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Is serum cystatin C a better marker of kidney function than serum creatinine in septic newborns?*

Czy stężenie cystatyny C w surowicy jest lepszym markerem czynności nerek niż stężenie kreatyniny u noworodków z sepsą?

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Introduction: Several studies have claimed that the estimation of serum cystatin C could be a better marker of kidney excretory function than serum creatinine. However, its role in the diagnosis of reduced kidney function was not unquestionably confirmed. The aim of this study was to analyze the concentrations of serum cystatin C in neonates with sepsis.

Material/Methods: Thirty-two neonates (gestational age from 34 to 40 weeks) admitted to the NICU during the first 14 days of life were enrolled. Serum cystatin C concentrations were estimated by ELISA during three successive days in neonates treated for infection. The study group consisted of 9 newborns with sepsis, 14 with severe sepsis and 9 with septic shock.

Results/Discussion: At the beginning of the observational period the mean serum concentration of cystatin C in the study group was 1.35 mg/L (95% CI 1.20–1.49). Surprisingly, the lowest concentration of cystatin was observed in patients with septic shock (1.23 mg/L; 95%CI 0.92–1.54) within the observation period. Higher concentrations were found in neonates with sepsis (1.47 mg/L; 95%CI 1.04–1.90) and severe sepsis (1.50; 1.12–1.87). There was no correlation between serum cystatin C concentration and serum creatinine or gestational age.

A significant correlation was discovered between chronological age and cystatin C (R=–0.439, p=0.01). There was a tendency for cystatin C to decline during the second observational day in patients with sepsis (to 1.53 mg/L; 95%CI: 1.19–1.86) and severe sepsis (to 1.32 mg/L; 95%CI: 1.07–1.57), while a slight insignificant increase in patient with septic shock (to 1.28 mg/L; 95%CI: 0.88–1.68) was revealed. The interrelation between age and cystatin C concentration disappeared in the following days of stay in the NICU. Even in patients who died in the course of septic shock the observed changes in cystatin C levels were small and did not exceed those of serum creatinine.

Conclusions: Cystatin C is not a useful marker of kidney function in neonates with sepsis.

Key words: **cystatin C • creatinine • newborns • kidney function • sepsis**

Streszczenie

Wprowadzenie: Wyniki opublikowanych badań dowodzą, że oznaczanie cystatyny C w surowicy może stanowić lepszy marker czynności wydalniczej nerek niż stężenie kreatyniny w surowicy. Jednakże

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znaczenie tego markera w diagnostyce upośledzonej czynności nerek u noworodków nie zostało jednoznacznie wyjaśnione. Celem badania jest analiza stężeń cystatyny C w surowicy u noworodków leczonych z powodu sepsy.

Materiał/Metody: Do badań włączono 32 noworodki (wiek płodowy 34–40 tygodni) przyjęte do Oddziału Intensywnej Terapii i Patologii Noworodka w ciągu pierwszych 14 dni życia. Stężenie cystatyny C oznaczono metodą ELISA w 3 kolejnych dobach leczenia z powodu zakażenia. Wśród analizowanych noworodków u 9 rozpoznano sepsę, u 14 – ciężką sepsę, a u 9 – wstrząs septyczny.

Wyniki/Dyskusja: W chwili włączenia do obserwacji średnie stężenie cystatyny C wynosiło 1,35 mg/L (95% CI 1,20–1,49). Nieoczekiwanie najniższe wartości cystatyny C obserwowano u pacjentów, u których w kolejnych dniach rozwinął się wstrząs septyczny – 1,13 mg/L (95% CI 0,91–1,34). Wyższe wartości stwierdzono u noworodków z sepsą 1,51 mg/L (95% CI 1,18–1,84) i ciężką sepsą 1,38 mg/L (95% CI 1,13–1,63). Nie wykazano korelacji ze stężeniem kreatyniny w surowicy oraz wiekiem płodowym. Stwierdzono natomiast istotną korelację pomiędzy wiekiem chronologicznym a stężeniem cystatyny C (R=–0,439, p=0,01). W kolejnych dniach obserwacji wykazano obniżanie się stężeń cystatyny C u chorych z sepsą (1,34 mg/L; 95% CI 0,89–1,78) i ciężką sepsą (1,24 mg/L; 95% CI 1,00–1,48), podczas, gdy u pacjentów we wstrząsie septycznym obserwowano wzrost wartości, choć niewielki i nieistotny statystycznie (1,25 mg/L; 95% CI 0,97–1,53). Zależność pomiędzy wiekiem a stężeniem cystatyny C zanikała w kolejnych dniach obserwacji. Nawet u pacjentów, którzy zmarli w przebiegu wstrząsu septycznego, obserwowane zmiany w stężeniu cystatyny C były niewielkie i nie przekraczały zmian w stężeniu kreatyniny.

Wnioski: Cystatyna C nie jest przydatnym parametrem uszkodzenia nerek u noworodków z sepsą.

Słowa kluczowe: **cystatyna C • kreatynina • noworodki • czynność nerek • sepsa**

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Abbreviations: **ABG** – arterial blood gases; **A&E** – accident and emergency; **AKI** – acute kidney injury; **CBC** – complete blood count; **CI** – confidence interval; **CRP** – C-reactive protein; **GA** – gestational age; **GFR** – glomerular filtration rate; **NICU** – neonatal intensive care unit; **SIRS** – systemic inflammatory response syndrome.

Introduction

Sepsis is one of the most severe disorders in newborns and young infants, responsible for almost one and a half million deaths yearly worldwide. Sepsis is typically divided to mild sepsis, severe sepsis and septic shock. The latter two may lead to multiorgan dysfunction syndrome, and if the inflammatory process is not stopped and reversed it may eventually cause multiorgan failure and death. Clinical signs and symptoms are not specific in newborns, which makes the disease even more difficult to diagnose. Early introduction of antibiotic therapy is essential in the management of generalized infection.

Symptoms suggesting kidney dysfunction occur relatively late, but may quickly be followed by acute kidney insufficiency. Acute kidney injury (AKI) is claimed to be recognized in about 50% of septic adult patients. The epidemiological data in newborns are missing, but clinical observations confirm the above-mentioned numbers. Both systemic inflammation and AKI are serious risk factors for unfavorable outcome. There are not many research data on kidney function in the short-term post-septic period or in long-term follow-up.

As soon as the diagnosis of AKI is made, the treatment including adequate hydration, use of diuretics for proper volume control, and diet can be introduced. Currently, serial measurements of serum creatinine and monitoring of diuresis are the only methods for assessment of kidney function. Serial serum creatinine measurements in the early postnatal period eliminate the impact of muscle mass variability or gender, but not that of diet and the declining effect of impaired creatinine elimination during pregnancy [5,7]. Initially raised serum creatinine values in newborns gradually decline during the first months, reaching adult values by the end of the first year [7]. Additionally, interference of bilirubin, hemoglobin and ketone bodies with creatinine measurements was observed [7].

Extensive research on new, more sensitive and specific markers has been conducted in the last twenty years. As a result, cystatin C was proposed for evaluation of kidney function.

Table 1. Clinical evaluation of the study group (N=32) – mean values (95%CI)

	Initial	After 24 hours	After 48 hours
Leucocytes (109/L)	12.3 (9.8–14.8)	10.9 (8.6–13.3)	10.7 (8.6–12.7)
CRP (mg/dL)	69.9 (51.8–88.0)	93.2 (71.6–114.9)	88.8 (65.4–112.2)
Creatinine (mg/dL)	0.88 (0.76–1.01)	0.83 (0.72–0.93)	0.75 (0.66–0.85)
Urea (mg/dL)	23.5 (18.8–28.2)	27.5 (21.4–33.6)	33.5 (21.6–45.4)
Glucose (mg/dl)	94.5 (80.9–108.0)	105.4 (85.6–125.3)	92.0 (79.8–104.2)
Aspartate aminotransferase, AST (IU/L)	300.0 (23–687)	Not estimated	678.6 (15–1550)
Alanine aminotransferase, ALT (IU/L)	89.0 (10–187)	Not estimated	163.0 (6–351)
Total protein (g/L)	44.8 (41.8–47.8)	40.5 (36.3–44.7)	39.7 (36.8–42.7)
Albumin (g/L)	28.1 (25.4–30.8)	25.5 (22.8–28.2)	24.1 (22.3–25.8)
Blood pressure (mmHg)	51.0 (46–56)	53.0 (49–58)	55.0 (50–60)
Heart rate (1/min)	145.0 (136–154)	153.0 (147–159)	152.0 (144–161)
Lactate (mg/dL)	3.6 (2.6–4.6)	4.5 (2.2–6.8)	3.0 (2.0–3.9)
Amino acid supplementation (g/kg/d)	0.94 (0.58–1.30)	1.61 (1.36–1.86)	1.73 (1.43–2.02)

Cystatin C (CystC), a 120-amino acid protein, is a cysteine protease inhibitor produced by all nucleated cells at a constant rate [1,13]. CystC is filtered in the glomerulus, reabsorbed and degraded by epithelium of proximal tubes, and passed into the urine [19,21,22]. The role of CystC in the diagnosis of reduced kidney function has not been confirmed in neonates. It is known that CystC does not cross the placenta and should then reflect only the infant's own renal function [7]. On the other hand, markedly higher concentrations of CystC were revealed shortly after delivery, caused by failure of placental removal. At birth, CystC concentration is higher than in adults and decreases within 2 months [7]. The reference values proposed by Finney [7] were defined as follows: mean value 1.37 (mg/L) with range 0.81–2.32 [7]. Armangil [2] meanwhile reported 1.25–2.84 mg/L (mean 1.8±0.3) on the first day of life followed by a significant decrease on the third day (mean: 1.65±0.3 mg/L).

Studies performed in adults showed a strong correlation between CystC and GFR [3,9,10,18], and these findings were confirmed in children and newborns [4,11]. The lack of influence of muscle mass (approx. ¼ of body weight) or inflammatory status on CystC value is considered to be an advantage [1,10,18], and allows this marker to be used in GFR evaluation [7]. Body weight, gender, diet, hydration and nutritional status have no influence on CystC concentration, but thyroid function may have some impact [5].

The aim of this study is to analyze the concentrations of cystatin C in neonates suffering from sepsis, intensively treated at the NICU, and to compare cystatin C values with creatinine concentration.

Material and Methods

Thirty-two neonates in the first 14 days of life, diagnosed with sepsis based on clinical symptoms and/or clinical history with risk factors of infection, confirmed later by positive microbiological blood culture in 24 cases, were enrolled. Sepsis (N=9) was defined as SIRS and evidence of infection (clinical symptoms or positive blood culture) and severe sepsis (N=14) was identified when the course of sepsis was complicated by dysfunction of two or more organs or systems. Septic shock (N=9) was recognized when the decrease in blood pressure occurred together with symptoms of compromised peripheral blood perfusion. All studied patients were outborns and were admitted to a single, third level university children's hospital from home (A&E department) or transferred to the unit from other hospitals by a neonatal ambulance transport service. Clinical evaluation of the study group is presented in Table 1. Clinical condition at the moment of inclusion was objectified using SNAP (Score for Neonatal Acute Physiology) and the mean value for the study group was 9.2 (7.3–11.0).

Inclusion criteria consisted of gestational age equal to or higher than 34 weeks of gestation and signs and symptoms of neonatal sepsis. Malformations of urinary system and confirmed severe perinatal asphyxia were the exclusion criteria. The study group consisted of 20 males and 12 females. The average gestational age was 37 weeks (range: 34–40) and the average birth weight was 2920 g (range: 1720–4470g). Mean Apgar score after 1 minute was 7 points (range: 1–10), and 8 after 5 minutes (range: 5–10). One patient was given 5 points in the Apgar score after 5 minutes and 1 point after the first minute, but further clinical observation and biochemical tests did not confirm perinatal asphyxia. The reasons for hospital admission included hyperbilirubinemia, failure to thrive, symptoms of respiratory distress and suspected infection. The mean chronological age on admission was 8 days of life (range: 1–14), and the sepsis was diagnosed within 5 days of hospitalization on average (range: 1–13).

Acute kidney injury (AKI) was scored according to the RIFLE classification based on serum creatinine (at least

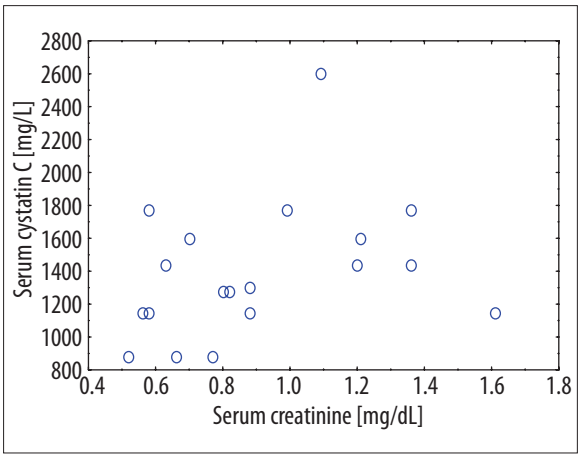

Fig. 1. Correlation between serum cystatin C and creatinine levels

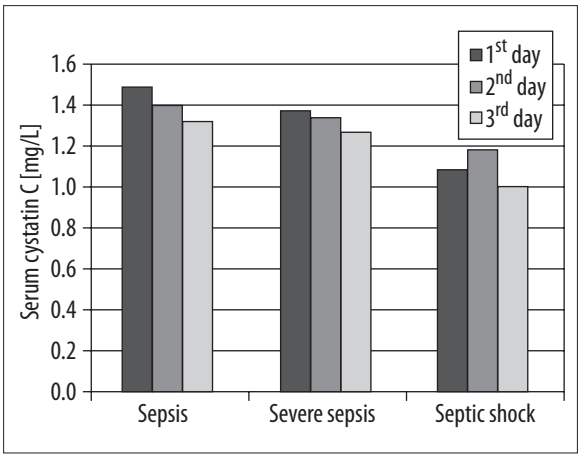

Fig. 2. Serum cystatin C levels in patients with sepsis, severe sepsis and septic shock on successive days of observation

1.5-fold increase from baseline values) and urinary output changes after admission to the NICU [15].

The study protocol was approved by the Institutional Bioethics Committee. The protocol did not allow for any changes from the basic algorithm of diagnosis and treatment accepted in the unit only for the purpose of this study. All included patients were cared for and treated in the standard way, and the preservation of some samples of serum for further biochemical analysis was the only exception.

All study participants were screened for microbiological colonization on admission and basic septic screening was performed, including CBC with blood smear, CRP, glucose, lactate, electrolytes and blood culture, as well as basic biochemical evaluation including creatinine, total protein, serum albumin and bilirubin. Urinalysis and urine culture were also performed. Serum samples were collected after the routine tests were completed, and frozen to –70°C in polypropylene tubes.

The observational period started when the patient presented evident clinical symptoms of infection and antibiotic therapy was introduced. The standard protocol included biochemical screening (glucose, lactate, creatinine, aspartate aminotransferase [AST], alanine aminotransferase [ALT]), CBC and ABG every second day or more often, according to clinical requirements. Cystatin C measurements were performed by ELISA according to the manufacturer's instructions (BioVendor, Modrice, Czech Republic). Creatinine was measured in serum samples by the Jaffe method (Olympus AU 640).

Intra and inter-assay coefficients of variability were 5.0–9.6% and 4.8–6.2% for high and low concentrations, respectively.

Statistical analysis

STATISTICA 8.0 (StatSoft Polska, Kraków, Poland) software was used for statistical analysis. All presented data were expressed as means and 95% confidence intervals. Normality of distribution was tested with the Kolmogorov-Smirnov test. Mann-Whitney U pair-wise comparison for independent variables and Wilcoxon pair-wise comparison for dependent variables were used as appropriate. Chi^2 test and Chi^2 test with Yates' correction were used to compare distributions between groups. Correlation coefficients were calculated according to Spearman. The p values <0.05 were considered as statistically significant.

Results

At the time of enrolment the mean serum concentration of CystC was 1.35 mg/L (95% CI 1.20–1.49). The lowest concentration was 1.23 mg/L (95% CI 0.92–1.54) and was observed in patients who developed septic shock during the following days. Surprisingly, slightly higher concentrations were found in neonates with sepsis (1.47 mg/L; 95% CI 1.04–1.90) and severe sepsis (1.50; 1.12–1.87).

Analysis of demographic factors revealed lack of a correlation between CystC and gestational age, 5' minute Apgar score, birth weight and gender. A significant correlation was found between chronological age and CystC levels (R=–0.439, p=0.01), but the interrelation disappeared on the following days of hospitalization. There was also no correlation with serum creatinine (Figure 1).

Comparison of creatinine and CystC values at successive time points (at the beginning of the observational period, and after 24 and 48 hours) in the three subgroups of patients (groups A, B and C) showed some statistically significant differences of creatinine concentrations between the subgroups. Such results were not found in regard to CystC (Table 2).

During the 3-day observation period a tendency for CystC level to decline in patients with sepsis (1.53 mg/L, 95%CI: 1.19–1.86) and severe sepsis (1.32 mg/L; 95%CI: 1.07–1.57) was found. In patients with septic shock CystC levels insignificantly increased (1.28 mg/L; 95%CI: 0.88–1.68) – Figure 2. Even in patients who died in the course of septic shock the observed changes in CystC were small and did not exceed those of serum creatinine.

Discussion

The results of the study revealed that assessment of CystC is not better, and in fact seems to be even worse than that of serum creatinine, in newborns treated for sepsis in the detection of sepsis-related AKI.

Table 2. Values of creatinine and cystatin C in three subgroups of newborns at successive time points. Mean value, 95%CI and statistical significance of differences between the subgroups A, B and C (Mann-Whitney U test) are presented

	Sepsis (N=9) (A)	Severe sepsis (N=14) (B)	Septic shock (N=9) (C)	Statistical significance
GA	36 (35–38)	37 (36–38)	39 (38–40)	A *vs* C p=0.02
Birth weight (g)	3146 (2551–3741)	2679 (2358–3000)	3284 (2905–3663)	NS
Day of life	10 (6–14)	7 (5–9)	8 (5–12)	NS
SNAP (pts)	6.6 (4.3–8.9)	9.3 (6.7–11.9)	11.7 (6.1–17.3)	A *vs* C p=0.003
		Creatinine (mg/dL)		
Initial	0.66 (0.42–0.90)	0.95 (0.78–1.13)	0.93 (0.64–1.22)	A *vs* B p=0.03 A *vs* C p=0.04
After 24 hours	0.68 (0.48–0.87)	0.86 (0.71–1.02)	0.92 (0.63–1.20)	A *vs* B p=0.03
After 48 hours	0.56 (0.42–0.70)	0.77 (0.66–0.88)	1.02 (0.76–1.27)	A *vs* B p=0.02 A *vs* C p=0.01 B *vs* C p=0.05
	48 hours *vs* Initial p=0.04	48 hours *vs* Initial p=0.04	NS	
		Cystatin C (mg/L)		
Initial	1.47 (1.04–1.90)	1.50 (1.12–1.87)	1.23 (0.92–1.54)	NS
After 24 hours	1.53 (1.19–1.86)	1.32 (1.07–1.57)	1.28 (0.88–1.68)	NS
After 48 hours	1.43 (1.05–1.81)	1.31 (1.05–1.58)	1.21 (0.95–1.47)	NS
	NS	NS	NS	
		Lactate [mg/dL]		
Initial	2.61 (1.18–4.04)	4.02 (2.49–5.54)	4.00 (0.70–7.30)	NS
After 24 hours	2.05 (1.47–2.62)	3.23 (2.26–4.19)	11.77 (1.83–25.67)	A *vs* C p=0.01 B *vs* C p=0.03
After 48 hours	1.81 (1.30–2.32)	2.92 (1.86–3.98)	4.57 (1.50–9.99)	NS
	NS	48 *vs* 24 hours p<0.05	24 hours *vs* Initial p<0.006	

Table 3. Serum cystatin C concentration in neonates with and without acute kidney injury (AKI) during the three successive days of observation (Mann-Whitney U test), values presented as mean value and 95%CI

	AKI patients (N=8)	Non-AKI patients (N=24)	Statistical significance
Initial	1.47 (1.23–1.71)	1.39 (1.13–1.65)	NS
After 24 hours	1.55 (1.06–2.030	1.28 (1.13–1.42)	NS
After 48 hours	1.29 (1.13–1.47)	1.33 (1.17–1.48)	NS

The study group was quite homogeneous and consisted only of newborns admitted to the hospital on their first days of life, not older than 15 days. On admission their clinical condition was diverse, ranging from very stable to unstable with symptoms of cardio-respiratory dysfunction.

Regardless of the severity of clinical condition the initial serum creatinine levels were elevated, which is considered physiological in newborns in their first 2–3 days of life. It has been shown that serum creatinine in the first three days of life revealed the kidney status of the mother, as creatinine is eliminated through the placenta along a gradient [2]. Analysis of serum creatinine concentrations separately in all three groups of patients revealed higher values in newborns suffering from severe sepsis and septic shock, indicating AKI in some patients, even taking into account limitations such as maternal kidney status, chronological age and muscle mass.

Surprisingly, CystC values were all in the normal range. There are few authors reporting on CystC concentrations, measured by nephelometric or turbidimetric methods, on the first days of life: Novo – 1.70±0.26 mg/L on the first and 1.51±0.19 mg/L on the third day of life [17]; Finney [7] – 0.81–2.32 mg/L during the first three months; Harmoinen [11] – 1.36–2.23 mg/L in the first week of life; and Treiber [20] 1.28–2.66 mg/L on the third day. The range 0.81–2.6 mg/L detected in our patients corresponds with the above data of clinically stable newborns, but measured with a different method (ELISA).

In contrast to a suggestion of Nejat et al. [16], who claimed that CystC was an effective and earlier surrogate marker of decreased renal function than plasma creatinine in a general ICU population, we could not confirm that on the basis of our results. Recently, Mårtensson et al. reported [14] a similar increase in serum CystC and creatinine levels in patients with AKI and sepsis. Thus the assessment of CystC as a functional marker of AKI seems to be useless at least in septic newborns. Some authors suggest that CystC is a better marker only for detection of chronic kidney injury, and that only chronic damage causes a steady and significant increase in CystC concentration [6,8,12,22].

The relatively low values found in the most severely ill patients are rather surprising. Regarding the normal range of CystC in newborns, patients with septic shock presented values in the lower range or even below. Cystatin C is found in the lysosomes of every cell, and actively participate in protein metabolism inside the cell. The marker is known for its resistance to the influence of inflammation. It seems that severe inflammatory status may disturb cell metabolism, causing a decrease in concentrations of some substances. Unfortunately, the literature on the topic is sparse, and fails to provide a good explanation.

Recently Måtterson et al. reported that sepsis *per se* does not affect circulating CystC level, and thus is a potentially valuable marker of kidney function, including in septic patients. Moreover, this group did not show a correlation between CRP and cystatin C values [14].

The main limitation of the study is the lack of glomerular filtration rate measurement by insulin clearance technique or similar. Moreover, we did not check the thyroid status, although all newborns were screened for congenital hypothyroidism. Finally, we did not enroll a group of healthy neonates as the control group. Thus we cannot compare the cystatin C values observed in septic neonates with those in healthy subjects.

We conclude that cystatin C is not a useful marker of kidney function in neonates with sepsis.

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