Ro J Pediatr. 2024;73(3)
DOI: 10.37897/RJP.2024.3.7

Testing for nephrological diseases in pediatrics – the role of *point-of-care* devices and the medical analysis laboratory in the current context

Monica Dugaesescu[1,2], Diana Stan[1], Lorena-Andreea Bocancia-Mateescu[1], Andreea-Cristina Mirica[1], Sorin Mocanu[1], Dana Stan[1]

[1]Research and Development, DDS Diagnostic, Bucharest, Romania
[2]Clinical Laboratory, Fundeni Clinical Institute, Bucharest, Romania

ABSTRACT

Background and objectives. Nephrological diseases in children are common, representing an important burden on patients and healthcare. The purpose of this study is to evaluate the transition of the most recent advances in the in vitro diagnostics (IVD) field, including point-of-care (POC) testing methods, to the clinical practice in pediatrics.

Materials and methods. Testing indications for pediatric nephrological diseases were identified in the available clinical guidelines and, for comparison, the developments in the IVD field were reviewed based on scientific literature about testing methods, performance evaluation, and POC testing implementation.

Results. Testing in the context of nephrological diseases is widely addressed in the available clinical guidelines. While performant POC tests have been developed, the recommendations for testing do not address this progress, nor their integration with traditional laboratory tests. For example, urine dipstick testing has a central role in the management of urinary tract infections of children and it is a basis for clinical decisions, the same method being available for both POC and laboratory tests.

Conclusions. Specific testing recommendations for nephrological conditions must be elaborated, based on the availability of the methods and their performances. Implementing POC testing is a challenge, but it can provide benefits for both the patient and the healthcare systems, in addition to the standard laboratory testing.

Keywords: point-of-care; pediatric kidney diseases, clinical guidelines, laboratory investigations

Abbreviations
IVD – in vitro diagnostics
POC – point-of-care

INTRODUCTION

Pediatric nephrological diseases, especially chronic conditions, are a challenge for patients, their families, and healthcare systems, having high morbidity and mortality. These diseases associate an enormous variety of biological modifications that need constant laboratory evaluation [1,2]. The main nephrological conditions affecting children include chronic kidney disease, glomerulonephritis, nephrotic syndrome, and urinary tract infections [1,3-5].

Pediatric chronic kidney disease is defined by renal damage or a decrease of the glomerular filtration rate that persists for at least 3 months, having a high prevalence and being associated with unfavorable outcomes. Conventional biomarkers used to evaluate chronic kidney disease in children include proteinuria and serum creatinine. The efficacy of

Corresponding author:
Monica Dugaesescu
E-mail: assistant.research2@ddsdiagnostic.com

Article History:
Received: 28 June 2024
Accepted: 25 September 2024

available therapies to decrease the progression of the disease is limited [6].

In children, glomerulonephritis is defined as a group of conditions that associate glomerular inflammation and lesions, with classical clinical presentation including hematuria, oedema, and hypertension, which appear due to immunological mechanism, host-related characteristics, and environmental factors, for example, infections [3].

Nephrotic syndrome in children is etiologically heterogenous. It is characterized by proteinuria (above 40 mg/m^2/hour or a urine protein-creatinine ratio of at least 200 mg/mL), with subsequent hypalbuminemia, oedema, hypovolemia, infections, and hypercoagulation, and, in children, it can be classified as either secondary, congenital and infantile and idiopathic [4,7]. The overall prognosis for nephrotic syndrome in children is favorable [7].

Among the most frequently diagnosed infections in children, urinary tract infections are often caused by *Escherichia coli*, but these conditions can be determined by many other pathogens, such as *Proteus spp.* or *Klebsiella spp.* Clinical manifestations depend on the age and the urinary tract segment involved. In the first 2 years of life, fever without an apparent infection site is the most common clinical presentation for urinary tract infections. After this age, more specific symptoms can be reported by children with urinary tract infections [5].

Regardless of etiology and clinical presentations, pediatric nephrological diseases require a complex laboratory evaluation [1,2]. However, laboratory investigations in children are challenging, starting from sample collection and obtaining a sufficient sample volume [8]. Point-of-care testing devices that can perform analysis of biological samples, with the advantage of being adapted to be used near-patient or for self-testing, at home. The value of implementing point-of-care testing has been well established in specific contexts, such as emergency departments [9]. In pediatrics, point-of-care testing can be of high interest due to the rapid assessment of biological parameters and the low sample volume required for testing [8].

The purpose of this study is to identify rapid testing methods with applicability in the pediatric nephrological pathology and their level of implementation in patient care management.

MATERIALS AND METHODS

The guidelines from relevant institutions for the field of nephrology for pediatric kidney diseases, including International Pediatric Nephrology Association, Kidney Disease: Improving Global Outcomes, National Institute for Health and Care Excellence, were analyzed and the testing indications for chronic kidney disease, glomerulonephritis, nephrotic syndrome and urinary infections in children were extracted. These data were compared to the latest scientific literature data about testing methods and *point-of-care* devices with application in this field. This data was obtained from a PubMed (https://pubmed.ncbi.nlm.nih.gov/) and ScienceDirect (https://www.sciencedirect.com/) search, using as keywords the words defining the laboratory investigations identified in the clinical guidelines included in the study and the term ”point-of-care”. The search filters for literature published within the past five years (2019-2024) and availability of free full text were applied.

RESULTS

Testing in the context of pediatric nephrological conditions has been widely addressed in specific clinical guidelines. The pediatric kidney diseases frequently associate complex biological alterations, that extend to more than the condition-specific diagnosis and renal function parameters and biomarkers [10-14].

The purpose of testing in the context of nephrological kidney diseases is diverse. It can include: the diagnosis, the kidney function evaluation, the detection of disease complications, the diagnosis of associated conditions, disease monitoring, therapeutic drug monitoring, for example, immunosuppressants' levels measurements in the context of glomerulopathies [10-14].

Categories of laboratory evaluations include serum biochemistry, urine analysis, sediment and culture, autoantibodies, complete blood count and erythrocyte indices, iron status evaluation, serum albumin and total protein, investigation of electrolytes and blood gases, inflammatory and immunological markers, vitamin D levels, lipid profile, markers of liver function, screening for infections [10-14].

Below, the laboratory investigations, according to the clinical guidelines' recommendations, are presented for each of the main nephrological conditions affecting children.

Chronic kidney disease in children

a. Kidney function assessment

In children with chronic kidney disease, serum creatinine should be measured with a specific method and it should be used to estimate the glomerular filtration rate. For proteinuria evaluation, reagent strips use is not recommended in children. However, if proteinuria is accidentally detected using reagent strips, testing must be performed to estimate the glomerular filtration rate and the albumin-creatinine ratio must be determined. For hematuria

testing, reagent strips use is recommended, without the need to confirm through microscopy [10].

b. Anemia evaluation

In children with chronic kidney disease, the development of anemia must be evaluated. This condition can be determined by the chronic kidney disease itself or by other causes. For this purpose, hemoglobin levels must be determined. Iron status evaluations should not be based solely on transferrin saturation and serum ferritin. The percentage of hypochromic red blood cells reporting is recommended, or reticulocyte hemoglobin content measurement. Routine erythropoietin level measurement is not recommended. When iron treatment is provided, serum ferritin levels must be determined and the subsequent iron therapy management must be guided by hemoglobin levels, percentage of hypochromic red blood cells, reticulocyte hemoglobin content or equivalent laboratory evaluations, transferrin saturation, and serum ferritin levels [10].

c. Other laboratory investigations

Serum phosphate measurements are relevant for the management of hyperphosphatemia in children with advanced chronic kidney disease. When the glomerular filtration rate is not severely affected, routine measurements for calcium, phosphate, parathyroid hormone and vitamin D is not necessary. However, in advanced stages, these laboratory investigations are needed [10].

Glomerulonephritis

In children with glomerulopathies, the assessment of kidney function through 24-hour urine collection for total protein excretion is not recommended and it should be replaced by determination of the first morning protein-creatinine ratio. To estimate the glomerular filtration rate, the modified Schwartz equation is preferred in children, but the Full Age Spectrum (FAS) equation can also be used. Routine evaluation of hematuria using urine sediment is recommended in all categories of glomerular diseases [11].

Pediatric nephrotic syndrome

a. Diagnosis of steroid-sensitive nephrotic syndrome

In children with steroid-sensitive nephrotic syndrome, one of the main laboratory diagnosis criteria is the nephrotic range of proteinuria. Proteinuria can be evaluated in this context by using urine dipstick tests in a spot urine, measuring urinary protein-creatinine ratio or determination of proteinuria in 24-h urine collection. Diagnosis blood tests should include complete blood count, creatinine, estimated glomerular filtration rate, urea, electrolytes, and albumin. In children with hematuria, further determinations are required, which can include complement C3, C4, antinuclear, anti-streptococcal, and antineutrophil cytoplasmic antibodies [12].

b. Monitoring of steroid-sensitive nephrotic syndrome

At-home proteinuria monitoring using dipstick testing, preferably in the first-morning urine void, is recommended to evaluate the therapy response or potential disease relapse. When dipstick testing for proteinuria is not available, the alternatives are heat coagulation and sulfosalicylic acid test. The frequency of at-home proteinuria testing depends on the disease phase. Other laboratory evaluations for monitoring in steroid-sensitive nephrotic syndrome include protein-creatinine ratio, complete blood count, creatinine, estimated glomerular filtration rate, urea, electrolytes, albumin, vitamin D levels (24-OH-vitamin D), therapy levels monitoring (mycophenolate acid, cyclosporin A, tacrolimus). Depending on the adverse effects spectrum of the administered medication, there are several investigations needed to be used for monitoring, including complete blood count, liver function tests, antineutrophil cytoplasmic antibodies titres, creatinine, estimated glomerular filtration rate, potassium levels, lipid levels, uric acid, magnesium levels, fasting glucose levels, CD19 counts and percentage, immunoglobulin IgG [12].

c. Initial evaluation and monitoring of steroid-resistant nephrotic syndrome

In children with steroid-resistant nephrotic syndrome, the following laboratory investigations are recommended for initial work up and monitoring: protein-creatinine ratio (spot urine or 24 h urine), hematuria evaluation, calcium/creatinine ration and low molecular weight proteinuria from spot urine samples, complete blood count, creatinine, BUN or urea, electrolytes, serum albumin, total protein, blood gas analysis, C-reactive protein, estimated glomerular filtration rate, alkaline phosphatase, parathormone, 25-OH vitamin D, lipid profile, coagulation tests, thyroid function tests, immunoglobulin G, glucose and fasting glucose, glycated Hemoglobin, C3 complement, antinuclear antibodies, anti-double-stranded DNA antibodies, extractable nuclear antigen, antineutrophil cytoplasmic antibodies, markers of infections (hepatitis B and C viruses, human immunodeficiency virus, syphilis), post-vaccination antibodies titres, therapeutic drug monitoring (cyclosporin A, mycophenolic acid, tacrolimus), creatine kinase measurement if statins are administered [13].

Urinary tract infections

In the context of suspected urinary tract infections in children, dipstick testing can be used to

evaluate the leukocyte esterase, nitrate, blood, and protein, the leukocyte esterase being the most sensitive single test in this context. The specificity of nitrite evaluation through dipstick testing is higher, but it is less sensitive. However, the blood and protein evaluation with urine strips is less relevant for urinary tract infections diagnosis, due to a lower sensitivity and specificity [15].

In babies and children between 3 months and 3 years with suspected urinary tract infections, dipstick testing can be performed. The subsequent case management is dependent on the leukocyte esterase and nitrite testing results. If one or both are positive, a urine culture is performed and antibiotic treatment is initiated. If the child is at least 3 years old, if both leukocyte esterase and nitrites are positive, the urinary tract infection diagnosis is considered positive, but if only one of these parameters is positive, further steps are required to confirm the diagnosis, such as urine culture and microscopy. Dipstick testing for nitrites and leucocyte esterase can safely be used instead of microscopy and culture, having a similar diagnostic value. Urine culture and microscopy are not routinely used and they are recommended in specific situations. To differentiate upper urinary tract infections from the lower infections, the use of C-reactive protein levels alone is not recommended [14].

Point-of-care technologies for pediatric nephrological conditions

A summary of the relevant laboratory explorations for pediatric nephrological diseases, according to clinical guidelines presented above and the corresponding *point-of-care* devices described in scientific literature is presented below. (Table 1)

DISCUSSION

Urine strip tests are a model of successful implementation on a large scale of a rapid testing method, based on the indications described in the clinical

TABLE 1. Laboratory investigations relevant to pediatric nephrological diseases and examples of technologies used for *point-of-care* testing devices

Laboratory investigation	*Point-of-care* technologies of detection	Biological sample	References
Creatinine	Sensor-based technologies	Blood	[16,17]
Proteinuria	Dipstick, biosensors, fluorescent detection, colorimetric – 3D paper based microfluidic devices	Urine	[18,19]
Hematuria	Dipstick, sensor-based technologies	Urine	[18,20]
Leukocyte esterase	Dipstick, sensor-based technologies	Urine	[18,20]
Nitrite	Dipstick, sensor-based technologies	Urine	[18,20]
Urinary creatinine	Colorimetric methods	Urine	[19]
Urinary albumin	Immunoturbidimetry, fluorescent detection, lateral flow assays	Urine	[19,21]
Electrolytes	Sensor-based blood analyzers	Blood	[22,23]
Urea	Sensor-based blood analyzers	Blood	[24]
Serum albumin	Sensor-based technologies, colorimetric	Blood	[25,26]
Uric acid	Sensor-based methods	Blood	[27,28]
Hemoglobin	Colorimetric, conductometric, sensor, and pulse co-oximetry-based methods	Blood	[29]
Ferritin	Lateral flow assays, sensor-based methods	Blood	[30,31]
Parathyroid hormone	Immunoassays, sensor-based methods	Blood	[32,33]
Vitamin D	Lateral flow immunoassays	Blood	[34]
Lipid levels	Reflectance photometry or biosensor-based technologies	Blood	[35,36]
Liver function tests	Colorimetric, paper-based microfluidic analytical devices	Blood	[26,37]
Blood glucose	Colorimetric, sensors	Blood	[26,35]
Glycated hemoglobin	Sensor-based technologies, automated boronate affinity assay	Blood	[38,39]
Total protein	Colorimetric	Blood	[26]
Anti-nuclear antibodies	Vertical flow assay	Blood	[40]
Anti-double stranded DNA antibodies	Vertical flow assay	Blood	[40]
C-reactive protein	Immunoturbidimetry, lateral flow assays	Blood	[41]
Complete blood count	Impedance, microfluidics	Blood	[42]
Hemostasis tests	Aggregometry, optical detection, viscoelastic testing	Blood	[43]
Blood gas	Sensor-based blood analyzers	Blood	[23]
HIV, viral hepatitis, syphilis	Lateral flow tests, point-of-care nucleic acid tests	Blood	[44-46]
Immunosuppressive drugs	Immunological, fluorescence-based and sensor-based technology	Blood	[47]

guidelines for pediatric nephrological conditions. The performance of these tests varies depending on the analyte of interest. There are specific indications for the use of urine strip tests depending on the analyte and the nephrological conditions. Recommendations for at-home use of these tests are also mentioned in clinical guidelines, with the purpose of disease monitoring [10-14]. However, these indications can be further elaborated to obtain maximum benefits for the patient.

Dipsticks contain reagent pads, which modify their color in the presence of the analyte of interest. The testing result can be visually interpreted, or simple equipment can be used to read the results, providing semi-quantitative or quantitative measurements. The most common application of this technology is urine analysis strips [9,19].

Except for the urine strip tests, other point-of-care testing devices were not broadly implemented in the current clinical practice in the context of pediatric nephrological diseases, and there are no additional recommendations for rapid testing methods in the specific clinical guidelines. However, there are various markers related to nephrological conditions that can be tested and monitored in pediatric patients, in the comfort of their own homes, additionally to the classical urine strip testing [10-14].

Lateral flow tests are among the most broadly used *point-of-care* technologies. These tests are based on the interaction between a capture molecule, which can be an antibody or an aptamer, often immobilized on a cellulose membrane, and the analyte of interest, combined with a detection reagent [48]. Based on the reagents involved in detection, the testing results using lateral flow assays can be read through colorimetric, fluorescent, magnetic photothermal, electrochemical, and dual-signal methods. While colorimetric detection can be interpreted either visually or with a specific reader, the other methods require equipment for result interpretation [49].

Vertical flow assays have also been developed to overcome some of the disadvantages of lateral flow tests. In addition to the rapidity of the testing procedure and result availability, vertical flow assays are more suitable for multiplex detection [40,50].

Various **sensor-based devices** have been developed for point-of-care testing. While the sensor-based technologies for *point-of-care* testing are diverse, biosensors are a topic of high interest, involving analyte detection through a specific bioreceptor coupled with a transducer that can convert the analyte-bioreceptor reaction into a measurable signal [51]. However, in the context of nephrological conditions *point-of-care* testing, multiple sensor-based technologies have value. For example, creatinine can be detected through electrochemical sensors, most frequently using enzyme-coupled detection. Non-enzymatic creatinine sensors include methods based on molecularly imprinted polymers or nanomaterials [17].

Microfluidics principles possess a series of advantages for *point-of-care* testing applications and it might be used to merge data from multi-omics levels, revolutionizing the field of diagnosis [52]. **Microfluidic paper-based analytical devices** can perform both simple and complex analysis, requiring small amounts of samples. The manufacturing costs are low, the devices are portable and the technology is flexible [53].

En emerging technology in the field of rapid testing are ***point-of-care* nucleic acid technologies.** The classical methods of analyzing DNA and RNA sequences have been adapted for rapid diagnosis applications, without limiting the sensitivity and specificity of detection, making these *point-of-care* devices an excellent option for infections screening [54], a topic which can also present interest for the investigations required in the context of specific pediatric nephrological diseases [11-13].

While multiple *point-of-care* testing devices have been developed based on the above-described technologies and not only, and some of them are commercially available, the clinical guidelines for pediatric nephrological conditions do not include these tools in the testing indications [10-14]. The impact of implementing these *point-of-care* technologies in the management of pediatric nephrological conditions must be evaluated and testing recommendations must be elaborated, to enable maximum benefits for patients [55].

The field of *point-of-care* testing can be further developed, because various rapid tests have a detection based on immunological reactions, by specific interaction between antibodies and antigens. The development of *point-of-care* devices for the detection of various antibodies relevant to glomerulopathies might become a field of interest. For example, rapid tests for antibodies associated with membranous nephropathy, such as anti-PLA2R or anti-THSD7A, can have a clinical utility, but the study of these autoimmunity markers is relatively novel [56].

There are multiple challenges for the development of adequate *point-of-care* testing devices in pediatric nephrological diseases. Various cofounders present in the sample matrix can interfere with creatinine measurements, which is a basic laboratory evaluation in kidney diseases. Furthermore, patients with chronic kidney diseases have fluid volume fluctuations. Finger-prick sample testing results can be influenced by the interference of the interstitial fluid with the sample, but also by the hemolysis occurring in the blood collected by this method, which can be a major issue for potassium

measurement. Parameters that are altered in chronic kidney diseases, such as potassium, calcium, albumin, urea, and uric acid, can interfere with the testing results using *point-of-care* methods for glucose and creatinine measurements [9].

CONCLUSION

Pediatric nephrological diseases require the integration of all available testing methods, including both *point-of-care* devices and classical laboratory testing, to ensure prompt and efficient case management, including the diagnosis, therapy, and monitoring of each patient.

Point-of-care testing devices can revolutionize patient care, with implications for rapid diagnosis of acute clinical presentations, at-home monitoring, and complications screening, in the context of pediatric nephrological conditions. To date, there is not enough evidence collected to support *point-of-care* testing devices inclusion in clinical guidelines. Various *point-of-care* technologies have been developed, some of them are commercially available at the moment, while others are still in the research stages.

A thorough evaluation of the clinical impact of using these *point-of-care* devices in the field of pediatric nephrological conditions must be performed, starting from those technologies which are already commercially available, to establish clear and adequate indications for rapid testing of each parameter of interest, and bring latest advancements closer to medical practice for enhanced patient benefit.

Conflict of interest: none declared

Financial support: none declared

Author's contributions

Conceptualization, M.D., Di.S.; methodology, M.D., Di.S.; resources, M.D., A.C.M.; data curation, M.D.; writing—original draft preparation, M.D., A.C.M.; writing—review and editing, L.A.B.M., S.M.; visualization, M.D., Da.S; supervision, Da.S. All authors have read and agreed to the published version of the manuscript.

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