Med. Surg. J. – Rev. Med. Chir. Soc. Med. Nat., Iaşi 2024, 128(3): 559-568 doi: 10.22551/MSJ.2024.03.14

URINARY NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN IN CHILDREN WITH RECURRENT URINARY TRACT INFECTIONS IN NORTH-EASTERN ROMANIA

C. P. Dușa[1*], Iuliana Magdalena Stârcea[1], Ionela Lăcrămioara Șerban[2]
"Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania
Faculty of Medicine
1. Department of Mother and Child Medicine
2. Department of Morpho-Functional Sciences (II)
[*]Corresponding author. E-mail: christian.dusa@gmail.com

URINARY NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN IN CHILDREN WITH RECURRENT URINARY TRACT INFECTIONS IN NORTH-EASTERN ROMANIA (Abstract): Urinary Neutrophil Gelatinase-Associated Lipocalin (uNGAL) is currently proposed as an improved diagnostic tool for urinary tract infection (UTI). Both normal and pathological standardized values are lacking. There is some evidence that children with recurrent UTI may have lower uNGAL values, thus promoting it as a prognostic biomarker. **Aim**: To compare baseline uNGAL values in patients with recurrent UTI to controls without history of UTI. **Materials and methods**: Patients and/or their caretakers signed an informed consent prior to participation. Recurrent UTI (rUTI) was defined as history of at least 2 UTI episodes in the last 6 months or 3 in the last year, confirmed by positive urine culture. The correspondent control group had no history of UTI. Obtained urine samples were frozen and kept until uNGAL assay measurement was performed as per the manufacturer's recommendations. Data analysis was performed using IBM® SPSS Statistics (version 29.0.20 (20)). **Results**: We found a significant difference in uNGAL values between the rUTI group and the control group (p=0.01), AUC = 0.815, cutoff = 5.27 ng/mL (TPR =1, FPR =0.3). uNGAL values in the rUTI group were not correlated with age (Pearson r = 0.243, p =0.423). uNGAL values were higher in the rUTI group. **Conclusions**: Patients with history rUTI have higher uNGAL values than those without history of UTI. uNGAL does not seem to be a protective factor and low values do not seem to be a predictive diagnostic tool for pediatric UTI. Further studies should take into consideration the patient's history of UTI regarding cut-off values. **Keywords**: NGAL, PEDIATRIC, RECURRENT URINARY TRACT INFECTION.

Urinary tract infection (UTI) in infants and young children is an important bacterial infection that can lead to permanent renal function loss. Current diagnosis options have low sensitivity and specificity and definitive diagnosis may postpone antibiotic administration up to 48 hours. Neutrophil gelatinase-associated lipocalin is a relatively new renal biomarker that has shown promise in early diagnosis of UTI and potential renal scarring. Baseline values of uNGAL have been proposed (1, 2), but a recent meta-analysis (2) has shown that underlying patient characteristics may influence determining cut-off values. Our study aims to compare the values of uN-

GAL in a population with history of rUTI, with a control group of patients without history of UTI from pediatric patients in Northeastern Romania, in order to check if baseline uNGAL values remain the same after having suffered UTI and to test if uNGAL can be considered a prognostic factor for UTI.

MATERIALS AND METHODS

This study was approved by the "Sf. Maria" Emergency Clinical Hospital for Children Ethics Committee (no. 5075/17 February 2021) and the "Grigore T. Popa" University of Medicine and Pharmacy Iași's Ethics Committee (no. 8753/28 May 2020) and informed consent was obtained prior to participation. Cases were patients with ages between 3 months and 18 years with a history of recurrent UTI (rUTI), from the Department of Pediatric Nephrology at "Sf. Maria" Emergency Clinical Hospital for Children from March 2021 to March 2022. RUTI was defined by two or more culture proven UTIs with at least 100,000 CFU/mL of a single urinary pathogen in the last 6 months, respectively three or more in the last year. Control patients were a convenience sample enrolled from the General Pediatrics Department at "Sf. Maria" Emergency Clinical Hospital for Children. Patients who provided urine samples for routine clinical purposes were approached for inclusion in this study as controls. None of the control patients required fluid replacement, resuscitation or hospital admission, or had any clinical parameters to suggest dehydration, such as tachycardia or decreased urine output. Controls were excluded if they had a history of a UTI, evidence of a UTI at the time of enrollment (proven UTIs with at least 100,000 CFU/mL of a single urinary pathogen), known or suspected renal dysfunction, or had any urologic history.

The following parameters were studied: patient diagnosis at the moment of admission, number of UTI recurrences, urinalysis and presence of pyuria, urine culture, presence of malformation, age and sex of the patient and presence of antibiotic prophylaxis in relation to the values of urinary NGAL.

A minimum of 5 mL of urine were collected from cases and controls. Samples were centrifuged, aliquot and stored at -80 degrees Celsius within 12 hours of collection. UNGAL measurements were performed as per manufacturer's recommendations in triplicate using *Human Neutrophil Gelatinase-Associated Lipocalin / NGAL (LCN2) ELISA Kit* from producer Abbexa®. Patient data was collected from the electronic medical record. Data was introduced in IBM® SPSS Statistics (version 29.0.20 (20)). Grouping variable statistics was analyzed. Non-parametric distributed variables, i.e. uNGAL in the risk and healthy patients were compared using the Mann-Whitney-U test. The area under the receiver operator characteristic (ROC) curve for identifying rUTI involvement was calculated using logistic regression models for uNGAL. The optimal uNGAL cut-off point for the identifying rUTI involvement, as well as the associated sensitivity and specificity were calculated. A p value of < 0.05 was considered statistically significant. The datasets generated during the current study are available from the corresponding author on reasonable request.

RESULTS

A total of 13 patients (10 female, 3 male) aged between 3 months and 18 years with recurrent UTI were introduced in the study, with 10 case controls with appropriate age/sex distribution.

Of the 13 patients, 2 had no demonstrated underlying malformation, while 11 presented different types of congenital anomalies of the kidney and urinary tract CAKUT (6 presented with different degrees of VUR (1-5) including one secondary to posterior urethral valve, 2 presented right kidney hypoplasia, 2 presented kidney hypoplasia, 1 neurogenic bladders). 7 of the 13 patients had received antibiotics as prophylaxis for UTI prior to admission.

All patients had history of at least 2 infections previous to the current admission. Of these 5 had a recurrence of 2 infections, 1 presented at least 3 infections, 2 had 4 recurrences and 2 had at least 6 infections by the time of admission. 3 of these patients had presented with more than 6 infections.

Pyuria (defined as above 10 leucocytes/ high-power field) was not found in any patients. Urine culture was negative (<1000 CFU/mL) in all patients. Creatinine values varied from 0.35 to 0.86 mg/dL. Creatinine clearance varied from 82.67 to 172.85 mL/min/1.73m^2 with a median of 111.27 mg/dL.

Of the 13 patients with rUTI, only 5 had undergone DMSA scan to confirm scarring. 3 of 5 presented 1 kidney scar, the rest presented 3 or more kidney scars.

uNGAL values varied from 5.78 ng/mL to 31.93 ng/mL in the rUTI cases, with a mean value of 16.23 ng/mL and a median of 13.74 ng/mL. The control group uNGAL values were between 0.17 ng/mL and 19.38 ng/mL, with a mean of 6.49 ng/mL and median of 3.39 ng/mL. Further description of uNGAL (ng/mL) value distribution can be seen in first table.

TABLE I.

uNGAL (ng/mL) distribution descriptive values

		uNGAL_rITU	uNGAL_control
Number of patients	Statistic	13	10
Range	Statistic	26.15	19.21
Minimum	Statistic	5.78	.17
Maximum	Statistic	31.93	19.38
Mean	Statistic	16.2377	6.4920
	Std. Error	2.62642	2.15737
Std. Deviation	Statistic	9.46970	6.82220
Variance	Statistic	89.675	46.542
Skewness	Statistic	.857	1.053
	Std. Error	.616	.687
Kurtosis	Statistic	-.689	-.454
	Std. Error	1.191	1.334

Mann-Whitney U and Wilcoxon W test were applied to test whether rUTI and control groups have identical (H0) or different uNGAL distributions (H1). uNGAL values were significantly higher in the rUTI group than in the case control (p =0.011) (Asymp. Sig. (2-tailed) = 0.011) (tab. II). uNGAL value distribution in the rUTI risk group and case control group are listed in first figure.

TABLE II.
Statistical test

	uNGAL
Mann-Whitney U	24.000
Wilcoxon W	79.000
Z	-2.544
Asymp. Sig. (2-tailed)	.011
Exact Sig. (2*(1-tailed Sig.)) (not corrected for ties)	.010

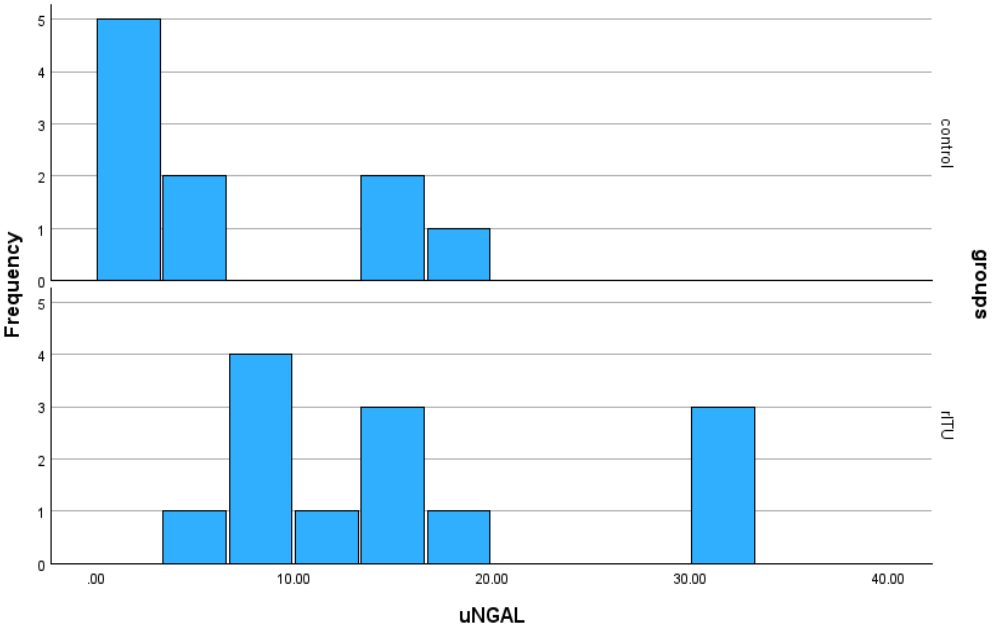

Fig. 1. uNGAL (ng/mL) value distribution in the rUTI risk group and case control group

ROC-AUC curve for NGAL values suggested the best cutoff points of 5.27 ng/mL FPR = 0.3, TPR = 1 with AUC = 0.815 (fig. 2).

Seven patients had various degrees of VUR (grade 1-5). For these patients, no significant correlation was found between uNGAL values and VUR degree (Pearson Correlation -0.173, p=0.711).

No significant correlation was found between uNGAL values and age expressed in months (Pearson Correlation 0.243, p=0.423), height expressed in cm (Pearson Correlation 0.098, p=0.750) or weight expressed in kg (Pearson Correlation 0.202, p=0.508).

uNGAL values did not significantly correlate with creatinine (Pearson Correlation 0.088, p=0.775) or creatinine clearance (Pearson Correlation -0.171, p=0.577). Creatinine clearance was calculated by the Schwartz formula ((k*height(cm))/serum creatinine (mg/dL).

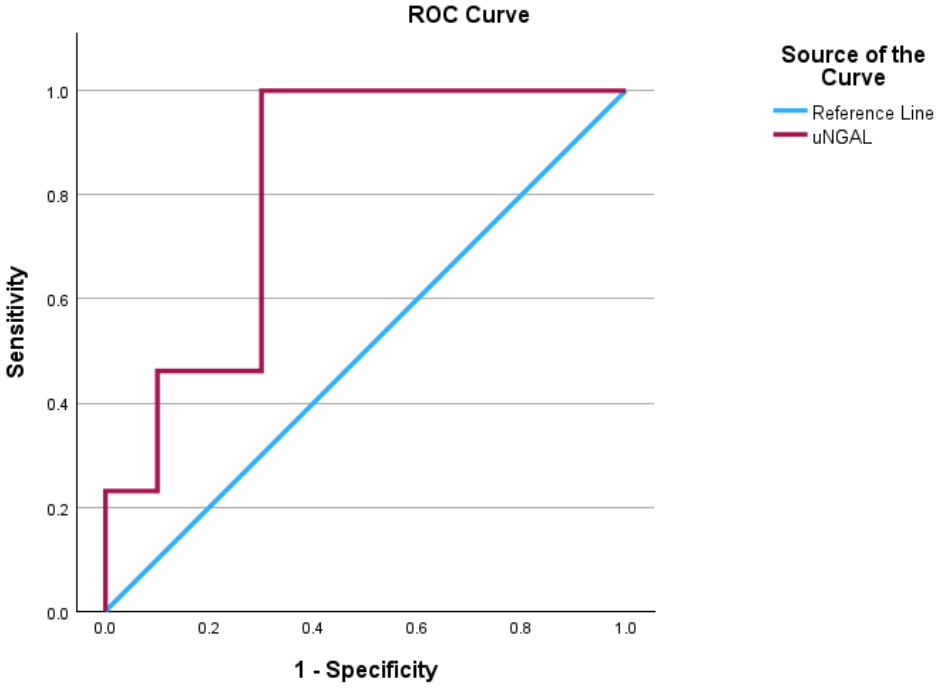

Fig. 2. ROC curve for uNGAL. AUC 0.815. p=0.002, (95% CI 0.62-1.01), cutoff uNGAL = 5.27 ng/mL, TPR = 1, FPR = 0.3.

DISCUSSION

Urinary tract infection (UTI) in infants and young children is an important bacterial infection with an incidence of 2% during the first 2 years of life. The prevalence of UTI is higher (5-24.2%) among children aged < 2 years presenting with fever (1-3). Early detection and proper management of UTIs is important since UTIs involving the kidney may cause permanent renal scarring and be a risk factor for future development of renal insufficiency (4). Other later-life risks related to renal scarring include hypertension, preeclampsia during pregnancy and proteinuria (5). Recurrent UTIs (rUTI) occur in approximately 12% of patients following an initial UTI (6). Acute pyelonephritis, especially in recurrent episodes may lead to renal parenchymal involvement and scarring with high prevalence rate (15%-60%) among children (7). Furthermore, it has been reported that while the incidence of primary VUR is 1% in the normal population it reaches 30–50 % in recurrent UTI and that 15–60 % of these affected children may have permanent renal scarring after the UTI (8).

Urinalysis is a convenient and readily available diagnostic option. However positive leucocyte esterase (LE) or nitrites have variable and often suboptimal sensitivities (78–88%) and specificities (72–97%) across different studies (9-11). These results are influenced by the different methods of urine collection and laboratory pro-

cedures (12). Inaccuracy of the UA leaves the physician to balance excess antibiotic treatment with potential toxicity and increase of antibiotic resistance risk against lack of action and potential kidney scarring. Therefore, it is difficult to provide a quick diagnostic of UTI in children and thus a reliable marker for the early diagnosis is warranted.

Tc-99m dimercaptosuccinic acid (DMSA) renal scintigraphy is considered the current gold standard in imaging renal parenchymal involvement during acute pyelonephritis (APN) and to detect late renal damage consequent to UTIs (13). Although DMSA scan is highly sensitive method in detecting renal inflammation and scaring, it is invasive to expose young children to radiation. Moreover, to confirm the diagnosis of renal scarring, DMSA must be repeated 4 to 6 months after the APN (13). Since consequences of renal scarring are serious, this aggressive method used to diagnose APN is justified. However, the need for a less invasive diagnostic tool is evident.

Numerous studies have evaluated the usefulness of inflammatory markers for predicting APN, and demonstrated that commonly used laboratory parameters such as white blood count (WBC), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) have low sensitivity and specificity for accurately predicting acute renal parenchymal involvement. At present, these tests are not recommended for routine use to differentiate APN from lower UTI in children (14) .

New biomarkers have emerged with promising roles in early diagnosis and prognosis of UTI. Neutrophil gelatinase-associated lipocalin (NGAL), a member of the lipocalin family, is an excellent biomarker for predicting and monitoring acute kidney injury (AKI) of diverse etiologies. It is a promising marker for detection of subclinical renal damage due to vesicoureteral reflux (VUR), renal scarring, and obstructive uropathy (15).

NGAL is a member of the lipocalin family that plays an important role in the innate immune response to the bacterial infection. NGAL a protein expressed in neutrophils and other tissues, including the collecting duct of the kidney and released from activated neutrophils, to prevent bacterial iron uptake and growth. It has been linked with acute kidney injury, but urinary NGAL (uNGAL) is significantly elevated with gram-negative UTIs in both adults and pediatric studies (12, 16-18). Different studies found urine NGAL values were increased in both, upper and lower UTI. Urinary NGAL concentrations cut-off values have not yet been established. However, there is indication that uNGAL may decline with age in infants (19). Multiple studies have had controversial results. No current recommendations are made regarding the use of urinary NGAL in pediatric populations (20-25).

To the best of our knowledge, this is the first analysis of uNGAL in pediatric patients with recurrent UTI in northeastern Romania.

Both urinary and blood NGAL (plasma or serum) have been researched for early prediction of UTI and APN in children. A strong argument in favor of measuring uNGAL over pNGAL or sNGAL is the non-invasiveness of the procedure. A meta-analysis by Forster and Devarajan 2017 suggests using pNGAL for pyelonephritis

and renal lesion diagnosis, while uNGAL seems to be superior in diagnosing genitourinary lesions, subclinical scarring and obstructions (26).

In 2009 Ichino *et al*, in an experimental rat UTI model, observed a marked increase of urine NGAL (uNGAL) at the early stage of infection and thereby suggested a potential utility of uNGAL as a marker of APN in humans (27). Several clinical studies have been conducted to assess the diagnostic value of uNGAL for detecting APN, but the results are not clear and, in some cases, pNGAL appears to have higher utility (20-25, 28).

Our cutoff points are close to Kim BH *et al* 2014. They suggested that for a cutoff value of 5.75 ng/mL uNGAL had no significant correlation with UTI (29). While we found that uNGAL is significantly higher in the risk group, there is no statistical correlation between NGAL values in these patients and the presence of UTI at the moment of sample collection. This indicates that uNGAL may be elevated in patients with malformations, but not necessarily related to infection. There are important differences between the two studies, regarding the number of patients and the inclusion criteria.

We also note that values of uNGAL in patients with recurrent UTIs was not significantly smaller than healthy controls, as suggested by Forster *et al* 2017 (30). The result difference could be attributed to the small sample size in both study groups. Median uNGAL values in healthy controls in the Forster group was also higher than both our groups (27.61 vs 13.74 and respectively 3.39 ng/mL). This would indicate that uNGAL does not seem to be a protective factor or predictive diagnostic tool for pediatric UTI.

In comparison with the study of Yilmaz *et al*, 2009, (31) who noted a cutoff value of 20ng/mL for diagnosis of UTI, we would like to note that the median value of non-infected, rITU group patients is smaller than their control group. This may be why in that study the authors noted that higher values would increase the chance of UTI four times. The source of confounding factors could also be related to the age difference (2 months to 12 years compared to 3 months to 17 years), inclusion criteria and sample size.

Yim HE *et al*, 2014 noted that for UTI diagnosis in patients with fever the best cutoff value for uNGAL was 23.95 ng/mL. However, that study only included patients at their first symptomatic febrile UTI. In our study, 3 patients, including one without malformation that had recurrent UTI, presented uNGAL values above 24 ng/mL with a negative urine culture. This suggests that the utility of uNGAL is highly variable and that further research is required to establish the specific situations and related best cutoff-points (32).

There were some limitations of our study. We only evaluated urinary NGAL concentration, but not serum/plasma NGAL concentration. This was a single-center study, with a small cohort of children. In the present study, due to lack of constant test availability, we could not perform DMSA scan for all patients to confirm or differentiate APN from lower UTI. Age can also be considered a limiting factor, in regards to acceptance of introduction into the study. However, in the study we found no correlation between age and uNGAL levels. Patients with early stages of chronic kidney disease have been

shown to present increased levels of uNGAL. No correlation was found between creatinine clearance and uNGAL values in our study, and we have to take into consideration clearance modifications were marginal (lowest value was 82.67 mL / min / 1.73 m^2, and corresponding to a serum creatinine value of 0.43 mg/dL). Finally, reliable reference intervals for uNGAL are lacking for both healthy children and UTI patients.

CONCLUSIONS

Urinary NGAL is significantly higher in patients with a history of recurrent UTI (rUTI), than controls with no history of UTI, with the best cutoff point of 5.27 ng/mL (FPR = 0.3, TPR = 1) with AUC = 0.815.

Further studies that propose uNGAL as a diagnostic method for UTI or non-invasive VUR monitoring should take into consideration the patient's history of UTI regarding cut-off values.

uNGAL does not seem to be a protective factor and low values do not seem to be a predictive diagnostic tool for pediatric UTI.

Further research is required to establish specific situations in which uNGAL may be useful and to identify the best cutoff values. Further research should also focus on differentiating lower UTI from acute pyelonephritis, benefits of evaluating plasma/serum or urinary NGAL values and extending the number of patients included for better statistical value.

CONFLICT OF INTEREST AND FUNDING

The authors declare that there is no conflict of interest, and they received no specific funding regarding this scientific research.

INSTITUTIONAL REVIEW BOARD STATEMENT

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of "Gr. T. Popa" University of Medicine and Pharmacy of Iasi no 8753/28 May 2020 and also by the Ethics Committee of "Sf. Maria" Emergency Clinical Hospital for Children no. 5075/17 February 2021.

INFORMED CONSENT STATEMENT

Informed consent was obtained from all subjects involved in the study.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are available from the corresponding author upon request.

REFERENCES

1. Valdimarsson S, Jodal U, Barregard L, and Hansson S. Urine neutrophil gelatinase-associated lipocalin and other biomarkers in infants with urinary tract infection and in febrile controls, *Pediatr Nephrol* 2017; 32(11): 2079-2087 / doi: 10.1007/s00467-017-3709-1.
2. Mattoo TK, Spencer JD. Biomarkers for urinary tract infection: present and future perspectives. *Pediatr Nephrol* 2024; 14 / doi: 10.1007/s00467-024-06321-9.

3. S. C. o. Q. I. a. M. Subcommittee on Urinary Tract Infection and RKB, Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics* 2011; 128(3): 595-610 / doi: 10.1542/peds.2011-1330.
4. Montini G, Tullus K, Hewitt I. Febrile urinary tract infections in children. *N Engl J Med* 2011; 21; 365(3): 239-250 / doi: 10.1056/NEJMra1007755.
5. Hollowell JG. Outcome of pregnancy in women with a history of vesico-ureteric reflux, *BJU Int* 2008; 102(7): 780-784 / doi: 10.1111/j.1464-410X.2008.07671.x.
6. Conway P.H, Cnaan A, Zaoutis T, Henry B.V, Grundmeier R.W, and Keren R. Recurrent urinary tract infections in children: risk factors and association with prophylactic antimicrobials. *JAMA* 2007; 298(2): 179-186 / doi: 10.1001/jama.298.2.179.
7. Saadeh SA, Mattoo TK. Managing urinary tract infections. *Pediatr Nephrol* 2011; 26(11): 1967-1976 / doi: 10.1007/s00467-011-1801-5.
8. Parmaksız G, Noyan A, Dursun H, İnce E, Anarat R, Nurcan C. Role of new biomarkers for predicting renal scarring in vesicoureteral reflux: NGAL, KIM-1, and L-FABP. *Pediatr Nephrol* 2016; 31: 97-103 / doi: 10.1007/s00467-015-3194-3.
9. Hoberman A, Chao HP, Keller DM, Hickey R, Davis HW, Ellis D. Prevalence of urinary tract infection in febrile infants. *J Pediatr* 1993; 123(1): 17-23 / doi: 10.1016/ s0022-3476 (05)81531-8.
10. Shaw KN, McGowan KL, Gorelick MH, Schwartz JS. Screening for urinary tract infection in infants in the emergency department: which test is best? *Pediatrics* 1998; 101(6): E1 / doi: 10.1542/peds.101.6.e1.
11. Chaudhari PP, Monuteaux MC, Bachur RG. Urine Concentration and Pyuria for Identifying UTI in Infants. *Pediatrics* 2016; 138(5): e20162370 / doi: 10.1542/peds.2016-2370.
12. 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; 140(6): e20171090 / doi: 10.1542/peds.2017-1090.
13. Peters CA, *et al.* Summary of the AUA Guideline on Management of Primary Vesicoureteral Reflux in Children. *J Urol* 2010; 184(3): 1134-1144 / doi: 10.1016/j.juro. 2010.05.065.
14. Shaikh N, Borrell JL, Evron J, Leeflang MM. Procalcitonin, C-reactive protein, and erythrocyte sedimentation rate for the diagnosis of acute pyelonephritis in children, *Cochrane Database Syst Rev* 2015; 20(1): CD009185 / doi: 10.1002/14651858.
15. Krzemien GJ, Pańczyk-Tomaszewska M, Turczyn A, Demkow U, Kotuła I, Szmigielska A. Serum neutrophil gelatinase-associated lipocalin for predicting anemia of inflammation in children with urinary tract infection, *Cent Eur J Immunol*, 2021; 46(4): 456-462 / doi: 10.5114/ceji.2021.112450.
16. McCaffrey J, Dhakal AK, Milford DV, Webb NJ, Lennon R. Recent developments in the detection and management of acute kidney injury, *Arch Dis Child* 2017; 102(1): 91-96 / doi: 10.1136/archdischild-2015-309381.
17. Devarajan P. Neutrophil gelatinase-associated lipocalin (NGAL): a new marker of kidney disease. *Scand J Clin Lab Invest Suppl* 2008; 241: 89-94 / doi: 10.1080/ 00365510802150158.
18. Singer E. *et al.* Neutrophil gelatinase-associated lipocalin: pathophysiology and clinical applications. *Acta Physiol (Oxf)* 2013; 207(4): 663-672 / doi: 10.1111/apha.12054.
19. 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; 61(1): 24-29 / doi: 10.3345/kjp.2018.61.1.24.

20. 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(2): 39-44 / doi: 10.12861/jrip.2015.09.
21. Bagshaw S.M. *et al.* Plasma and urine neutrophil gelatinase-associated lipocalin in septic versus non-septic acute kidney injury in critical illness. *Intensive Care Med* 2010; 36(3): 452-461 / doi: 10.1007/s00134-009-1724-9.
22. Yamanouchi S, *et al.* Reduced urinary excretion of neutrophil gelatinase-associated lipocalin as a risk factor for recurrence of febrile urinary tract infection in children, *Pediatr Nephrol* 2021; 36(6): 1473-1479 / doi: 10.1007/s00467-020-04863-2.
23. Yun B.A, Yang E.M, and Kim C.J. Plasma Neutrophil Gelatinase-Associated Lipocalin as a Predictor of Renal Parenchymal Involvement in Infants with Febrile Urinary Tract Infection: A Preliminary Study. *Ann Lab Med* 2018; 38(5): 425-430 / doi: 10.3343/ alm. 2018.38.5.425.
24. Ghasemi K, Esteghamati M, Borzoo S, Parvaneh E, Borzoo S. Predictive Accuracy of Urinary neutrophil gelatinase associated lipocalin (NGAL) for renal parenchymal involvement in Children with Acute Pyelonephritis, *Electron Physician* 2016; 8(2): 1911-1917 / doi: 10.19082/1911.
25. Nickavar A, Safaeian B, Valavi E, Moradpour F. Validity of Neutrophil Gelatinase Associated Lipocaline as a Biomarker for Diagnosis of Children with Acute Pyelonephritis, *Urol J* 2016; J3.2860-2863 / doi: 10;13(5):2860-2863.
26. Forster CS, Devarajan P. Neutrophil gelatinase-associated lipocalin: utility in urologic conditions. *Pediatr Nephrol* 2017; 32(3): 377-381 / doi: 10.1007/s00467-016-3540-0.
27. Ichino M, *et al.* Increased urinary neutrophil gelatinase associated lipocalin levels in a rat model of upper urinary tract infection. *J Urol* 2009; 181(5): 2326-2331 / doi: 10.1016 /j. juro. 2009. 01.010.
28. Yamanouchi S, *et al.* Urinary C-megalin for screening of renal scarring in children after febrile urinary tract infection. *Pediatr Res* 2018; 83(3): 662-668 / doi: 10.1038/pr.2017.276 Erratum in: *Pediatr Res* 2022; 92(2): 610-611.
29. Kim BH, *et al.* Evaluation of the optimal neutrophil gelatinase-associated lipocalin value as a screening biomarker for urinary tract infections in children. *Ann Lab Med* 2014; 34(5): 354-359 / doi: 10.3343/alm.2014.34.5.354.
30. Forster CS, *et al.* Urinary NGAL deficiency in recurrent urinary tract infections. *Pediatr Nephrol* 2017; 32(6): 1077-1080 / doi: 10.1007/s00467-017-3607-6.
31. Yilmaz A, *et al.* Early prediction of urinary tract infection with urinary neutrophil gelatinase associated lipocalin. *Pediatr Nephrol* 2009; 24(12): 2387-2392 / doi: 10.1007/ s00467-009-1279-6.
32. 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; 29(11): 2181-2189 / doi: 10.1007/s00467-014-2845-0.