ZB MED Publication Portal for Life Sciences
PUBLISSO
www.publisso.de

Biomarkers in children with kidney diseases

Angela Ciuntu[1]
Jana Bernic[2]
[1]Department of Pediatrics, Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau, Moldova
[2]Department of Pediatric Surgery, Orthopedics, and Anesthesiology "Natalia Gheorghiu", Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau, Moldova

Abstract

Novel biomarkers are used to facilitate the early diagnosis, timely treatment, and prognosis of renal pathology in children. Technological progress on the one hand and a remarkable clinical significance of biomarkers on the other hand are subjects of scientific and clinical value.

In spite of marked progress in this field, sensitivity and specificity of novel biomarkers represent a concern that is still prevailing. Furthermore, the identification of a perfect biomarker is of particular importance and faces a number of issues: organ specificity; secretion after cell injury; early production after a reversible organ injury; proportional extent of cell injury; appropriate use as a treatment-monitoring tool, with a quick reduction in response to effective treatment; and easy and prompt assessment.

Discovery of biomarkers is a subject of special interest. They emphasize the issues related to the incidence of urinary tract infections (UTI), idiopathic nephrotic syndrome (INS) and acute kidney injury (AKI). In addition, studies are conducted to identify specific markers for chronic kidney disease (CKD), facilitate a well-timed diagnosis and treatment, and improve patients' outcome.

Summary of recommendations

1. The markers of glomerular injury are the glomerular filtration rate (GFR), creatinine, blood urea nitrogen (BUN) and cystatin C.
2. The estimated glomerular filtration rate (eGFR) is used for diagnosis, staging, and monitoring of the kidney function.
3. Measurement of renal function at the time of the scan can aid in the interpretation of a radionuclide study, provide a measurement of renal function independent of the estimated GFR, and serve as a baseline for monitoring changes.
4. Albuminuria and proteinuria are considered as markers of glomerular integrity, and as one of the most important risk factors for progression of chronic kidney disease.
5. The markers of tubular injury among others are neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1), and N-Acetyl-β-D-glucosaminidase (NAG-β).
6. The renal fibrosis is dependent on the excessive production of profibrotic growth factors and extracellular matrix. Transforming growth factor-β1 (TGF-β1) and connective tissue growth factor (CTGF) are two of the major growth factors that promote renal fibrosis.
7. Biomarkers in kidney diseases have diagnostic and prognostic properties by monitoring disease progression, also they represent targets for further therapies that result in many therapeutic implications.

1 Introduction

The **National Institute of Health Biomarkers Definitions Working Group** defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [1]. In kidney diseases, the biomarkers constitute a useful tool for early diagnosis, providing prognostic information, monitoring disease progression, and predicting therapeutic response [1].

GMS
10.5680/lhuii000060

An ideal biomarker of renal injury should have the following characteristics: 1) organ specificity, 2) secretion after cell injury, 3) early production after a reversible organ injury, 4) proportional increase according to the extent of cell injury, 5) possibility to use as a treatment-monitoring tool, with a quick reduction in response to effective treatment, 6) techniques that are promptly and easily accessible and 7) minimally invasive and cost-efficient [2].

Kidney disease is highly prevalent all over the world in acute and chronic forms. Patients with kidney dysfunction have a higher morbidity and mortality.

Nowadays, biomarkers are considered to be an important tool to ensure a better approach to the diagnosis and treatment of children with renal disease. It is worth mentioning that research aimed to discover new biomarkers continues, and the management of kidney diseases such as acute kidney injury (AKI), chronic kidney disease (CKD) [3], [4], [5], and urinary tract infections (UTI) in childhood is continually improving [6], [7], as well as that of idiopathic nephrotic syndrome (INS) in children [8].

2 Methods

A systematic literature search was performed in PubMed, MEDLINE and the Cochrane data base with the following key words: “urinary tract infections”, “nephrotic syndrome”, “acute kidney injury”, “chronic kidney disease”, “biomarkers”. The search was limited only to children aged between 0 and 18 years old. Only publications with abstracts have been considered.

More than 830 publications were found. After screening by titles and abstracts, only 124 studies have been included in the final analysis. These publications were supplemented by additional articles obtained from their bibliographies published before 2008 but considered very important for analysis. The studies were rated according to the level of evidence and the strength of recommendations graded according to a system used in the EAU guidelines modified from the Oxford Centre for Evidence-based Medicine [9].

3 Results

3.1 Markers of glomerular filtration

3.1.1 Glomerular filtration rate

The best overall indicator of the glomerular function is the glomerular filtration rate (GFR) [10]. The **Kidney Disease Improving Global Outcomes (KDIGOs) guidelines** recommend the original pediatric GFR formulas which were derived independently by Schwartz and Counahan-Barratt in the mid-1970s. [11], [12].
In 2009, using data from the Chronic Kidney Disease in Children (CKiD) study, Schwartz and colleagues developed an updated ‘bedside’ formula based on a standardized creatinine method traceable to isotope dilution mass spectrometry (IDMS) and using the plasma disappearance of iohexol as the reference standard. However, the validity of Schwartz's bedside equation, when applied to children with mild CKD or normal kidney function, is unclear, given that the formula was developed in children with CKD stage 2–4 [13].

3.1.2 Creatinine

According to KDIGO, serum creatinine is the most commonly used endogenous marker. Creatinine is simple, cost-effective, convenient, and practical but less accurate because of the influence of non-GFR determinants such as muscle mass which increases with age in children, making growth a confounding variable in the interpretation of kidney function from creatinine alone [10], [14]. It is filtered not only by the glomerulus but undergoes extra-renal elimination by the gut, is secreted by the tubules, and is generated by muscle mass or diet [15]. Another important limitation is the wide variation of the serum creatinine level within age, gender, metabolism, nutrition, and hydration status [15]. Levels of serum creatinine may affect the early recognition of acute renal failure by using the pediatric RIFLE (**r**isk, **i**njury, **f**ailure, **l**oss, and **e**nd-stage renal failure) criteria [16].

Thus, the KDIGO clinical practice guideline for the evaluation and management of CKD, recommends the diagnosis, classification, and staging of the disease by estimated glomerular filtration rate (eGFR), and suggests the use of CKD-EPI as the preferred prediction equation [10]. The ‘gold standard’ for the

measurement of GFR is urinary clearance of an ideal filtration marker, defined as substance that is freely filtered at the glomerulus, neither reabsorbed, nor secreted, synthesized, or metabolized by the tubules, and does not alter the function of the kidney [17].

3.1.3 Blood Urea Nitrogen (BUN)

Blood Urea Nitrogen (BUN) is a nitrogen-containing compound formed in the liver as the end product or protein metabolism and urea cycle. In comparison with creatinine, urea is increased earlier in renal disease. However, it is a less sensitive marker of renal failure, as it can be affected by hydration, as well as dietary protein intake and protein catabolic rate [18].

The ratio of BUN/creatinine can be useful to differentiate prerenal from renal causes when the BUN is increased. In prerenal disease, the ratio is close to 20:1, while in intrinsic renal disease it is close to 10:1 [19].

3.1.4 Cystatin C (Cys-C)

Cystatin C (Cys-C) is a low-molecular-weight protein that belongs to the cystatin superfamily of reversible inhibitors of cysteine proteases [20]. It is formed at a constant rate and freely filtered by the kidneys. Serum levels of Cys-C are inversely correlated with GFR. One of the main advantages of Cys-C compared to creatinine as a GFR marker is that it is not affected by age, muscle mass or diet which facilitates its use in children. Various reports have indicated that it is a more reliable marker of GFR than creatinine, particularly in early renal impairment [21], [22], [23]. Serum Cys-C is a sensitive, but not a specific marker for the prediction and the diagnosis of AKI in children; like creatinine, its level may be affected by conditions other than GFR [24], [25], [26].
Cys-C has also been incorporated into eGFR equations such as the combined creatinine-Cys-C KDIGO CKD-EPI equation [10], [27].

3.1.5 Radionuclide techniques

As in adults, GFR in children can be measured by injecting an exogenous marker, which is inert and excreted exclusively via glomerular filtration. As an alternative, plasma disappearance techniques following a single injection of one of several exogenous markers, inulin [28], iohexol [29], 51Cr-EDTA [30], 99mTc-DTPA [31], and iothalamate [32], can be used to measure GFR. According to the recently published reviews [33], [34], [35], plasma clearance of 51Cr-EDTA, iohexol and inulin are sufficiently accurate to measure GFR, while 99mTc- DTPA and iothalamate are only sufficiently accurate if performed as renal clearance with urine collection.

3.2 Markers of glomerular integrity

3.2.1 Albuminuria

Albuminuria is a relevant marker of chronic renal impairment, a predictor of incipient nephropathy in diabetics and precedes any decline in eGFR [36]. Urine albumin may be measured in 24-hour urine collections or early morning/random specimens as an albumin/creatinine ratio. Nevertheless, the combination of albuminuria with eGFR has been found to improve the prediction of CKD progression to end stage kidney diseases (ESKD) [37], [38].

3.2.2 Proteinuria

Proteinuria is strongly associated with the risk of progression to ESKD not only as marker of the degree of structural alterations of glomerular filtration barrier (GFB) and proximal tubular epithelial cells (PTECs) but also because proteinuria itself is responsible for further renal damage at different levels [38].

Several studies showed a strong correlation between some proteinuria components and the extent of tubulointerstitial damage (TID) [39], [40]. Proteinuria is associated not only with TID but also with glomerular damage [38].

3.3 Acute diseases of the kidney and biomarkers

Biomarkers have been identified for the following acute diseases of the kidney: acute pyelonephritis (APN) or lower urinary tract infection. UTI represents one of the most important causes of febrile illness in the pediatric age group. Among infants presenting with fever, the overall prevalence of UTI was 7.0% [41].

3.3.1 Cytokines and Acute Phase Reactants

3.3.1.1 Interleukins (IL)

The importance of cytokines, especially interleukins and acute phase reactants in the diagnosis of UTI was highlighted in many studies.

3.3.1.2 IL-6 and IL-8

IL-6 and IL-8 are important pro-inflammatory proteins expressed in response to an infection [42]. Thus, in a prospective study Krzemień et al. [43] established that urine levels of IL-6 and IL-8 and TGF-β1 were significantly higher in infants with febrile UTI compared to those with non-febrile UTI and asymptomatic bacteriuria (ABU) and positively correlated with systemic inflammatory markers. Also, the urine cytokines and systemic inflammatory markers do not differentiate between upper and lower UTI in infants [43]. IL-6 and IL-8 are not suitable markers for differentiating between APN and lower UTI in children [44].

3.3.1.3 Urinary IL-8

Urinary IL-8 might serve as a predictive biomarker for renal scarring after an acute episode of pyelonephritis. Since urinary IL-8 emerges as a renal-specific diagnostic and prognostic marker, it may be suitable as a selective screening tool for children with febrile UTI [45]. In children with asymptomatic hematuria, a higher activity of urinary IL-6 with IgA nephropathy (IgAN) was demonstrated. It was suggested that urinary IL-6 may be used as screening tool in children with hematuria and as a guide for renal biopsy [46].

3.3.1.4 Urinary IL-18

Urinary IL-18, a member of the IL-1 family of cytokines, is a mediator of renal ischemia-reperfusion injury, inducing acute tubular necrosis, and neutrophil and monocyte infiltration in the renal parenchyma. The diagnostic accuracy of urinary IL-18 for AKI tends to be better in pediatric patients and early AKI predictive time. However, it has a moderate predictive value for all clinical settings [47].

3.3.1.5 Tumor necrosis factor (TNF)

Tumor necrosis factor (TNF) is a central mediator of inflammation, cell proliferation, cellular differentiation, and cellular apoptosis [48]. A pediatric study used the TNF pathway in the recurrence of focal segmental glomerulosclerosis (FSGS) and showed improvement in proteinuria after TNF antibodies therapy [49].
A prospective cohort pilot study of children with nephrotic syndrome (NS) revealed that mean post-treatment TNFα level was significantly higher in the steroid-resistant nephrotic syndrome (SRNS) than in the steroid-sensitive nephrotic syndrome (SSNS) patients. In the SRNS patients, mean serum TNFα levels were similar before and after treatment [50].
Plasma levels of TNFR1 and TNFR2 also are described as markers of progressive CKD in pediatric patients [51].

3.3.2 Chemokines

3.3.2.1 Urinary Monocyte Chemoattractant Protein-1 (MCP-1)

Urinary Monocyte Chemoattractant Protein-1 (MCP-1) is a chemokine which recruits monocytes and promotes their transformation into macrophages. Urinary levels of MCP-1 were significantly increased in children with CKD [52]. MCP-1 is useful to distinguish between glomerular and non-glomerular disease, being significantly increased in patients with glomerular injury [52]. In multiple ongoing trials, MCP-1 was identified as a potential therapeutic target in patients with CKD [53]. Also, the urinary fractional excretion of MCP-1 values show that inflammation precedes the tubular dysfunction. Fractional excretion may become a useful tool in the assessment of inflammation and tubular damage in children with CKD [54].

3.3.2.2 Transforming growth factor β1 (TGF-β1)

Transforming growth factor β1 (TGF-β1) is a multifunctional cytokine involved in multiple pathological processes, especially kidney diseases. TGF-β1 is an indicator of progression of renal involvement, a marker of glomerular and interstitial fibrosis and its influence on the development of renal scarring [55], [56], [57]. TGF-β1 polymorphisms predispose to progressive renal disease [58]. Urinary TGF-β1 levels proved to be higher in patients with FSGS in comparison to patients with minimal change disease (MCD) [59]. Children with obstructive uropathy had a higher urinary level of TGF-β1 than children with non-obstructive uropathy [60]. TGF-β can be either beneficial or detrimental depending on disease state. Therefore, the benefits of therapeutic intervention via TGF-β for controlling inflammation and fibrosis remain to be seen [61], [62].

3.3.2.3 Conjunctive tissue growth factor (CTGF)

Conjunctive tissue growth factor (CTGF) is another of the major growth factors that promote renal fibrosis [63], [64].

3.3.2.4 Procalcitonin (PCT)

Procalcitonin (PCT) had long been recognized as a biomarker of severe bacterial infection [65]. A meta-analysis of serum PCT in the diagnosis of APN among pediatrics with lower UTIs showed that the cut-off value of serum PCT, 1.0 ng/mL, has a preferable diagnostic performance compared with 0.5 ng/mL for APN [65]. PCT is a more convincing predictor than C-reactive protein or white blood cell count for selectively identifying children with APN during the early stages of UTI, as well as those with late scarring [66].

Withal, PCT is an early predictor of renal parenchymal injury in children with UTI, with optimum cut off for sensitivity, specificity, positive, and negative predictive value of this biomarker [67].

3.3.3 Other novel biomarkers

3.3.3.1 Neutrophil Gelatinase-Associated Lipocalin (NGAL)

Neutrophil Gelatinase-Associated Lipocalin (NGAL) is a protein produced by neutrophils and kidney tubular cells with increased synthesis during tubular injury [68].
Most of clinical studies demonstrated usefulness of urinary NGAL (uNGAL) for early diagnosis of UTI in children [69], [69], [70], [70] and for monitoring of treatment response [71], [72], [73]. The accuracy of uNGAL in UTI diagnosis in febrile infants <3 months of age was high and useful for early diagnosis and UTI treatment in this age group [73]. It was established that uNGAL has a high sensitivity and specificity for differentiating APN from other febrile infections [74]. On the other hand, uNGAL had lower sensitivity and specificity than serum NGAL for diagnosing febrile UTI as well as that uNGAL was not useful for

diagnosing non-febrile UTI [75].
Interestingly, uNGAL is also a potentially useful marker for the detection of subclinical renal damage such as scarring, vesicoureteral reflux, or obstruction [76], [77].

3.3.3.2 The kidney injury molecule-1(KIM-1)

The kidney injury molecule-1 (KIM-1) is a type-1 transmembrane protein, with an immunoglobulin and mucin domain. It is not detectable in normal kidney tissue or urine but is expressed at very high levels in dedifferentiated proximal tubule epithelial cells after tubular damage [78]. Urinary KIM-1 (uKIM-1) is a marker of disease severity in children with NS as levels were higher in SRNS as compared with steroid-dependent nephrotic syndrome (SDNS) [79]. Thus, KIM-1 expression is closely correlated with the presence of fibrosis and inflammation. Children with type 1 diabetes, without known albuminuria, had higher levels of uKIM-1 when compared to non-diabetic controls [80]. The expression level of uKIM-1 is sensitive for the early diagnosis of AKI and CKD, as well as useful to effective assessment of renal pathological damage and disease progression [81].
Studies showed that in urine samples from adults and children, the level of KIM-1 correlates highly with the incidence and prognosis of CKD [82], [83], [84].

3.3.3.3 Matrix metalloproteinases (MMPs)

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases, known to play a role in tissue remodelling through the degradation of extracellular matrix components [85]. MMP-9 is a potential biomarker of renal fibrosis, cardiovascular outcomes, and progressive renal injury [86]. MMP-9 has relatively good specificity and tissue inhibitor of metalloproteinase (TIMP1) has good sensitivity for predicting scar formation in children with APN. Combined analysis of both markers makes the specificity higher [87]. In children with CKD serum, MMP-2 levels kept increasing from the beginning of renal failure progression, and the levels of TIMP-1 and TIMP-2 correlated with TGF-β1 [88], suggesting that these markers indicate increased cell damage, inflammation, and aggravation of proteolytic processes in CKD children [88]. MMP-9 urinary levels were significantly elevated in children with FSGS, as compared with control subjects [89]. In a cohort of pediatric patients with CKD, MMP-9 serum concentrations were significantly higher in children with CKD compared to children without CKD [90].

3.3.3.4 Vitamin-D-binding protein (VDBP)

Vitamin-D-binding protein (VDBP) is a low-molecular weight protein that is filtered through the glomerulus as a 25-(OH) vitamin D 3/VDBP complex [91]. In patients with SRNS, urinary VDBP (uVDBP) levels were significantly increased compared to patients with SSNS, during remission and relapse. Therefore, uVDBP could be used as a non-invasive biomarker to predict steroid sensitivity in children with INS [92].

3.3.3.5 Alpha-1B-glycoprotein (A1BG)

Alpha-1B-glycoprotein (A1BG) is an acute phase protein, its concentration in serum increases in response to inflammatory processes. It has been detected in the urine of children with SRNS, and it has been shown that A1BG can be used to differentiate SRNS from SSNS [93], [93], [94].

3.3.3.6 Soluble urokinase-type plasminogen activator receptor (suPAR)

Soluble urokinase-type plasminogen activator receptor (suPAR) is the cleaved molecule derived from Urokinase-type plasminogen activator receptor (Upar), which is a glycosyl-phosphatidylinositol-anchored membrane protein present on multiple cells, including podocytes [95]. Wei C et al. demonstrated that serum suPAR levels were increased in two thirds of pediatric and adult patients with biopsy-proven FSGS, including both native and recurrent FSGS cases [96].

Many studies demonstrated that suPAR is inversely correlated with GFR in children [97], [98]. Another important fact, identified by Gellermann J et al., is that suPAR may be a biomarker of future decline in

GFR, as proteinuria is an established risk factor for CKD progression. Additionally, plasma suPAR concentration was higher in pediatric patients with SRNS versus SSNS [99].

3.3.3.7 MicroRNAs (miRNAs)

MicroRNAs (miRNAs) are post-transcriptional negative regulators of gene expression and play an important physiological role in a variety of biological processes, including the evolution of renal disease [100], [101], [102]. Urinary miRNAs are validated as diagnostic and prognostic biomarkers of acute cell rejection, interstitial fibrosis and tubular atrophy [103]. Moreover, miRNA profiling in urine was identified as a potential tool for monitoring graft function and anticipating progression to chronic allograft dysfunction in kidney transplantation [104]. Luo Y et al. [105], in a cohort study of 159 children and adolescents with proteinuria and NS, detected a significant increase in exosomal miRNAs compared to healthy controls. However, even if these exosomal miRNAs are correlated with proteinuria, the usefulness of these miRNAs for disease monitoring and stratification should be taken with caution [105]. Chen T. et al demonstrated that exosomal miRNA failed to differentiate between the 3 forms of NS: MCD, mesangial proliferation or FSGS [106].

3.3.3.8 Bone Morphogenetic Protein-7 (BMP-7)

Bone Morphogenetic Protein-7 (BMP-7) is a TGF-β1 antagonist, with anti-fibrotic and anti-inflammatory properties. It plays an essential role in both the development and regeneration of the kidney [107]. A large variety of evidence shows an anti-fibrotic role of BMP-7 in CKD, and this effect is largely mediated via counterbalancing the profibrotic effect of TGF-β. Increasing evidence from different independent experiments approved the anti-fibrotic effect of BMP-7 in renal fibrotic disease regardless of its primary causes [108].

3.3.3.9 Urinary Procollagen III N-Terminal Propeptide (uPIIINP)

Urinary Procollagen III N-Terminal Propeptide (uPIIINP), a propeptide byproduct of collagen 3 deposition, is a marker of renal tubulointerstitial fibrosis. The urinary concentration of PIIINP is associated with CKD progression, and this association is independent of baseline eGFR and other CKD risks. This is a very important tool for noninvasive assessment of kidney tubule function [109]. Urinary PIIINP was found to be a marker of CKD progression in a study on subjects of renal transplant [110]. For pediatric CKD, the main part is caused by congenital anomalies of the kidney and urinary tract (CAKUT), and uPIINP is a useful biomarker for the evaluation of obstruction nephropathy [111].

3.3.3.10 N-acetyl-β-D glucosaminidase (NAG-β)

N-acetyl-β-D glucosaminidase (NAG-β) is a proximal tubule lysosomal enzyme that showed increased levels in toxic tubular damage, chronic glomerular disease, diabetic nephropathy; it is also useful in the settings of cardiopulmonary bypass surgery [112], [113], [114]. It is highly sensitive in the detection of AKI. Also, urinary NAG-β (uNAG-β) was able to predict the renal outcome of critically ill patients with AKI. This feature makes it a potential and sensitive biomarker of AKI [115].

Mishra et al. [116] evaluated the excretion of uNAG-β among three subgroups of patients with INS, namely, those who presented with first episode, those with relapses, and those with steroid resistance, as a sensitive biomarker of renal parenchymal disease. Thus, this urinary biomarker obviously has both prognostic and discriminatory roles in childhood with INS [116]. **The utility of biomarkers in kidney diseases is summarized in table 1**.

Table 1: The clinical utility of different renal biomarkers in children with kidney diseases

Biomarkers	Diseases	Clinical utility
uIL-6	UTI, Ig AN	Diagnostic
uIL-8	UTI	Diagnostic, prognostic
uIL-18	AKI	Diagnostic
serumTNF-α	NS, CKD	Differentiate SSNS from SRNS Prognostic
uMCP-1	CKD	Diagnostic, differentiate of glomerular and non-glomerular diseases
uTGF-β	MCD, FSGS, obstructive uropathy	Diagnostic, prognostic, indicator of progression of renal impairment
CTGF	CKD	Diagnostic
serum PCT	UTI	Diagnostic
uNGAL	UTI, obstructive nephropathy	Diagnostic, differentiate diagnostic, monitoring of treatment response
pNGAL	UTI	Diagnostic
uKIM-1	SN, AKI, CKD, Type I diabetes	Diagnostic, differentiate SDNS from SRNS Prognostic
uMMP-9	APN, FSGS	Diagnostic
serum MMP-9	APN, CKD	Diagnostic
uVDBP	NS	Diagnostic, differentiate SRNS from SSNS
urinary A1BG	NS	Differentiate SRNS from SSNS
serum suPAR	NS, FSGS, CKD	Diagnostic, differentiate SRNS from SSNS Prognostic
urinary miRNAs	NS, MCD, FSGS, CKD	Diagnostic, differentiate diagnostic Prognostic
BMP-7	CKD	Diagnostic
uPIIINP	Obstructive nephropathy, CKD	Diagnostic Prognostic
uNAG-β	NS, AKI	Differentiate SSNS from SRNS Diagnostic

4 Further research

Early diagnosis and the outcomes of kidney diseases could be enhanced through the development of novel sensitive biomarkers that would allow to increase the quality of assessment of these disorders and ameliorate clinical decisions. The most promising biomarkers are **proteomics**, including transcriptomics, urinary proteomics and metabolomics, that can facilitate a more precise and early diagnosis of renal disorders [117], [118], [119].

Another direction is the genetic testing of children with kidney disease that became more widespread with the discovery of more than 50 monogenic causes of INS that led to significant clinical implications [120].

The usefulness of these biomarkers should be validated in longitudinal clinical studies and from the perspective of the modern pediatric paradigm regarding individualized, personalized treatment, which requires a wider and more varied arsenal of highly accurate paraclinical investigations.

5 Conclusion

An increased number of studies regarding to sensitive and selective biomarkers are useful for diagnosis and evaluation of mechanisms characteristic for renal disorders and to confirm the importance of this topic.

Older biomarkers of kidney function and injury (GFR, eGFR, creatinine, ratio of BUN: creatinine, albuminuria, proteinuria) are still used in clinical practice, being very cost-effective. But the use of these biomarkers has many limitations [22]. Thus, serum creatinine is an insensitive and late biomarker, compared to newly proposed AKI biomarkers, such as serum Cys-C and uNGAL.

The capacity to make an early diagnosis and monitor the evolution of kidney disease in children was enhanced considerably in the last years, after finding more specific and sensitive biomarkers, as uNGAL and serum Cys-C, that can predict AKI early in critically ill children, as biomarkers for diagnostic, prognostic, monitoring the treatment of UTI, AKI, CKD – cytokines and acute phase reactants (IL-6, IL-8, IL-18, TNF-α, PCT), pNGAL, uNGAL, uKIM, uMMP-9, uVDBP, A1BG, uPIIINP, uNAG-β, and biomarkers of renal fibrosis – urinary TGF-β and CTGF.

Biomarkers that could distinguish SRNS from SSNS – uVDBP, uNGAL, urinary A1BG, serum suPAR – were found to be significantly elevated in SRNS.
Complicated pathogenetic mechanisms of development and progression of children kidney diseases demand not a single marker, but a combination of them, to reflect all the changes that happen during the disease.

References

1. Strimbu K, Tavel JA. What are biomarkers? Curr Opin HIV AIDS. 2010 Nov;5(6):463-6. DOI: 10.1097/COH.0b013e32833ed177
2. Cruz DN, Goh CY, Haase-Fielitz A, Ronco C, Haase M. Early biomarkers of renal injury. Congest Heart Fail. 2010 Jul;16(4 Suppl 1):S25-31. DOI: 10.1111/j.1751-7133.2010.00163.x
3. Malhotra R, Siew ED. Biomarkers for the early detection and prognosis of acute kidney injury. Clin J Am Soc Nephrol. 2017 Jan 6;12(1):149-73. DOI: 10.2215/CJN.01300216
4. Greenberg JH, Kakajiwala A, Parikh CR, Furth S. Emerging biomarkers of chronic kidney disease in children. Pediatr Nephrol. 2018 Jun;33(6):925-33. DOI: 10.1007/s00467-017-3701-9
5. Konukoglu D. Biomarkers for acute kidney injury. Int J Med Biochem. 2018;1(2):80-7. DOI: 10.14744/ijmb.2018.09719
6. Lee H-E, Kim DK, Kang HK, Park K. The diagnosis of febrile urinary tract infection in children may be facilitated by urinary biomarkers. Pediatr Nephrol. 2015 Jan;30(1):123-30. DOI: 10.1007/s00467-014-2905-5
7. Jung N, Byun HJ, Park JH, Kim JS, Kim HW, Ha JY. Diagnostic accuracy of urinary biomarkers in infants younger than 3 months with urinary tract infection. Korean J Pediatr. 2018 Jan;61(1):24-9. DOI: 10.3345/kjp.2018.61.1.24
8. Uwaezuoke Samuel N. The role of novel biomarkers in childhood idiopathic nephrotic syndrome: a narrative review of published evidence. Int J Nephrol Renovasc Dis. 2017 Jun 1;10:123-8. DOI: 10.2147/IJNRD.S131869
9. Abrams P, Khoury S, Grant A. Evidence-based medicine overview of the main steps for developing and grading guideline recommendations. Prog Urol. 2007 May;17(3):681-4. DOI: 10.1016/s1166-7087(07)92383-0
10. Kidney Disease: Improving Global Outcomes (KDIGO) CKD work group [Internet]. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013 Jan;3(1) [cited 2020 Nov 6]. Available from: https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf
11. Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics.1976;58:259-63.
12. Counahan R, Chantler C, Ghazali S, Kirkwood B, et al. Estimation of glomerular filtration rate from plasma creatinine concentration in children. Arch Dis Child. 1976 Nov;51(11):875-8. DOI: 10.1136/adc.51.11.875
13. Schwartz GJ, Munoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009;20:629-37. Epub 2009 Jan 21. DOI: 10.1681/ASN.2008030287

14. Mian AN, Schwartz GJ. Measurement and estimation of glomerular filtration rate in children. Adv Chronic Kidney Dis. 2017 Nov;24(6):348-56. DOI: 10.1053/j.ackd.2017.09.011
15. Levey AS, Inker LA, Coresh J. GFR Estimation: from Physiology to public health. Am J Kidney Dis. 2014;63(5):820-34. Epub 2014 Jan 28. DOI: 10.1053/j.ajkd.2013.12.006
16. Plötz FB, Bouma AB, van Wijk JA, Kneyber MC, Bökenkamp A. Pediatric acute kidney injury in the ICU: an independent evaluation of pRIFLE criteria. Intensive Care Med. 2008 Sep;34(9):1713-7. Epub 2008 Jun 3. DOI: 10.1007/s00134-008-1176-7
17. Inker LA, Levey AS, Coresh J. Estimated glomerular filtration rate from a panel of filtration markers - hope for increased accuracy beyond measured glomerular filtration rate? Adv Chronic Kidney Dis. 2018;25(1):67-75. DOI: 10.1053/j.ackd.2017.10.004
18. Clarkson MR, Magee CN, Brenner BM. Poket Companion to Brenner and Rector's The Kidney. 2nd ed. Philadelphia: Saunders/Elsevier; 2011. Chapter 1 - Clinical Assessment of the Patient with Kidney Disease; p. 3-20.
19. Somers MJG. Fluid and electrolyte therapy in children. In: Avner ED, Harmon WE, Niaudet P, eds. Pediatric Nephrology. 5th ed. Philadelphia: Lippincott, Williams and Wilkins; 2004. p. 275-98.
20. Anders Grubb. Cystatin C is indispensable for evaluation of kidney disease. EJIFCC. 2017 Dec;28(4):268-76.
21. Beker BM, Corleto MG, Fieiras C, Musso CG. Novel acute kidney injury biomarkers: their characteristics, utility and concerns. Int Urol Nephrol. 2018 Apr;50(4):705-13. Epub 2018 Jan 6. DOI: 10.1007/s11255-017-1781-x
22. Kari JA, Shalaby MA, Sofyani K, Sanad AS, Ossra AF, Halabi RS, Aljuhani MH, Toffaha WM, Moria FA, Sabry S, Ahmed HA, Alhasan KA, Sharief S, Safdar O. Urinary neutrophil gelatinase-associated lipocalin (NGAL) and serum cystatin C measurements for early diagnosis of acute kidney injury in children admitted to PICU. World J Pediatr. 2018 Apr;14(2):134-42. Epub 2018 Feb 20. DOI: 10.1007/s12519-017-0110-x
23. McCaffrey J, Coupes B, Chaloner C, Webb NJ, Barber R, Lennon R. Towards a biomarker panel for the assessment of AKI in children receiving intensive care. Pediatr Nephrol. 2015 Oct;30(10):1861-71. Epub 2015 Apr 15. DOI: 10.1007/s00467-015-3089-3
24. Nakhjavan-Shahraki B, Yousefifard M, Ataei N, Baikpour M, Ataei F, Bazargani B, Abbasi A, Ghelichkhani P, Javidilarijani F, Hosseini M. Accuracy of cystatin C in prediction of acute kidney injury in children; serum or urine levels: which one works better? A systematic review and meta-analysis. BMC Nephrol. 2017 Apr 3;18(1):120. DOI: 10.1186/s12882-017-0539-0
25. Safdar OY, Shalaby M, Khathlan N, Elattal B, Bin Joubah M, Bukahri E, Saber M, Alahadal A, Aljariry H, Gasim S, Hadadi A, Alqahtani A, Awleyakhan R, Kari JA. Serum cystatin is a useful marker for the diagnosis of acute kidney injury in critically ill children: prospective cohort study. BMC Nephrol. 2016 Sep 13;17(1):130. DOI: 10.1186/s12882-016-0346-z
26. Liu X, Foster MC, Tighiouart H, Anderson AH, Beck GJ, Contreras G, Coresh J, Eckfeldt JH, Feldman HI, Greene T, Hamm LL, He J, Horwitz E, Lewis J, Ricardo AC, Shou H, Townsend RR, Weir MR, Inker LA, Levey AS; CRIC (Chronic Renal Insufficiency Cohort) Study Investigators. Non-GFR determinants of low-molecular-weight serum protein filtration markers in CKD. Am J Kidney Dis. 2016 Dec;68(6):892-900. Epub 2016 Sep 20. DOI: 10.1053/j.ajkd.2016.07.021
27. Freed TA, Coresh J, Inker LA, Toal DR, Perichon R, Chen J, Goodman KD, Zhang Q, Conner JK, Hauser DM, Vroom KET, Oyaski ML, Wulff JE, Eiríksdóttir G, Gudnason V, Torres VE, Ford LA, Levey AS. Validation of a metabolite panel for a more accurate estimation of glomerular filtration rate using quantitative LC-MS/MS. Clin Chem. 2019 Mar;65(3):406-18. Epub 2019 Jan 15. DOI: 10.1373/clinchem.2018.288092
28. van Rossum LK, Cransberg K, de Rijke YB, Zietse R, Lindemans J, Vulto AG. Determination of inulin clearance by single injection or infusion in children. Pediatr Nephrol. 2005 Jun;20(6):777-81. Epub 2005 Apr 15. DOI: 10.1007/s00467-004-1782-8
29. Schwartz GJ, Furth S, Cole SR, Warady B, Muñoz A. Glomerular filtration rate via plasma iohexol disappearance: pilot study for chronic kidney disease in children. Kidney Int. 2006 Jun;69(11):2070-7. DOI: 10.1038/sj.ki.5000385
30. Chantler C, Garnett ES, Parsons V, et al. Glomerular filtration rate measurement in man by the single injection methods using 51Cr-EDTA. Clin Sci. 1969;37:169-80.
31. Mulligan JS, Blue PW, Hasbargen JA. Methods for measuring GFR with technetium-99m-DTPA: an analysis of several common methods. J Nucl Med. 1990;31:1211-9.
32. Dowling TC, Frye RF, Fraley DS, Matzke GR. Comparison of iothalamate clearance methods for

measuring GFR. Pharmacotherapy. 1999 Aug;19(8):943-50. DOI: 10.1592/phco.19.11.943.31576
33. Soveri I, Berg UB, Björk J, Elinder CG, Grubb A, Mejare I, Sterner G, Bäck SE; SBU GFR Review Group. Measuring GFR: a systematic review. Am J Kidney Dis. 2014 Sep;64(3):411-24. Epub 2014 May 17. DOI: 10.1053/j.ajkd.2014.04.010
34. Carrara Fabiola, Gaspari Flavio. GFR measured by iohexol: the best choice from a laboratory perspective. J Lab Precis Med. 2018;3:77. DOI: 10.21037/jlpm.2018.09.07
35. Delanaye P, Jager KJ, Bökenkamp A, Christensson A, Dubourg L, Eriksen BO, Gaillard F, Gambaro G, van der Giet M, Glassock RJ, Indridason OS, van Londen M, Mariat C, Melsom T, Moranne O, Nordin G, Palsson R, Pottel H, Rule AD, Schaeffner E, Taal MW, White C, Grubb A, van den Brand JAJG. CKD: A call for an age-adapted definition. J Am Soc Nephrol. 2019 Oct;30(10):1785-805. Epub 2019 Sep 10. DOI: 10.1681/ASN.2019030238
36. Lopez-Giacoman S, Madero M. Biomarkers in chronic kidney disease, from kidney function to kidney damage. World J Nephrol. 2015 Feb 6;4(1):57-73. DOI: 10.5527/wjn.v4.i1.57
37. Hallan SI, Ritz E, Lydersen S, Romundstad S, Kvenild K, Orth SR. Combining GFR and albuminuria to classify CKD improves prediction of ESRD. J Am Soc Nephrol. 2009 May;20(5):1069-77. Epub 2009 Apr 8. DOI: 10.1681/ASN.2008070730
38. Patel VB, Preedy VR. Biomarkers in kidney disease. Dordrecht: Springer Netherlands; 2016. p. 516-7. DOI: 10.1007/978-94-007-7699-9
39. Satirapoj B. Tubulointerstitial biomarkers for diabetic nephropathy. J Diabetes Res. 2018 Feb 8;2018:2852398. DOI: 10.1155/2018/2852398
40. Toblli JE, Bevione P, Di Gennaro F, Madalena L, Cao G, Angerosa M. Understanding the mechanisms of proteinuria: therapeutic implications. Int J Nephrol. 2012;2012:546039. Epub 2012 Jul 4. DOI: 10.1155/2012/546039
41. Leung AKC, Wong AHC, Leung AAM, Hon KL. Urinary Tract Infection in Children. Recent Pat Inflamm Allergy Drug Discov. 2019;13(1):2-18. DOI: 10.2174/1872213X13666181228154940
42. Dahiya A, Goldman RD. Management of asymptomatic bacteriuria in children. Can Fam Physician. 2018;64(11):821-4.
43. Krzemień G, Szmigielska A, Turczyn A, Pańczyk-Tomaszewska M. Urine interleukin-6, interleukin-8 and transforming growth factor β1 in infants with urinary tract infection and asymptomatic bacteriuria. Cent Eur J Immunol. 2016;41(3):260-7. DOI: 10.5114/ceji.2016.63125
44. Mahyar A, Ayazi P, Maleki MR, Daneshi-Kohan MM, Sarokhani HR, Hashemi HJ, Talebi-Bakhshayesh M. Serum levels of interleukin-6 and interleukin-8 as diagnostic markers of acute pyelonephritis in children. Korean J Pediatr. 2013 May;56(5):218-23. Epub 2013 May 28. DOI: 10.3345/kjp.2013.56.5.218
45. Renata Y, Jassar H, Katz R, Hochberg A, Nir RR, Klein-Kremer A. Urinary concentration of cytokines in children with acute pyelonephritis. Eur J Pediatr. 2013 Jun;172(6):769-74. Epub 2013 Feb 7. DOI: 10.1007/s00431-012-1914-2
46. Kanemoto K, Matsumura R, Anzai M, et al. Urinary excretion of interleukin-6 in pediatric IgA nephropathy patients. J Nephrol Therapeutic. 2014;S11. DOI: 10.4172/2161-0959.S11-004
47. Liu Y, Guo W, Zhang J, Xu C, Yu S, Mao Z, Wu J, Ye C, Mei C, Dai B. Urinary interleukin-18 for detection of acute kidney injury: a meta-analysis. Am J Kidney Dis. 2013 Dec;62(6):1058-67. Epub 2013 Jul 2. DOI: 10.1053/j.ajkd.2013.05.014
48. Al-Lamki RS, Mayadas TN. TNF receptors: signaling pathways and contribution to renal dysfunction. Kidney Int. 2015 Feb;87(2):281-96. Epub 2014 Aug 20. DOI: 10.1038/ki.2014.285
49. Bitzan M, Babayeva S, Vasudevan A, Goodyer P, Torban E. TNFα pathway blockade ameliorates toxic effects of FSGS plasma on podocyte cytoskeleton and β3 integrin activation. Pediatr Nephrol. 2012 Dec;27(12):2217-26. Epub 2012 Apr 27. DOI: 10.1007/s00467-012-2163-3
50. Weissbach A, Garty BZ, Lagovsky I, et al. Serum tumor necrosis factor-alpha levels in children with nephrotic syndrome: a pilot study. Isr Med Assoc J. 2017 Jan;19(1):30-3.
51. Moreira JM, da Silva AN, Marciano Vieira ÉL, Teixeira AL, Kummer AM, Simões E Silva AC. Soluble tumor necrosis factor receptors are associated with severity of kidney dysfunction in pediatric chronic kidney disease. Pediatr Nephrol. 2019 Feb;34(2):349-52. Epub 2018 Oct 29. DOI: 10.1007/s00467-018-4124-y
52. Vianna HR, Soares CM, Silveira KD, Elmiro GS, Mendes PM, de Sousa Tavares M, Teixeira MM, Miranda DM, Simões E Silva AC. Cytokines in chronic kidney disease: potential link of MCP-1 and dyslipidemia in glomerular diseases. Pediatr Nephrol. 2013 Mar;28(3):463-9. Epub 2012 Nov 18. DOI: 10.1007/s00467-012-2363-x

53. de Zeeuw D, Bekker P, Henkel E, Hasslacher C, et al.The effect of CCR2 inhibitor CCX140-B on residual albuminuria in patients with type 2 diabetes and nephropathy: a randomised trial. Lancet Diabetes Endocrinol. 2015;3:687-96. DOI: 10.1016/S2213-8587(15)00261-2
54. Musiał K, Bargenda A, Drożdż D, Zwolińska D. New markers of inflammation and tubular damage in children with chronic kidney disease. Dis Markers. 2017;2017:9389432. Epub 2017 Jul 20. DOI: 10.1155/2017/9389432
55. Black LM, Lever JM, Agarwal A. Renal Inflammation and Fibrosis: a double-edged sword. J Histochem Cytochem. 2019 Sep;67(9):663-81. Epub 2019 May 22. DOI: 10.1369/0022155419852932
56. Mariani LH, Martini S, Barisoni L, Canetta PA, Troost JP, Hodgin JB, Palmer M, Rosenberg AZ, Lemley KV, Chien HP, Zee J, Smith A, Appel GB, Trachtman H, Hewitt SM, Kretzler M, Bagnasco SM. Interstitial fibrosis scored on whole-slide digital imaging of kidney biopsies is a predictor of outcome in proteinuric glomerulopathies. Nephrol Dial Transplant. 2018 Feb 1;33(2):310-8. DOI: 10.1093/ndt/gfw443
57. Lopes TG, de Souza ML, da Silva VD, Dos Santos M, da Silva WIC, Itaquy TP, Garbin HI, Veronese FV. Markers of renal fibrosis: how do they correlate with podocyte damage in glomerular diseases? PLoS One. 2019 Jun 20;14(6):e0217585. DOI: 10.1371/journal.pone.0217585
58. Hye-Jin Ki, Se Yun Kim, Sang Ho Lee.Transforming growth factor-β receptor 2 gene polymorphisms are associated with end-stage renal disease. Kidney Res Clin Pract. 2015 Jun;34(2):93-7.
59. Woroniecki RP, Shatat IF, Supe K, Du Z, Kaskel FJ. Urinary cytokines and steroid responsiveness in idiopathic nephrotic syndrome of childhood. Am J Nephrol. 2008;28(1):83-90. Epub 2007 Oct 3. Erratum in: Am J Nephrol. 2008;28(1):179. DOI: 10.1159/000109396
60. Zieg J, Blahova K, Seeman T, Bronsky J, Dvorakova H, Pechova M, Janda J, Matousovic K. Urinary transforming growth factor-β1 in children with obstructive uropathy. Nephrology (Carlton). 2011 Aug;16(6):595-8. DOI: 10.1111/j.1440-1797.2011.01459.x
61. Lv W, Booz GW, Wang Y, Fan F, Roman RJ. Inflammation and renal fibrosis: Recent developments on key signaling molecules as potential therapeutic targets. Eur J Pharmacol. 2018 Feb 5;820:65-76. Epub 2017 Dec 8. DOI: 10.1016/j.ejphar.2017.12.016
62. Tampe D, Zeisberg M. Potential approaches to reverse or repair renal fibrosis. Nat Rev Nephrol. 2014 Apr;10(4):226-37. Epub 2014 Feb 11. DOI: 10.1038/nrneph.2014.14
63. Nguyen TQ, Tarnow L, Andersen S, Hovind P, Parving HH, Goldschmeding R, van Nieuwenhoven FA. Urinary connective tissue growth factor excretion correlates with clinical markers of renal disease in a large population of type-1 diabetic patients with diabetic nephropathy. Diabetes Care. 2006 Jan;29(1):83-8. DOI: 10.2337/diacare.29.1.83
64. Toda N, Mukoyama M, Yanagita M, Yokoi H. CTGF in kidney fibrosis and glomerulonephritis. Inflamm Regen. 2018 Aug 6;38:14. DOI: 10.1186/s41232-018-0070-0
65. Zhang H, Yang J, Lin L, Huo B, Dai H, He Y. Diagnostic value of serum procalcitonin for acute pyelonephritis in infants and children with urinary tract infections: an updated meta-analysis. World J Urol. 2016 Mar;34(3):431-41. Epub 2015 Jul 4. DOI: 10.1007/s00345-015-1630-4
66. Leroy S, Fernandez-Lopez A, Nikfar R, Romanello C, Bouissou F, Gervaix A, Gurgoze MK, Bressan S, Smolkin V, Tuerlinckx D, Stefanidis CJ, Vaos G, Leblond P, Gungor F, Gendrel D, Chalumeau M. Association of procalcitonin with acute pyelonephritis and renal scars in pediatric UTI. Pediatrics. 2013 May;131(5):870-9. Epub 2013 Apr 29. DOI: 10.1542/peds.2012-2408
67. Barati L, Safaeian B, Mehrjerdian M, Vakili MA. Early prediction of renal parenchymal injury with serum procalcitonin. J Renal Inj Prev. 2016 May 28;5(3):108-11. DOI: 10.15171/jrip.2016.23
68. Argyri I, Xanthos T, Varsami M, Aroni F, Papalois A, Dontas I, Fanos V, Iacovidou N. The role of novel biomarkers in early diagnosis and prognosis of acute kidney injury in newborns. Am J Perinatol. 2013 May;30(5):347-52. Epub 2012 Sep 21. DOI: 10.1055/s-0032-1326985
69. Lubell TR, Barasch JM, Xu K, Ieni M, Cabrera KI, Dayan PS. Urinary neutrophil gelatinase-associated lipocalin for the diagnosis of urinary tract infections. Pediatrics. 2017 Dec;140(6):e20171090. Epub 2017 Nov 16. DOI: 10.1542/peds.2017-1090
70. Valdimarsson S, Jodal U, Barregård L, Hansson S. Urine neutrophil gelatinase-associated lipocalin and other biomarkers in infants with urinary tract infection and in febrile controls. Pediatr Nephrol. 2017 Nov;32(11):2079-87. Epub 2017 Jul 29. DOI: 10.1007/s00467-017-3709-1
71. Petrovic S, Bogavac-Stanojevic N, Peco-Antic A, Ivanisevic I, Kotur-Stevuljevic J, Paripovic D, Sopic M, Jelic-Ivanovic Z. Clinical application neutrophil gelatinase-associated lipocalin and

kidney injury molecule-1 as indicators of inflammation persistence and acute kidney injury in children with urinary tract infection. Biomed Res Int. 2013;2013:947157. Epub 2013 Jul 9. DOI: 10.1155/2013/947157

72. Yim HE, Yim H, Bae ES, Woo SU, Yoo KH. Predictive value of urinary and serum biomarkers in young children with febrile urinary tract infections. Pediatr Nephrol. 2014 Nov;29(11):2181-9. Epub 2014 Jun 13. DOI: 10.1007/s00467-014-2845-0
73. Nickavar A, Safaeian B, Valavi E, et al. Validity of neutrophil gelatinase associated lipocaline as a biomarker for diagnosis of children with acute pyelonephritis. Pediatr Urol. 2016;13:2860-3.
74. Arambašić J, Mandić S, Debeljak Ž, Mandić D, Horvat V, Šerić V. Differentiation of acute pyelonephritis from other febrile states in children using urinary neutrophil gelatinase-associated lipocalin (uNGAL). Clin Chem Lab Med. 2016 Jan;54(1):55-61. DOI: 10.1515/cclm-2015-0377
75. Krzemień G, Pańczyk-Tomaszewska M, Adamczuk D, Kotuła I, Demkow U, Szmigielska A. Neutrophil gelatinase-associated lipocalin: a biomarker for early diagnosis of urinary tract infections in infants. Adv Exp Med Biol. 2018;1047:71-80. DOI: 10.1007/5584_2017_107
76. Forster CS, Devarajan P. Neutrophil gelatinase-associated lipocalin: utility in urologic conditions. Pediatr Nephrol. 2017 Mar;32(3):377-81. Epub 2016 Oct 26. DOI: 10.1007/s00467-016-3540-0
77. Rafiei A, Mohammadjafari H, Bazi S, Mirabi AM. Urinary neutrophil gelatinase-associated lipocalin (NGAL) might be an independent marker for anticipating scar formation in children with acute pyelonephritis. J Renal Inj Prev. 2015;4:39-44. DOI: 10.1016/j.ijid.2016.02.729
78. Westhoff JH, Seibert FS, Waldherr S, Bauer F, Tönshoff B, Fichtner A, Westhoff TH. Urinary calprotectin, kidney injury molecule-1, and neutrophil gelatinase-associated lipocalin for the prediction of adverse outcome in pediatric acute kidney injury. Eur J Pediatr. 2017 Jun;176(6):745-55. Epub 2017 Apr 14. DOI: 10.1007/s00431-017-2907-y
79. Bieniaś B, Zajączkowska M, Borzęcka H, Sikora P, Wieczorkiewicz-Płaza A, Wilczyńska B. Early markers of tubulointerstitial fibrosis in children with idiopathic nephrotic syndrome: preliminary report. Medicine (Baltimore). 2015 Oct;94(42):e1746. DOI: 10.1097/MD.0000000000001746
80. Ucakturk A, Avci B, Genc G, Ozkaya O, Aydin M. Kidney injury molecule-1 and neutrophil gelatinase associated lipocalin in normoalbuminuric diabetic children. J Pediatr Endocrinol Metab. 2016;29:145-51. DOI: 10.1515/jpem-2015-0138
81. Jin Y, Shao X, Sun B, Miao C, Li Z, Shi Y. Urinary kidney injury molecule-1 as an early diagnostic biomarker of obstructive acute kidney injury and development of a rapid detection method. Mol Med Rep. 2017 Mar;15(3):1229-35. Epub 2017 Jan 5. DOI: 10.3892/mmr.2017.6103
82. Waikar SS, Sabbisetti V, Arnlov J, Carlsson AC, Coresh J, Feldman HI, Foster MC, Fufaa GD, Helmersson-Karlqvist J, Hsu CY, Kimmel PL, Larsson A, Liu Y, Lind L, Liu KD, Mifflin TE, Nelson RG, Riserus U, Vasan RS, Xie D, Zhang X, Bonventre JV Chronic Kidney Disease Biomarkers Consortium Investigators. Relationship of proximal tubular injury to chronic kidney disease as assessed by urinary kidney injury molecule-1 in five cohort studies. Nephrol Dial Transplant. 2016;31:1460-70. Epub 2016 Jun 7. DOI: 10.1093/ndt/gfw203
83. Castillo-Rodriguez E, Fernandez-Prado R, Martin-Cleary C, Pizarro-Sánchez MS, Sanchez-Niño MD, Sanz AB, Fernandez-Fernandez B, Ortiz A. Kidney injury marker 1 and neutrophil gelatinase-associated lipocalin in chronic kidney disease. Nephron. 2017;136(4):263-7. Epub 2016 Oct 22. DOI: 10.1159/000447649
84. Carter JL, Parker CT, Stevens PE, Eaglestone G, Knight S, Farmer CK, Lamb EJ. Biological variation of plasma and urinary markers of acute kidney injury in patients with chronic kidney disease. Clin Chem. 2016 Jun;62(6):876-83. Epub 2016 Mar 29. DOI: 10.1373/clinchem.2015.250993
85. Ronco P, Chatziantoniou C. Matrix metalloproteinases and matrix receptors in progression and reversal of kidney disease: therapeutic perspectives. Kidney Int. 2008 Oct;74(7):873-8. Epub 2008 Jul 23. DOI: 10.1038/ki.2008.349
86. Zakiyanov O, Kalousová M, Zima T, Tesař V. Matrix metalloproteinases in renal diseases: a critical appraisal. Kidney Blood Press Res. 2019;44(3):298-330. Epub 2019 Jun 11. DOI: 10.1159/000499876
87. Abedi SM, Mohammadjafari H, Rafiei A, Bazi S, Yazdani P. Urinary matrix metalloproteinase 9 and tissue inhibitor of metalloproteinase 1 biomarkers for predicting renal scar in children with urinary tract infection. Turk J Urol. 2017 Dec;43(4):536-42. Epub 2017 Dec 1. DOI: 10.5152/tud.2017.06337
88. Musiał K, Zwolińska D. Novel indicators of fibrosis-related complications in children with chronic

kidney disease. Clin Chim Acta. 2014 Mar 20;430:15-9. Epub 2013 Dec 31. DOI: 10.1016/j.cca.2013.12.031

89. Korzeniecka-Kozerska A, Wasilewska A, Tenderenda E, Sulik A, Cybulski K. Urinary MMP-9/NGAL ratio as a potential marker of FSGS in nephrotic children. Dis Markers. 2013;34(5):357-62. DOI: 10.3233/DMA-130980
90. Musiał K, Zwolińska D. Matrix metalloproteinases (MMP-2,9) and their tissue inhibitors (TIMP-1,2) as novel markers of stress response and atherogenesis in children with chronic kidney disease (CKD) on conservative treatment. Cell Stress Chaperones. 2011 Jan;16(1):97-103. Epub 2010 Sep 6. DOI: 10.1007/s12192-010-0214-x
91. Chaykovska L, Heunisch F, von Einem G, Alter ML, Hocher CF, Tsuprykov O, Dschietzig T, Kretschmer A, Hocher B. Urinary vitamin-D binding protein and KIM-1 Are Potent New Biomarkers of Major Adverse Renal Events in Patients Undergoing Coronary Angiography. PLoS One. 2016 Jan 11;11(1):e0145723. DOI: 10.1371/journal.pone.0145723
92. Bennett MR, Pordal A, Haffner C, Pleasant L, Ma Q, Devarajan P. Urinary vitamin D-binding protein as a biomarker of steroid-resistant nephrotic syndrome. Biomark Insights. 2016 Jan 13;11:1-6. DOI: 10.4137/BMI.S31633
93. Piyaphanee N, Ma Q, Kremen O, Czech K, Greis K, Mitsnefes M, Devarajan P, Bennett MR. Discovery and initial validation of α 1-B glycoprotein fragmentation as a differential urinary biomarker in pediatric steroid-resistant nephrotic syndrome. Proteomics Clin Appl. 2011 Jun;5(5-6):334-42. Epub 2011 May 18. DOI: 10.1002/prca.201000110
94. Bennett MR, Pleasant L, Haffner C, Ma Q, Haffey WD, Ying J, Wagner M, Greis KD, Devarajan P. A novel biomarker panel to identify steroid resistance in childhood idiopathic nephrotic syndrome. Biomark Insights. 2017 Mar 8;12:1177271917695832. DOI: 10.1177/1177271917695832
95. Sever S, Trachtman H, Wei C, Reiser J. Is there clinical value in measuring suPAR levels in FSGS? Clin J Am Soc Nephrol. 2013 Aug;8(8):1273-5. Epub 2013 Jul 25. Erratum in: Clin J Am Soc Nephrol. 2013 Oct;8(10):1839. DOI: 10.2215/CJN.06170613
96. Wei C, Trachtman H, Li J, Dong C, Friedman AL, Gassman JJ, McMahan JL, Radeva M, Heil KM, Trautmann A, Anarat A, Emre S, Ghiggeri GM, Ozaltin F, Haffner D, Gipson DS, Kaskel F, Fischer DC, Schaefer F, Reiser J; PodoNet and FSGS CT Study Consortia. Circulating suPAR in two cohorts of primary FSGS. J Am Soc Nephrol. 2012 Dec;23(12):2051-9. Epub 2012 Nov 8. DOI: 10.1681/ASN.2012030302
97. Harita Y, Ishizuka K, Tanego A, Sugawara N, Chikamoto H, Akioka Y, Tsurumi H, Miura K, Gotoh Y, Tsujita M, Yamamoto T, Horike K, Takeda A, Oka A, Igarashi T, Hattori M. Decreased glomerular filtration as the primary factor of elevated circulating suPAR levels in focal segmental glomerulosclerosis. Pediatr Nephrol. 2014 Sep;29(9):1553-60. Epub 2014 Apr 6. DOI: 10.1007/s00467-014-2808-5
98. Sinha A, Bajpai J, Saini S, Bhatia D, Gupta A, Puraswani M, Dinda AK, Agarwal SK, Sopory S, Pandey RM, Hari P, Bagga A. Serum-soluble urokinase receptor levels do not distinguish focal segmental glomerulosclerosis from other causes of nephrotic syndrome in children. Kidney Int. 2014 Mar;85(3):649-58. Epub 2014 Jan 15. DOI: 10.1038/ki.2013.546
99. Gellermann J, Schaefer F, Querfeld U. Serum suPAR levels are modulated by immunosuppressive therapy of minimal change nephrotic syndrome. Pediatr Nephrol. 2014 Dec;29(12):2411-4. Epub 2014 Aug 17. DOI: 10.1007/s00467-014-2913-5
100. Zhang W, Zhang C, Chen H, Li L, Tu Y, Liu C, Shi S, Zen K, Liu Z. Evaluation of microRNAs miR-196a, miR-30a-5P, and miR-490 as biomarkers of disease activity among patients with FSGS. Clin J Am Soc Nephrol. 2014 Sep 5;9(9):1545-52. Epub 2014 Aug 8. DOI: 10.2215/CJN.11561113
101. Bhatt K, Kato M, Natarajan R. Mini-review: emerging roles of microRNAs in the pathophysiology of renal diseases. Am J Physiol Renal Physiol. 2016 Jan 15;310(2):F109-18. Epub 2015 Nov 4. DOI: 10.1152/ajprenal.00387.2015
102. Brandenburger T, Salgado Somoza A, Devaux Y, Lorenzen JM. Noncoding RNAs in acute kidney injury. Kidney Int. 2018 Nov;94(5):870-81. DOI: 10.1016/j.kint.2018.06.033
103. Muthukumar T, Lee JR, Dadhania DM, Ding R, Sharma VK, Schwartz JE, Suthanthiran M. Allograft rejection and tubulointerstitial fibrosis in human kidney allografts: interrogation by urinary cell mRNA profiling. Transplant Rev (Orlando). 2014 Jul;28(3):145-54. Epub 2014 May 27. DOI: 10.1016/j.trre.2014.05.003
104. Maluf DG, Dumur CI, Suh JL, Scian MJ, King AL, Cathro H, Lee JK, Gehrau RC, Brayman KL, Gallon L, Mas VR. The urine microRNA profile may help monitor post-transplant renal graft

function. Kidney Int. 2014 Feb;85(2):439-49. Epub 2013 Sep 11. DOI: 10.1038/ki.2013.338

105. Luo Y, Wang C, Chen X, Zhong T, Cai X, Chen S, Shi Y, Hu J, Guan X, Xia Z, Wang J, Zen K, Zhang CY, Zhang C. Increased serum and urinary microRNAs in children with idiopathic nephrotic syndrome. Clin Chem. 2013 Apr;59(4):658-66. Epub 2013 Jan 23. DOI: 10.1373/clinchem.2012.195297
106. Chen T, Wang C, Yu H, Ding M, Zhang C, Lu X, Zhang CY, Zhang C. Increased urinary exosomal microRNAs in children with idiopathic nephrotic syndrome. EBioMedicine. 2019 Jan;39:552-61. Epub 2018 Nov 19. DOI: 10.1016/j.ebiom.2018.11.018
107. Tsujimura T, Idei M, Yoshikawa M, Takase O, Hishikawa K. Roles and regulation of bone morphogenetic protein-7 in kidney development and diseases. World J Stem Cells. 2016 Sep 26;8(9):288-96. DOI: 10.4252/wjsc.v8.i9.288
108. Li RX, Yiu WH, Tang SC. Role of bone morphogenetic protein-7 in renal fibrosis. Front Physiol. 2015 Apr 23;6:114. DOI: 10.3389/fphys.2015.00114
109. Ix JH, Biggs ML, Mukamal K, Djousse L, et al. Urine Collagen Fragments and CKD Progression-The Cardiovascular Health Study. J Am Soc Nephrol. 2015;26(10):2494-503.
110. Teppo AM, Törnroth T, Honkanen E, Grönhagen-Riska C. Urinary amino-terminal propeptide of type III procollagen (PIIINP) as a marker of interstitial fibrosis in renal transplant recipients. Transplantation. 2003 Jun 27;75(12):2113-9. DOI: 10.1097/01.TP.0000066809.60389.48
111. Jianguo W, Zhenzhen L, Xianghua L, Zhanzheng Z, Suke S, Suyun W. Serum and urinary procollagen III aminoterminal propeptide as a biomarker of obstructive nephropathy in children. Clin Chim Acta. 2014 Jul 1;434:29-33. Epub 2014 Apr 24. DOI: 10.1016/j.cca.2014.04.005
112. Bazzi C, Petrini C, Rizza V, Arrigo G, Napodano P, Paparella M, D'Amico G. Urinary N-acetyl-beta-glucosaminidase excretion is a marker of tubular cell dysfunction and a predictor of outcome in primary glomerulonephritis. Nephrol Dial Transplant. 2002 Nov;17(11):1890-6. DOI: 10.1093/ndt/17.11.1890
113. Han WK, Wagener G, Zhu Y, Wang S, Lee HT. Urinary biomarkers in the early detection of acute kidney injury after cardiac surgery. Clin J Am Soc Nephrol. 2009 May;4(5):873-82. Epub 2009 Apr 30. DOI: 10.2215/CJN.04810908
114. Gonzalez F, Vincent F. Biomarkers for acute kidney injury in critically ill patients. Minerva Anestesiol. 2012;78(12):1394-403.
115. Vanmassenhove J, Vanholder R, Nagler E, Van Biesen W. Urinary and serum biomarkers for the diagnosis of acute kidney injury: an in-depth review of the literature. Nephrol Dial Transplant. 2013 Feb;28(2):254-73.
116. Mishra OP, Jain P, Srivastava P, Prasad R. Urinary N-acetyl-beta-D glucosaminidase (NAG) level in idiopathic nephrotic syndrome. Pediatr Nephrol. 2012;27(4):589-96.
117. Oliverio AL, Bellomo T, Mariani LH. Evolving clinical applications of tissue transcriptomics in kidney disease. Front Pediatr. 2019;7:306.
118. Chen Z, Kim J. Urinary proteomics and metabolomics studies to monitor bladder health and urological diseases. BMC Urol. 2016 Mar 22;16:11. DOI: 10.1186/s12894-016-0129-7
119. Dubin RF, Rhee EP. Proteomics and metabolomics in kidney disease, including insights into etiology, treatment, and prevention. Clin J Am Soc Nephrol. 2020 Mar 6;15(3):404-11. Epub 2019 Oct 21. DOI: 10.2215/CJN.07420619
120. Lovric S, Ashraf S, Tan W, Hildebrandt F. Genetic testing in steroid-resistant nephrotic syndrome: when and how? Nephrol Dial Transplant. 2016 Nov;31(11):1802-13. Epub 2015 Oct 27. DOI: 10.1093/ndt/gfv355

Corresponding authors: Professor Angela Ciuntu MD,PhD, Nicolae Testemitanu State University of Medicine and Pharmacy, Department of Pediatrics, Stefan cel Mare si Sfant, 165, 2004 Chisinau, Moldova, Phone: 37379842912, E-mail: angela.ciuntu@usmf.md

Citation note: Ciuntu A, Bernic J. Biomarkers in children with kidney diseases. Version: 2021-10-20. In: Bjerklund Johansen TE, Wagenlehner FME, Matsumoto T, Cho YH, Krieger JN, Shoskes D, Naber KG, editors. Urogenital Infections and Inflammations. Berlin: German Medical Science GMS Publishing House; 2017-. DOI: 10.5680/lhuii000060