# Urinary kidney injury molecule 1 levels reflect the severity of clinical conditions in newborns treated in intensive care unit

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**Objective: Kidney injury molecule-1 (KIM-1), a new diagnostic marker of acute kidney-injury (AKI) was tested in septic newborns to evaluate its usefulness for AKI detection.**

**Material and Methods: KIM-1 concentrations were assessed by ELISA during the three subsequent days in 27 septic (including 8 with AKI according to AKIN criteria) and 29 non-septic newborns. 95% CI of the mean KIM-1 was 0.04-2.2 ng/ml in controls.**

**Results: Median values of KIM-1 were significantly higher in septic than non-septic newborns [1.42 (0.56-2.04) vs 0.58 (0.16-1.24) ng/ml], [1.03 (0.54-2.32) vs 0.36 (0.12-1.08) ng/ml] and [0.98 (0.28-1.68) vs 0.32 (0.07-1.22) ng/ml] on the 1st, 2nd and 3rd day respectively, with statistical significance only in the first assessment. In septic AKI newborns KIM-1 was slightly, not-significantly higher than in non-AKI septic patients.**

**Conclusion: High variability of KIM-1 levels and its connection to inflammatory markers diminishes its usefulness in the diagnosis of mild and moderate AKI episodes in septic newborns.**

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**Key words:**
- KIM-1
- newborns
- acute kidney injury
- sepsis

## Cząsteczka uszkodzenia nerek 1 w moczu odzwierciedla ciężkość stanu klinicznego noworodków leczonych w oddziale intensywnej terapii

**Cel badania: Cząsteczka uszkodzenia nerek – 1 (Kidney injury molecule-1 (KIM-1)), nowy marker diagnostyczny ostrego uszkodzenia nerek (acute kidney-injury (AKI)), został zbadany w grupie noworodków z sepsą, w celu określenia jego użyteczności w rozpoznawaniu AKI.**

**Materiał i Metodyka: KIM-1 oznaczano metodą ELISA w moczu 27 noworodków z sepsą (w tym 8 z rozpoznanym AKI według kryteriów AKIN) i u 29 nie-septycznych noworodków, w kolejnych trzech dniach obserwacji. 95% CI średniej wartości KIM-1 w grupie kontrolnej wynosił 0,04-2,2 ng/ml.**

**Wyniki: Mediana wartości KIM-1 była znacząco wyższa w grupie noworodków septycznych w porównaniu z nie-septycznymi [1,42 (0,56-2,04) vs 0,58 (0,16-1,24) ng/ml], [1,03 (0,54-2,32) vs 0,36 (0,12-1,08) ng/ml] i [0,98 (0,28-1,68) vs 0,32 (0,07-1,22) ng/ml] odpowiednio w 1-szej, 2-giej i 3-ciej dobie, ale tylko w 1-szej dobie różnica wykazywała istotność statystyczną. U noworodków septycznych z AKI wartości KIM-1 były nieznacznie, nieznacząco statystycznie wyższe niż u noworodków septycznych bez AKI.**

**Wnioski: Duża zmienność stężeń KIM-1 i ich powiązanie ze stężeniami wskaźników stanu zapalnego obniża znaczenie KIM-1 w rozpoznawaniu łagodnego i umiarkowanego AKI w grupie noworodków z sepsą.**

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**Słowa kluczowe:**
- KIM-1
- noworodki
- ostre uszkodzenie nerek
- sepsa

### Introduction

One of the most dangerous illnesses in newborns and young infants is infection, and especially sepsis, responsible for almost one and a half million deaths each year, worldwide. In some, hardly predictable cases sepsis progresses to severe sepsis, septic shock and finally multiorgan dysfunction syndrome (MODS), including acute kidney injury (AKI). This last entity, especially its most severe stage – acute renal failure (ARF), is associated with high mortality rates both in adults and infants. The epidemiological data concerning burden of AKI morbidity in newborns are incomplete, and mostly rely on clinical observation in highly selected cohorts. It is also not clear why some patients progress quicker to ARF than others. Newborns develop clinical symptoms of AKI relatively late, but while already occurred, the symptoms may rapidly progress to the stage when treatment is ineffective. The diagnosis of AKI in neonates is currently based on the increased serum concentration of creatinine, analyzed in serial measurements. Despite that oliguria is traditionally the second main diag-

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nostic criterion of AKI [1], according to Koralkar [2] we should be using modified AKIN definition, excluding urine output in evaluation of AKI in this population, having in mind that neonates commonly develop non-oliguric AKI. On the other hand, serial creatinine measurements – even basic for AKI diagnosis – give delayed information regarding the accumulation of the endogenous marker as the effect of decreased glomerular filtration rate (GFR) [3]. Therefore, serum creatinine is considered as a functional kidney marker but not a direct surrogate of kidney tissue injury, that is regarded as the main limitation of creatinine assessment. In newborns, there is additional limitation in the interpretation of creatinine value, namely the gestational and chronological age of the newborn. The less mature newborn the higher value can be expected [4]. Additionally, during the first days after delivery, neonatal serum creatinine level depends on intrauterine placental transfer and reflect maternal creatinine concentration. Therefore some centres incorporated cystatin C into routine panel of renal markers, but opinions regarding its usefulness in early diagnosis of AKI are inconclusive [5-8].

As mentioned above, serum creatinine does not directly determine kidney injury, and it stands behind the search for a new biomarkers of AKI. Interleukin 18 (IL-18) and kidney injury molecule 1 (KIM-1) are potential biomarkers of kidney injury evaluated in urine samples. KIM-1 is postulated as a new sensitive marker of proximal tubule injury. KIM-1 became wildly recognized in experimental and preclinical studies, however its' clinical usefulness requires confirmation. Some authors suggest that tubular injury markers, KIM-1 among them, enable detection of subclinical kidney injury in asymptomatic paediatric patients with reduced left ventricular systolic function [9]. KIM-1 is also more specific biomarker used to ischemic renal injury in a group of adult patients after cardiosurgery with cardiopulmonary bypass [10]. The search for a marker distinguishing prerenal and intrinsic paediatric AKI did not support the role of KIM-1 [11], but that was an isolated report. More promising data is brought by Westhoff et al., who claimed the usefulness of KIM-1 in prediction of need for renal replacement therapy in paediatric patients with AKI [12]. Similarly, Chinese project on KIM-1 urinary concentration in adult AKI patients, revealed that the marker serum concentration is much higher in AKI group with deterioration in renal function than in those with transient AKI [13].

Evaluation of soluble form of KIM-1 in urine samples may also reduce the necessity of blood testing for kidney injury monitoring in neonates at high risk for AKI. Some of the previously analysed so called structural markers, including siderocalin (also known as NGAL, Neutrophil gelatinase-associated lipocalin) are substantially affected by inflammatory processes which limit their clinical application in septic patients. Searching for a biomarker less influenced by inflammation, we tested KIM-1 levels in urine of septic newborns with and without AKI.

The aim of this study was to assess the impact of inflammation on urine KIM-1 in septic newborns with and without acute kidney injury.

**Table I**
**Initial demographic and clinical characteristics of the study group (N=56).**
Wyjściowa charakterystyka demograficzna I kliniczna badanej grupy (N=56).

| | Non-septic [N=29] | Septic [N=27] | Statistical significance |
|---|---|---|---|
| **Gender (M/F)** | 15/14 | 20/7 | 0.08 |
| **Gestational age (wks)** | 39 (37-39) | 39 (36-39) | 0.88 |
| **Birth weight (g)** | 3270 (2920-3600) | 3240 (2760-3550) | 0.67 |
| **Apgar 5' (pts)** | 10 (9-10) | 10 (8-10) | 0.21 |
| **Day of life** | 6 (4-11) | 7 (2-13) | 0.92 |
| **NTISS 1st day (pts)** | 4 (2-6) | 16 (9-26) | <0.001 |
| **NTISS 2nd day (pts)** | 4 (2-6) | 16 (10-23) | <0.001 |
| **NTISS 3rd day (pts)** | 4 (2-6) | 16 (7-23) | <0.001 |
| **WBC 1st day (x $10^3$)** | 11.2 (9.5-12.4) | 12.6 (7.1-19.9) | 0.44 |
| **WBC 2nd day (x $10^3$)** | 11.0 (9.9-12.3) | 11.9 (8.9-14.4) | 0.44 |
| **WBC 3rd day (x $10^3$)** | 12.2 (10.1-13.6) | 11.9 (8.0-14.5) | 0.93 |
| **PLT 1st day (x $10^3$)** | 256 (185-326) | 222 (143-273) | 0.09 |
| **PLT 2nd day (x $10^3$)** | 282 (188-340) | 220 (143-283) | 0.02 |
| **PLT 3rd day (x $10^3$)** | 285 (193-341) | 224 (116-324) | 0.10 |
| **CRP 1st day (mg/dl)** | 0.5 (0.2-1.6) | 28.0 (1.4-91.0) | <0.001 |
| **CRP 2nd day (mg/dl)** | 0.5 (0.2-1.4) | 39.0 (6.6-71.0) | <0.001 |
| **CRP 3rd day (mg/dl)** | 0.6 (0.2-1.0) | 19.6 (6.3-52.0) | <0.001 |
| **PCT 1st day (ng/ml)** | 0.14 (0.10-0.18) | 9.0 (1.47-34.5) | <0.001 |
| **PCT 2nd day (ng/ml)** | 0.15 (0.07-0.16) | 9.2 (1.14-23.2) | <0.001 |
| **PCT 3rd day (ng/ml)** | 0.14 (0.09-0.33) | 3.28 (0.76-11.8) | <0.001 |
| **Creatinine 1st day (mg/dl)** | 0.79 (0.69-0.87) | 0.81 (0.55-1.06) | 0.68 |
| **Creatinine 2nd day (mg/dl)** | 0.68 (0.57-0.91) | 0.82 (0.52-1.04) | 0.51 |
| **Creatinine 3rd day (mg/dl)** | 0.61 (0.55-0.79) | 0.68 (0.44-0.94) | 0.59 |
| **KIM-1/ uCr x $10^5$ 1st day** | 21 (5-51) | 89 (60-402) | 0.002 |
| **KIM-1/ uCr x $10^5$ 2nd day** | 38 (10-98) | 80 (39-225) | 0.04 |
| **KIM-1/ uCr x $10^5$ 3rd day** | 38 (2-83) | 130 (61-223) | 0.006 |

*Median values, 1-3 quartiles and statistical significance of differences between subgroups are presented.*

*Przedstawiono wartości średnie, kwartyle i istotność statystyczna różnic pomiędzy podgrupami.*

## Material and Methods

Fifty-six newborns in gestational age equal or higher than 34 wks (27 septic and 29 non-septic patients) transferred to Intensive Care and Neonatal Pathology Department (NICU) from obstetric units from other hospitals by specialist neonatal ambulance, were enrolled into the study. Infection, SIRS, respiratory insufficiency, hyperbilirubinaemia or failure to thrive were the main reasons for hospitalization. The last two diagnosis and non-infectious respiratory insufficiency consisted the control group, while newborns with suspected or confirmed infectious were considered for inclusion into the study group. Confirmed perinatal asphyxia and malformation of urinary system were the exclusion criteria. The study protocol was approved by the Local Bioethics Committee (KNW/*0022/KB1/120/11*) and performed in a single third level nursery (intensive care unit) of the university children's hospital. There were not any changes in the diagnostic or treatment algorithm commonly accepted in the unit for this category of patients which would be related only to the study. The protocol ensured that all included newborns were treated within the standards of care and the preservation of urine samples for further biochemical analysis was the only difference.

Early postnatal status was estimated based on 5$^{th}$ minute Apgar score, while severity of clinical conditions at admission and during hospitalization was evaluated on the basis of Neonatal Therapeutic Intervention Scoring System (NTISS). Study group characteristics is presented in the Table I.

At admission, septic screen including CBC (complete blood count) with blood smear, C-reactive protein (CRP), procalcitonin (PCT), blood culture was performed and microbiological swabs were collected from all patients for colonization screening. Other laboratory blood tests (glucose, electrolytes, creatinine, total protein, serum albumin, and bilirubin among others) were completed and urine samples were collected for routine analysis, microbiological culture and for freezing to -70°C in polypropylene tubes.

During hospitalization, both groups underwent routine clinical procedures, including CBC, blood gases and electrolytes, glucose, creatinine and cystatin C analyses. Treatment was introduced according to diagnosed health problem. CRP and PCT serum levels were used for the monitoring of inflammatory reaction (according to centre standards).

Urinary KIM-1 and creatinine concentrations were assessed during the three subsequent days in frozen samples collected every 24 hours from the beginning of observational period.

### *Laboratory measurements*

Urine KIM-1 measurements were performed using commercially available ELISA kits (BioAssay Works, Ijamsville, DM, U.S.) with intra- and interassay coefficients of variation of 3.6 and 7.9 %, respectively (the sensitivity 0.01 ng/ml). Cystatin C measurements were performed by ELISA according to the manufacturer instruction (R&D, Minneapolis, MN, U.S.), with intra- and interassay coefficients of variation <5.9 %. In the control group 95% CI of the mean KIM-1 was 0.04-2.02 ng/ml (reference range).

### *Data analysis*

AKI was diagnosed according to AKIN criteria, on the basis of serial measurements of serum creatinine [2]. Increased in serum creatinine to values equal or higher than 150% of the initial value, but not less than 0.3 mg/dl within 48h was considered as AKI in the study population.

In addition to urinary KIM-1, KIM-1 to urinary creatinine (uCr) ratio was calculated.

Sepsis was defined as SIRS and evidence of infection (positive microbiological culture, clinical symptoms). Severe sepsis was identified, when the course of sepsis was complicated by dysfunction of two or more organs or systems.

### *Statistical analysis*

Analyses were performed using the STATISTICA 10.0 (StatSoft Polska, Tulsa, OK, U.S.) software. Normality of distribution was tested with the Kolmogorov-Smirnov test. The data presented are expressed as median values with 1 and 3 quartiles or means with 95% confidence intervals as appropriate. Chi$^2$ test and Chi$^2$ test with Yates's correction were used to compare distribution between groups. Mann-Whitney U test and Friedman ANOVA were used for comparison of independent variables. Correlation coefficients were calculated according to Spearman. p values <0.05 were considered as statistically significant.

## Results

Median values of KIM-1 were significantly higher in septic newborns than non-septic individuals [1.42 (0.56-2.04) vs 0.58 (0.16-1.24) ng/ml] on the first day, [1.03 (0.54-2.32) vs 0.36 (0.12-1.08) ng/ml] on the second day, and [0.98 (0.28-1.68) vs 0.32 (0.07-1.22) ng/ml] on the third day, however the differences were statistically significant only in the first assessment (Fig. 1). KIM-1 to uCr ratio showed significantly lower values in non-septic population.

KIM-1 levels as well as KIM-1/uCr ratios were not related to birth weight, gestational age, 5'Apgar score, but were associated with NTISS value (R=0.499; p<0.001 on the first day for KIM-1 and R=0.606; p<0.001 for KIM-1/uCr), serum CRP (R=0.317; p=0.02 on the first day for KIM-1 and R=0.32; p=0.04 for KIM-1/uCr) and PCT levels (R=0.299; p=0.03 for KIM-1 and R=0.469; p=0.01 for KIM-1/uCr).

In septic group, there were 8 newborns who developed AKI (risk or injury). Only one of them presented low urinary output and no one required renal replacement therapy. In this group of patients, KIM-1 values were slightly (not significantly) greater than in non-AKI septic patients: on the second day, and on the third day of observation (Tab. II). In addition, there was an overlap with values in the control group (5-95 percentiles: 0.04-2.2 ng/ml). When analyzing KIM-1 to uCr ratio no statistically significant differences between AKI and non-AKI were showed.

In the multiple regression analysis the variability of urinary KIM-1 was explained by CRP but not by markers of kidney function (serum creatinine or alternatively cystatin C, or urinary output). The effect was significant at the first and second day (β=0.54, p<0.001 and β=0.64, p<0.001,

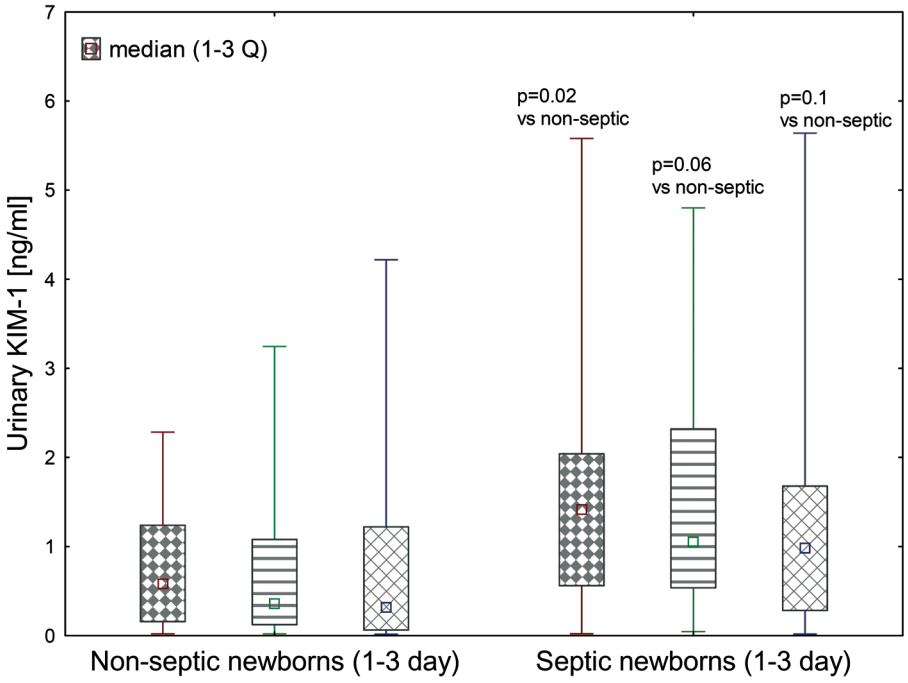


**Figure 1**
**Urinary KIM-1 in septic and non-septic newborns in three consecutive days.**
KIM-1 w moczu u noworodków z sepsą i bez sepsy w trzech kolejnych dniach.

**Table II**

**The values of urinary output, serum creatinine, cystatin C and urinary KIM-1 in the subgroups of AKI and non-AKI patients on the following time-points.**

Diureza, stężenie w surowicy kreatyniny i cystatyny C oraz KIM-1 w moczu w podgrupach pacjentów z AKI I bez AKI w kolejnych przedziałach czasowych.

| | AKI [N=8] | Non-AKI [N=19] | Statistical significance |
|---|---|---|---|
| **UO1st day (ml/kg/h)** | 3.0 (2.9-4.9) | 4.6 (3.3-5.5) | 0.24 |
| **UO 2nd day (ml/kg/h)** | 4.9 (4.1-5.0) | 4.8 (4.1-5.7) | 0.82 |
| **UO3rd day (ml/kg/h)** | 5.3 (5.2-5.5) | 6.1 (5.1-7.1) | 0.14 |
| **sCr 1st day (mg/dl)** | 0.85 (0.81-1.64) | 0.76 (0.55-1.02) | 0.27 |
| **sCr 2nd day (mg/dl)** | 1.17 (1.06-1.41) | 0.74 (0.50-0.97) | <0.001 |
| **sCr 3rd day (mg/dl)** | 0.99 (0.74-1.15) | 0.62 (0.44-0.82) | 0.05 |
| **CystC 1st day (mg/l)** | 1.98 (1.80-2.37) | 1.64 (1.33-1.92) | 0.02 |
| **CystC 2nd day (mg/l)** | 1.54 (1.34-1.88) | 1.47 (1.28-1.71) | 0.46 |
| **CystC 3rd day (mg/l)** | 1.88 (1.57-2.03) | 1.50 (1.23-1.84) | 0.11 |
| **uKIM-1 1st day (ng/ml)** | 1.02 (0.46-1.62) | 1.58 (0.62-2.12) | 0.44 |
| **uKIM-1 2nd day (ng/ml)** | 1.44 (0.54-2.52) | 0.98 (0.54-2.52) | 0.53 |
| **uKIM-1 3rd day (ng/ml)** | 1.22 (0.34-1.43) | 0.92 (0.24-1.68) | 0.99 |
| **uKIM/Cr x $10^5$ 1st day** | 260 (60-461) | 251 (89-414) | 0.68 |
| **uKIM/Cr x $10^5$ 2nd day** | 207 (71-386) | 149 (78-219) | 0.42 |
| **uKIM/Cr x $10^5$ 3rd day** | 240 (63-418) | 179 (60-299) | 0.31 |

*Mean value, 95%CI and statistical significance of differences between the subgroup are presented.*
*Przedstawiono wartości średnie, 95% CI i istotność statystyczną różnic pomiędzy podgrupami.*

respectively), but not on the third day (β=0.18, p=0.21). The similar results were obtained when multiple regression analysis was performed for KIM-1/uCr ratio with the same variables as above. Significance of relation was showed only for the first two days of observation (β=0.69, p<0.001 and β=0.45, p<0.005, respectively).

At the time of enrolment serum concentrations of creatinine were similar in neonates with sepsis and non-septic group, and the lack of differences persisted until the end of observational period (Tab. I). However, the comparison of AKI and non-AKI septic subgroups revealed statistically significant difference in creatinine values, but only on the second day of observation (Tab. II). Septic neonates were characterised by significantly increased levels of CRP and PCT. While in patients with severe sepsis platelet count was decreased.

## Discussion

The results of the study revealed that urinary KIM-1 measurement is not a useful marker of AKI in septic newborns. KIM-1 did not help us to distinguish between AKI and non-AKI population, due to great overlap in values with the results in non-AKI group. The small number of AKI patients diagnosed based on serial creatinine measurements unable us from drawing strong conclusions, but the results were not satisfying. Thus the long-term search for the ideal marker of AKI in this specific population has clearly not been completed, yet.

Recent decade led to the discovery of several new potential AKI biomarkers, after many years since cystatin C has been as alternative to creatinine for the estimation of GFR also during the first days of life [14-18], with limited ability for early detection of AKI in septic neonates [5,19]. Very promising was siderocalin (NGAL), however very strongly influenced by inflammatory process, limit its usefulness in septic neonates [20-24].

The AKI biomarker assessed in this study was KIM-1, reported as an early marker of tubular injury with increase in 12 hours after renal damage [25,26]. Du et al [27] emphasizes the role of KIM-1 in detecting AKI in pediatric patients especially in emergency care settings. Takasu et al. [28] describes the role of KIM-1 in septic injury to the kidneys, showing its tight connection with the injury process and indication for monitoring of the intensity of damage. Moore, Legrand and Devarajan [29-31] also pointed out the value of KIM-1 as marker of nephrotoxicity and kidney injury in early postoperative period. Testing is easy and feasible, especially if commercially available point-of-care device would be in use [32]. KIM-1 was evaluated as well as a marker of graft function [33]. According to Shao [34], KIM-1 is promising biomarker for AKI, particularly if induced by toxicity or ischemia. The results of our study show not spectacular increase in KIM-1, limits its value correlating with inflammatory markers. Toxicity or ischemia were not revealed, however their risk factors could not be excluded (e.g. potential nephrotoxicity of gentamicin).

Early detection of kidney injury in the process of sepsis was investigated by Schaalan and Mohamed [35]. They found 85% specificity and 88% sensitivity for KIM-1, regarding it as an important marker indicating the progress of sepsis to sepsis-AKI. We cannot so optimistically agree with the above statement, but the reason for the differences in our findings may lie in the severity of sepsis and duration of symptoms.

Liangos et al. [36] has analyzed KIM-1 role as a prognostic marker in severely ill patients with acute renal failure treated in an intensive care unit. Even KIM-1 was not superior to APACHE II, but its' values correlated much better with the outcome than serum creatinine or urinary output. Fan et al. [37] proposed the value of KIM-1 higher than 7,3 ng/ml to differentiate the group of severely ill patients (characterized by APACHE II score more than 25) from the other septic patients with lower APACHE II scores, with 61% specificity and 96% sensitivity. Episodes of sepsis recognized in our patients were of moderate clinical course, and that is probably why we did not observed such high values of KIM-1. The other reason could be the young age of our patients.

Our study revealed that septic state is a strong confounder limiting usefulness of urinary KIM-1 in the detection of AKI. We showed a transient increase in its urinary levels in septic patients without the increase in serum creatinine enabling the diagnosis of AKI. KIM-1 values were elevated in septic patients in comparison to non-septic group, only at the first day of observation, and the difference subsided on the next days. We cannot claim that the rise in KIM-1 is only caused by sepsis, but is definitely due to inflammatory process. As it has been already found, KIM-1 may increase in various renal inflammatory processes (acute and chronic), and also in renal carcinomas [25,31,38]. The study population presented declared clinical symptoms and we could easily connect the rise in KIM-1 with infection, but this is not the main point.

Septic status is not the only confounder that limit usefulness of the marker in AKI detection. Asphyxia and hypoxia belongs to these factors, both inducing

hypoxia-reperfusion injury to the kidney tissues, followed by inflammatory reaction. However, the lack of asphyxiated newborns precluded any comparison in this aspect with the results presented by Sarafidis [39].

Our observation in some aspects is similar to presented by other groups of investigators. In our study, gestation age was not correlating with KIM-1, similarly as in Saeidi study and in contrast to data previously shown by Askenazi et al. [40,41]. It may be caused by the fact that study group in Askenazi's project consisted of newborns born between 26 and 36 weeks of gestation, so some of them were still in the process of kidney development and maturation.

As suggested by other researchers, we compared groups (septic vs non-septic, AKI vs non-AKI) applying urinary KIM-1 to urinary creatinine ratio [42]. The results confirmed our observation using KIM-1 levels, but we could not notice any superiority of using KIM-1/uCr ratio over KIM-1 measurements alone.

It is known that recognition of even small increase in serum creatinine is associated with the rise in mortality and morbidity [27]. However, establishing the diagnosis of AKI on the first few days of life based solely on serum creatinine concentration can be impaired by an impact of maternal serum creatinine level and functional immaturity of the tubules [43]. Search for new AKI biomarkers is therefore justified, especially since late diagnosis decreases the chances of timely treatment [44].

Inclusion of newer markers helping to evaluate kidney condition is announced the future aim by some very enthusiastic authors [45,46], but it does not mean that the diagnostic process will be faster or simpler. Other researchers are more skeptical and do not see much help with incorporating new potential, more expensive biomarkers of AKI [47]. At this point and based on our finding we have to be rather careful with using new laboratory parameters in everyday practice. However, it may change with better knowledge of these new markers. After all, we are still using creatinine even we know it's limitation.

Summarizing the results, the following conclusions can be proposed:

Increased KIM-1 concentration in septic newborns is affected by inflammation and reflects the severity of clinical condition.

High variability of KIM-1 levels diminishes its usefulness in the diagnosis of mild and moderate AKI episodes in septic newborns.

Our preliminary findings preclude elimination of serial measurements of serum creatinine in the monitoring of newborns at high risk of AKI.

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