \times \text{Urine Osm}} \right\} \times 100$$

In general, expected values of TTKG are <3–5 in hypokalemic states and 6–10 in hyperkalemia. TTKG in preterm neonates is rather low due to low-potassium excretory capacity of the tubules, but it does increase quickly over the course of the first few weeks of postnatal life [34].

5.5.4 Tubular Reabsorption of Phosphorus (TRP)

Phosphorus excretion is mainly dependent upon tubular handling as 85–95 % of filtered phosphorus is reabsorbed via proximal tubular cells [15]. Tubular reabsorption of phosphorus is significantly lower after 3 months of age [5].

$$\text{TRP} = \left\{ 1 - \left(\frac{\text{Urinary Phosphorus} \times \text{Plasma Creatinine}}{\text{/Plasma Phosphorus} \times \text{Urinary Creatinine}} \right) \times 100 \right\}$$

5.5.5 Random Urinary Calcium to Creatinine Ratio (UCa/Cr)

Urinary calcium estimation is useful in the evaluation of a patient with frequency, dysuria, hematuria, nephrocalcinosis, and nephrolithiasis. Random UCa/Cr is dependent on age ranging from 0.2 to 0.8 and the dietary intake of calcium (Table 5.4) [44, 49]. It is also significantly increased with the use of loop diuretics. Confirmation of true calcium excretion is obtained by collecting 24-h urine for calcium (<4 mg/kg/day).

Table 5.4 Norms for spot urinary calcium to creatinine ratio

Age	mg/mg	mmol/mmol
0–6 months	<0.8	<2.24
6–18 months	<0.6	<1.68
2–18 years	<0.2	<0.56

5.5.6 Urinary Uric Acid Estimation

Urinary uric acid excretion is another major indicator of renal tubular function. Newborns and infants tend to excrete a large amount of the filtered uric acid due to tubular immaturity. Adults excrete about 10 % of the filtered load, and this level is achieved at around 1 year of life. Neonates can excrete as much as 30–50 % of the filtered load. Uric acid excretion is related to weight and the gestational age of the newborn [40]. It can be assessed by using the fractional excretion of uric acid (FeUA):FeUA = {Urinary UA (mg/dL)/Serum UA (mg/dL)/Urinary Creatinine (mg/dL)/Serum Creatinine (mg/dL)/} × 100

As uric acid excretion also depends on the glomerular filtration, one can assess uric acid excretion per deciliter glomerular filtration, 3.3 mg/dL for children <2 years of age and <0.56 mg/dL for children >2 years of age [51, 52]: UA/GFR = {Urine UA (mg/dL) × Plasma Creatinine (mg/dL)/Urine Creatinine (mg/dL)}

5.6 Assessment of Fetal Renal Function

In the antenatal period, the placenta performs most of the functions that a well-developed and mature kidney performs. Nevertheless, the developing kidney does not stay idle either. Various physiologic mechanisms are underway, which can be assessed by various tests, even though some of these tests are crude and not very sensitive but can predict things to come in the future. Fetal renal function can be assessed by

1. Adequacy of amniotic fluid
2. Fetal urinary biochemical marker
3. Fetal blood sampling
4. Fetal renal biopsy
5. Fetal ultrasonography (see Chap. 8 for details)

Initially amniotic fluid is produced by the placenta but gradually fetal urine becomes the main source by 20 weeks of gestation. Any reduction in the amniotic fluid should alert the perinatologist to potential fetal renal dysfunction which can hamper lung development and maturity especially before 24 weeks of gestation. Similarly

Table 5.5 Predictors of poor neonatal renal function on the basis of fetal urinary markers

Index test	Threshold
Sodium	>100 mmol/L or >95th percentile
Chloride	>90 mmol/L or >95th percentile
Calcium	>1.2 mmol/L or >95th percentile
Osmolality	>200 mOsm/kg
Beta-2 microglobulin	>6 mg/L
Cystatin C	>1 mg/L
Retinol-binding protein	32 mg/L
Alpha-1 microglobulin	47 mg/L

Cobet et al. [9], Morris et al. [30], Muller et al. [31], Vanderheyden et al. [54]

excess of amniotic fluid can be associated with renal anomalies like congenital nephrosis and Bartter syndrome.

Fetal urine has been used to assess renal function for more than quarter century [17]. It is commonly done in cases of obstructive uropathies with dilated urinary tracts. Fetal urine can be assessed for sodium, chloride, calcium, urinary osmolarity, beta-2 microglobulins, and cystatin C. Of those markers, sodium, beta-2 microglobulins, and cystatin C best correlate with postnatal renal tubular function rather than glomerular filtration (Table 5.5).

Fetal urine becomes progressively more dilute with advancing gestational age; it is isotonic by 20 weeks of gestation. Urinary sodium concentrations decrease to <90 mmol/L by 30 weeks of gestation; higher values are indicators of poor renal tubular function. In a meta-analysis of fetal urine studies, it is suggested to use a gestation-specific threshold for urinary Na and beta-2 microglobulins for better diagnostic accuracy.

Cystatin C has evolved into a relatively more sensitive marker of renal function in adults and children. It has also been evaluated in amniotic fluid [33], fetal urine [31, 32], and fetal blood [6] to assess fetal renal function. Cystatin C is a protein (molecular weight 13.8 kD), so it does not cross placental barrier; it is filtered by glomeruli and reabsorbed and metabolized by renal tubules. In normal circumstances, cystatin C is not excreted in urine unless renal tubular cells are injured leading to alterations in tubular cell reabsorption and/or catabolism. Urinary cystatin C has the added advantage of being independent of gestational age.

Fetal blood sampling has become relatively safe with the development of the ultrasound-assisted chordocentesis. Usual clinical markers of renal function like urea, creatinine, and electrolytes pass through the placental barrier, so they are not good markers of renal function in the fetal blood [35]. Various higher molecular weight proteins like alpha-1 microglobulin (30 kD) [9, 36], beta-2 microglobulin (11.8 kD) [4, 11], retinol-binding protein (21 kD), and cystatin C (13.8 kD) [6] are used as markers in fetal blood sample.

Fetal renal biopsies are only in experimental procedure due to its invasiveness and high failure rate.

5.7 Future Developments

5.7.1 Novel Biomarkers and Future Directions

The need to identify novel biomarker to predict AKI has been a major area of research for nephrologists, neonatologists, and cardiologist in the last decade. Among the various promising biomarkers for prediction, stratification, characterizations, and monitoring the course and prognostication of acute kidney injury, four main biomarkers have been studied the most. These are neutrophil gelatinase-associated lipocalin {NGAL}, kidney injury molecule 1 {KIM-1}, and interleukin 18 {IL-18}.

(I) NGAL is a 25 kD, 178 amino acid long protein that has a role in renal tubular cell protection and proliferation. In a prospective study of children undergoing cardiopulmonary bypass, NGAL in the urine and serum samples predicted AKI within 2–6 h, while the creatinine rose 48–72 h later [27]. NGAL has also been found to be a predictor of renal dysfunction and the need for dialysis in renal transplant population [28], hemolytic uremic syndrome [53], contrast nephropathy [22], critically ill children in

pediatric ICU setting [56], and chronic kidney disease (CKD) [29]. Unfortunately all these studies were rather small so large multicenter studies are warranted for this promising biomarker.

(II) KIM-1 is a transmembrane protein whose production is upregulated primarily in ischemic tubular injury. It is more specific for ischemic [21] and nephrotoxic AKI [24], then other forms of AKI and CKD. It is detected in high concentration in urine with 6 h of cardiopulmonary bypass in patients who subsequently develop AKI.

(III) IL-18 is an inflammatory mediator, which can be measured in the urine in ischemic AKI [38] but does not rise in nephrotoxic injury, urinary tract infection, or in chronic renal injury. It can also help predict delayed graft function in kidney transplant population [39].

There are other novel biomarkers like proximal renal tubular epithelial antigen, adenosine deaminase-binding protein, N-acetyl-beta-glucosaminidase, and liver fatty acid-binding protein which are being tested to improve our ability to identify renal injury as early as possible and to change the potential course and outcomes. Efforts are also being devoted to use many of these biomarkers either sequentially or as panels to improve their yield and reduce the morbidity and hopefully the mortality.

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