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DIAGNOSTIC MARKERS FOR EARLY SEPSIS DIAGNOSIS IN CHILDREN WITH SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

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*Sepsis caused by infection remains a major cause of mortality among children. One of the main reasons for high sepsis mortality rates is the inability to obtain early diagnosis. Sensitive and specific biomarkers are greatly needed in rapid diagnosis of sepsis. The main aim of study was to investigate the ability of high-mobility group box-1 protein (HMGB1), lipopolysaccharide-binding protein (LBP), Interleukin-6 (IL-6), procalcitonin (PCT) and C reactive protein (CRP) to differentiate sepsis patients. Eighty-four children with Systemic Inflammatory Response Syndrome (SIRS) were included in the prospective study. Sepsis was recognised in 23% (n = 19) of them. LBP, IL-6, CRP and PCT levels were significantly higher among the sepsis group (*P *< 0.05). HMGB1 levels in the sepsis patients did not significantly differ from SIRS patients. In ROC analysis in sepsis patients, identification markers LBP, IL6 and CRP performed quite similarly (*P *< 0.001), with the best result being for IL6. Our data suggest that in early sepsis diagnosis in children, LBP, IL-6, PCT and CRP are probably the superior diagnostic markers, with the best performance by IL6. LBP and IL-6 are superior markers for sepsis patients' disease process monitoring. HMGB1 does not have a diagnostic value for sepsis patient identification.*

Key words: *sepsis, SIRS, children, diagnostic markers.*

INTRODUCTION

Sepsis caused by infection remains a major cause of mortality and morbidity among children in Latvia and throughout the world (Proulx *et al*., 1996; Watson *et al*., 2005). Hospital mortality among USA children with severe sepsis was 10.3% (Watson *et al*., 2003), in Latvia between 1995 and 2000, in the only tertiary level hospital 24.4% of sepsis cases were fatal (Gardovska *et al*., 2001). The diagnosis of sepsis remains difficult due to a variety of reasons: in children early warning signs and symptoms often are non-specific; microbiological results seldom made become available within 48–72 h; and false-negative results are common. The most important measures in reducing mortality from sepsis are the early recognition and prompt initiation of therapy (Brilli *et al*., 2005; Randolph *et al*., 2005; Mishra *et al*., 2006). In 2002, in the First International Pediatric Sepsis Consensus Conference specific clinical definitions of systemic inflammatory response syndrome (SIRS) and sepsis in children were defined (Randolph *et al*., 2005). Together with early clinical sepsis recognition, laboratory tests are of great value in rapid diagnosis. In the adult population, the International Sepsis Definitions Conference (2001) proposed the use of biochemical and immunological markers rather than relying on clinical signs to identify the inflammatory response (Levy *et al*., 2003). For many years, hematological tests (total leukocyte count, neutrophils, band form counts) and C-reactive protein (CRP) have been used for reliable diagnosis of sepsis. However, there do not have the specificity required to distinguish between viral and bacterial infections, autoimmune diseases, cancer and trauma (Ballou and Kushner, 1992). Later the calcitonin prohormone, procalcitonin (PCT) was proposed as a specific marker of sepsis in children and adults (Hatheril *et al*., 1999; Guven *et al*., 2002; Casado-Flores *et al*., 2003).

Lipopolysaccharide-binding protein (LBP) is an acute phase protein involved in the endotoxin-mediated immune response (Meisner, 2005). Increased serum LBP levels have been reported in children with sepsis (Berner *et al*., 2002; Pavcnik-Arnol *et al*., 2004; Ubernauf *et al*., 2007).

Interleukin-6 (IL-6), a proinflammatory cytokine that stimulates both B- and T-lymphocytes is involved in the induction of fever (Ng *et al*., 2003; Carcillo *et al*., 2006) and has attracted attention as an early inflammatory marker, with levels correlating well with the severity and prognosis of sepsis (Dahmet *et al*., 2005; Ng *et al*., 2006).

From 1999, when the protein secreted by macrophages stimulated with lipopolysaccharide was found and identified as high-mobility group box-1 protein (HMGB1), interest in

this proinflammatory cytokine was noticeably increased (Sunden-Cullberg *et al*., 2006). HMGB1 has been reported as a "late-onset" cytokine. Higher HMGB1 levels have been reported in sepsis patients compared to the healthy controls (Gaini *et al*., 2007), some studies have demonstrated increased levels of HMGB1 in patients with infection and sepsis, whereas other investigators found no significant difference between infected and non-infected patients (Wang *et al*., 1999; Hatada *et al*., 2005; Gaini *et al*., 2007a; Gaini *et al*., 2007b).

The currently available evidence indicates that none of markers to date meet the requirements for early and reliable diagnosis of sepsis. Some results show that measurements of combinations of biochemical markers may offer better prospects for early diagnosis.

In children (particularly in all children age groups), comparatively fewer studies on early sepsis diagnosis and inflammatory markers (LBP, HMGB1) have been made.

The main aim was to investigate the levels of HMGB-1, LBP, IL6, PCT and CRP in children with sepsis and SIRS and to examine the ability of these markers to differentiate sepsis from non-sepsis patients.

MATERIALS AND METHODS

Patients. Children with SIRS (n = 84) treated in the Children's Clinical University Hospital between January 2008 and January 2009 were included in this prospective study. The group of patients enrolled in study was determined by previous screening of children with changes in body temperature (fever or hypothermia). SIRS criteria were assessed, taking into account the values of vital signs appropriate to the child's age group, including body temperature, heart rate, respiratory rate and leukocyte count (Goldstein *et al*., 2005). Classification of the status of SIRS was done by two clinicians blind of all the laboratory results.

Inclusion criteria were:

1. Presence of at least two of the following four criteria, of which one must be temperature or leukocyte count changes:

- Temperature > 38.5 or < 36 °C;
- Tachycardia (at least 2 SD above normal age group value) or bradycardia in children < 1 year old (at least 2 SD below normal age group value);
- Respiratory rate > 2SD above normal age group value;
- Elevated or reduced leukocyte count according to normal age group values, or > 10% immature neutrophils.

2. Child's age between seven days and 18 years.

3. Consent of parents for child's participation in the study.

The enrolled children were divided into six age groups according to the definitions of the International Sepsis Consensus Conference.

Exclusion criteria

- Antibacterial therapy within the last 48 h
- Immunodeficiency
- Chronic/terminal liver or kidney illness
- Vaccination within five days before the start of the illness
- Any chronic illness that alters CRP levels
- Congenital metabolic defects
- Chromosomal anomalies
- Consent of parents not obtained.

A venous blood sample at time 0 and at the 24th and 48th hours of the study was drawn. All analyses were made immediately, excepted HMGB, for which the samples were processed at frozen at –80 °C within 30 min of sampling.

Clinical and demographic data of the patients, systemic inflammatory response syndrome criteria, biochemical markers of inflammation (HMGB1, LBP, IL-6, PCT, CRP), and total leukocyte count were analysed.

Sepsis was defined as systemic inflammatory response syndrome (SIRS) in the presence, or as a result, of suspected or proven infection. The infection was defined as proven (by positive culture, tissue strain), but evidence of infection included positive clinical findings, imaging or laboratory tests (white blood cells in sterile body fluid, pneumonia in radiographic imaging, petechial or purpuric rash).

The study protocol had been approved by the Central Medical Ethics Committee of Latvia.

Laboratory assays. HMGB1 levels were measured with a commercially available enzyme-linked immunosorbent assay (HMGB1 ELISA kit; Shino-Test Corporation, Tokyo, Japan). The measuring range was 1 to 80 ng/ml, the coefficient of variation being < 10%. Recovery of HMGB1 in this ELISA was 80–120%.

IL6 and LBP were by chemiluminescent immunometric assay Immulite® 2000 (Siemens Medical, Germany). The analytical sensivity for IL6 was 2 pg/ml and 0.2 μg/ml for LBP.

The BRAHMS PCT-Q immunochromatografic test (Brahms-Diagnostica, Germany) for the semi-quantitative detection of PCT was used. PCT concentration ranges < 0.5, ≥ 0.5, ≥ 2 and ≥ 10 ng/ml were detected with the help of a reference card.

CRP levels were measured by the latex method (COBAS INTEGRA; Roche professional Diagnostics), the lowest as-

say sensitivity being 0.085 mg/L. CRP levels < 20 vmg/L were accepted as normal.

White blood cells and neutrophils were counted on Advia 2120 (Siemens Medical, Germany).

All the laboratory analyses were carried out at the Children Clinical University Hospital, only HMGB 1 was analysed in the laboratory of Clinical Immunology and Immunogenetics, Rīga Stradiņš University.

Statistical analyses. Results were presented as numbers (n), percent (%), means ± standard deviation, and as medians and interquartile ranges (IQR). Comparisons of measured variables between SIRS and sepsis groups were performed using the Mann-Whitney 2-independent sample test. A two-tailed P value < 0.05 was considered statistically significant. Receiver operator characteristic (ROC) curves and area under the curve (AUC) were calculated for examined markers. A two-tailed P value was calculated for AUC. Sensitivities and specificities were calculated from cross-tabulations. To detect significant correlations, the Spearman's rank correlation test was used. All statistical calculations were performed using the SPSS and Epi Info 2000 statistical packages.

RESULTS

SIRS diagnosis and patients characteristics. In the prospective study 84 SIRS patients were enrolled, in 23% (n = 19) of them sepsis was recognised. Patients were divided into two groups — patients with SIRS without sepsis (n = 65) and patients with sepsis (n = 19). SIRS was most often diagnosed by the fever in combination with tachycardia at least 2 SD above normal age values, observed in 61% (n = 51) of all patients. Fever in combination with a respiratory rate increased by > 2SD above normal age was noted in 53% (n = 45) of the cases. Fever associated with changes in leukocyte count elevated or depressed for age was in 42% (n = 35) of patients. Hypothermia was not detected. Similar criteria combinations confirmed the SIRS diagnosis in both the SIRS and sepsis patients groups; there was no statistically significant difference between them.

The clinical and demographical data of patients are presented in Table 1.

Levels of CRP, PCT, IL6, LBP and HMGB1 for SIRS and sepsis patients. HMGB1 levels in the sepsis patient group did not significantly differ from the SIRS patient group. LBP levels were significantly higher among sepsis group children compared those without sepsis ($P < 0.05$). IL 6 levels were significantly higher among sepsis group patients compared with patients with SIRS without sepsis ($P < 0.05$). CRP levels were significantly higher among the sepsis group compared with the SIRS group ($P < 0.05$) (Table 2). The PCT concentration was significantly higher in the sepsis patients; a highest concentration above 10 ng/ml was detected in significantly more cases in the sepsis group (32%, n = 6) than in the SIRS group (3%, n = 2), and the lowest PCT concentration was detected in significantly more inpatients in the SIRS group (62%, n = 40) compared with those in the sepsis patient group (16%, n = 3) ($P < 0.01$).

Table 1

CLINICAL AND DEMOGRAPHICAL DATA OF THE PATIENTS

	SIRS patients (n = 65)	Sepsis patients (n = 19)	P value
Age (months)			
Mean (minimal–maximal)	71.3 (1–214)	94.7 (1–211)	NS
SE	8.8	16.3	
SD	70.8	70.8	
95% C.I.	17.9	34.1	
Day of hospitalisation			
Mean (minimal–maximal)	3.2 (1–14)	3.1 (1–6)	NS
SE	0.3	0.4	
SD	2.3	1.6	
95% C.I.	0.6	0.8	
Inclusion time in the study (day of ilness mean, minimal–maximal)	4.4 (1–17)	4.3 (2–11)	NS
SE	0.3	0.5	
SD	2.8	2.3	
95% C.I.	0.7	1.1	
Treatment time in the hospital			
Mean (minimal–maximal)	7.1 (1–30)	11.6 (7–26)	< 0.01
SE	0.7	1.2	
SD	5.6	5.1	
95% C.I.	1.4	2.6	

Data are presented as the absolute number (%) or the median ± standard deviation, standard error, with 95% confidence interval. SIRS, systemic inflammatory response syndrome; NS, not significant.

Table 2

LEVELS OF HMGB1, LBP, IL-6, CRP IN SIRS AND SEPSIS PATIENTS GROUPS

Variable[1]	SIRS patients (n = 65)	Sepsis patients (n = 19)
HMGB 1 (ng/ml)		
Median	2.2	3.5
IQR	0–5.0	1.8–4.0
P value2		NS
Lipopolysaccharide-binding protein (μg/ml)		
Median	25.2	38.3
IQR	17.4–41.9	25.5–76.9
P value		< 0.01
Interleukin 6 (pg/ml)		
Median	21.3	133.0
IQR	14.0–57.0	49.1–388.5
P value		< 0.01
C-reactive protein (mg/l)		
Median	59.9	137.8
IQR	28.0–100.3	82.0–217.9
P value		< 0.01

Mann-Whitney test. Data presented as median and interquartile range (IQR). [1]$P < 0.01$. [2]Compared with the previous group. SIRS, systemic inflammatory response syndrome. HMGB1, high mobility box-1 protein; LBP, lipopolysaccharide-binding proteine; IL-6, interleukine-6; CRP, C-reactive protein. NS, not significant.

Table 3

CORRELATION BETWEEN HIGH MOBILITY BOX-1 PROTEIN (HMGB1)/LIPO-POLYSACCHARIDE-BINDING PROTEIN (LBP) AND THE STUDIED INFLAMMATORY MARKERS.

HMGB1 versus marker	Spearman's r	*P* value	LBP versus marker	Spearman's r	*P* value	IL6 versus marker	Spearman's r	*P* value
LBP	0.028	NS	HMGB1	0.028	NS	HMGB1	0.11	NS
IL6	0.11	NS	IL6	0.662	< 0.001	LBP	0.662	< 0.001
CRP	0.033	NS	CRP	0.695	< 0.001	CRP	0.538	< 0.001

NS, not significant.

Correlations between markers. No correlations were found between HMGB1 and any of the other biomarkers. LBP correlated moderately well with IL6 ($r = 0.662$, $P < 0.001$) and CRP*(*$r = 0.695$, $P < 0.001$). A moderate correlation was found between IL6 and LBP (r = 0.662, $P < 0.001$) and CRP ($r = 0.538$, $P < 0.001$; Table 3).

Diagnostic abilities of HMGB1, LBP, IL6 and CRP in diagnosing sepsis patients. To determine sepsis patients from SIRS patients population in ROC analysis, LBP, IL6 and CRP had quite similar AUC values. IL-6 had the highest AUC of 0.79 ($P < 0.001$), CRP had an AUC of 0.78 ($P < 0.001$), and LBP an AUC of 0.73 ($P < 0.001$) (Fig. 1). The diagnostic cut-off level with the optimal sensitivity and specificity of LBP, IL-6 and CRP are shown in Table 4.

Abilities of HMGB1, LBP, IL6 and CRP in monitoring of the disease process of sepsis patients. The median IL-6 and LBP levels decreased significantly ($P < 0.001$) in sepsis patients group on the second day of the study (Table 5).

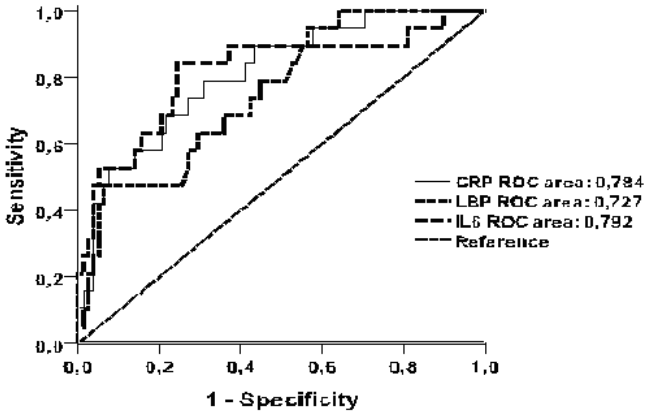

Fig. 1. Receiver operating characteristic curves (ROC) comparing LBP, Il-6 and CRP prediction of sepsis. LBP, lipopolysaccharide-binding proteine; IL-6, interleukine-6; CRP, C-reactive protein. $P < 0.001$.

Table 4

OPTIMUM DIAGNOSTIC CUT-OFF VALUE, SENSITIVITY AND SPECIFICITY OF LBP, IL-6 AND CRP IN DIAGNOSING SEPSIS IN CHILDREN

Variable	Cut-off level	Sensitivity (%)	Specificity (%)
CRP	80.4 mg/L	78.9	64.6
LBP	24.5 μg/ml	78.9	50.8
IL6	44.5 pg/ml	78.9	70.8

LBP, lipopolysaccharide-binding protein; IL -6, interleukin-6; CRP, C-reactive protein

Table 5

LEVELS OF HMGB1, LBP, IL-6, CRP IN SEPSIS PATIENTS GROUPS AT 0 AND 24th HOUR OF STUDY

Variable	Hour of study	Median	IQR	*P* value
CRP	0	137.8	80.8 – 218.4	0.099
	24	125.7	54.1 – 217.5	
IL-6	0	133.0	45.2 – 488.0	< 0.001
	24	25.2	12.8 – 49.1	
LBP	0	38.3	24.6 – 81.2	0.001
	24	32.0	16.9 – 43.5	
HMGB1	0	2.9	1.3 – 5.7	0.836
	24	3.5	1.5 – 4.0	

Wilcoxon test. Data presented as median and interquartile range (IQR). IQR, Interquartile ranges; $P < 0.01$. HMGB1, high mobility box-1 protein; LBP, lipopolysaccharide-binding proteine; IL -6, interleukine-6; CRP, C-reactive protein. NS, not significant.

DISCUSSION

Only a comparatively narrow range of reports have been devoted to SIRS and sepsis in children. Our data broadly correspond to other studies about sepsis development in SIRS patients: 23% (n = 19) of the children we examined with SIRS developed sepsis, accordingly 26% of adults with SIRS developed sepsis in the study by Rangel–Fausto *et al.* (1995), and 23% of children in the Proulx study (Proulx *et al*., 1996). In our patients, SIRS diagnosis was confirmed by combination of fever with tachycardia > 2 SD above the age-normal values in 61% (n = 51) of cases, and this was also observed in 85% of the children in the Carvalho study (Carvalho *et al*., 2005). Fever and breathing rate of > 2 SD above the age-normal value was noted in 53% (n = 45) of cases in our study compared to 48% in the literature (Carvalho *et al*., 2005). The mean age of SIRS patients in our study was 71.3 months, but that of sepsis patients was 94.7 months, whereas the age most frequently mentioned in the literature is 24 months (Carvalho *et al*., 2005), the possible difference arose because we did not have a neonatal patient group — our hospital does not have a maternity ward.

In recent years, HMGB1 has been very intensively investigated as a proinflammatory cytokin. In 1999, *Wang et al.* (1999) found increased levels of HMGB1 in 25 critically ill patients with sepsis. Gaini *et al*. (2007b) maintained that

HMGB1 levels failed to discriminate between patients with infection and those without infection, but HMGB1 levels were significantly higher in patients compared with healthy controls. Similar findings were reported by Sunden-Cullberg *et al*. (2005). Angus *et al*. (2007) found that HMGB1 levels did not differ between those with and without sepsis. One possible explanation for these divergent results could be the different laboratory methods used (Western blot and ELISA). Using ELISA techniques markedly lower HMGB1 levels were found. In our study using an ELISA technique, median HMGB1 levels were 3.5 ng/ml for sepsis patients, which are similar to the lower HMGB1 levels observed in others studies where ELISA technique was used — Hatada *et al*. (2005) observed median HMGB1 levels of 4.5 ng/ml in infected patients, Yasuda *et al.* (2006) measured HMGB1 levels of 7.7ng/ml in infected patients with severe pancreatitis. Gaini *et al*. (2007a) in one of their studies noted median HMGB1 levels of 2.2 ng/ml in sepsis patients, and median levels of 4.3 ng/ml in sepsis patients in their another study (Gaini *et al*., 2007b). Our median HMGB1 levels did not differ significantly between the group of SIRS patients and of sepsis patients. We found no correlation between levels of HMGB1 and levels of the other investigated markers and, for this reason ROC analysis was not conducted for HMGB1 in the diagnosis of sepsis patients. We have several explanations for the above results: our patient population consisted of children, and to date no other study has been conducted in a population of children; patients were less ill compared with patients from intensive care units; HMGB1 is the "late-onset" cytokine and patients in our study were included in comparatively early stage of disease. HMGB1 was not a good indicator in identifying and monitoring sepsis patients. Future studies need to broaden the children population under investigation and to test for their correlation of HMGB1 levels with the disease process.

Elevated LBP levels have been seen in infections caused by Gram positive and negative bacteria both in adult (Blairon *et al*., 2003; Froon *et al*., 1994) and children populations (Ubenauf *et al*., 2007). We found a moderate correlation between LBP and CRP, which concurs with the findings of Gaini *et al*. (2007a) and partly with their findings in their other publication where a strong correlation was found (Gaini *et al*., 2006). We saw a moderate correlation between LBP and IL6, which was also found by Gaini and collegues (Gaini *et al*., 2006). Our LBP levels were significantly higher in sepsis patients — median 38.3 μg/ml compared with median LBP level 25.2 μg/ml in the SIRS group patients. Gaini *et al*. (2006) quoted a median LBP level of 33.5 μg/ml for sepsis patients and 40.4 μg/ml for severe sepsis patients. Our results for LBP levels in sepsis patients corresponded with the results of a study on children with invasive bacterial infections — median LBP levels of 45.0 μg/ml LBP for this group (Gaini *et al*., 2007a). Pavcnik-Arnol *et al*. (2004) found lower LBP concentrations in SIRS patients with sepsis from population of critically ill neonates (27.1 μg/ml) and in children with SIRS without sepsis (10.5 μg/ml). Our results on the LBP ability to diagnose sepsis partly substantiates this sensitivity 79.9% and specificity 50.8%, with a cut-off level of 24.5 μg/ml. In other studies, a cut-off level of 20 μg/ml LBP was associated with 91% sensitivity and 85% specificity (Pavcnik-Arnol *et al.,* 2004); 81% sensitivity and 68.4% (Gaini *at al*., 2006). LBP did not perform perfectly on ROC analysis in its ability to identify sepsis patients, with an AUC of 0.73 which differs from that reported in a study by Pavcnik-Arnol *et al*. (2007): AUC for LBP was 0.97 in neonates aged under 48 h, 0.93 in neonates over 48 h and 0.82 in older children. Our results differ possibly because of the differences in the age groups explored — older children were studied in our hospital which explains why our AUC results were closer to those reported by Pavcnik-Arnol *et al*. (2007) in children not in the neonatal age group. Also, our study did not cover critically ill patients as in other studies.

The levels of the inflammatory cytokine IL6 at the outset were markedly higher in sepsis patients than in SIRS patients. These results match those of other studies on the role of IL6 in differentiation of SIRS from sepsis patients in intensive care units, facial–maxillary surgery, general surgery and neonatal age patients (Mokart *et al*., 2005; Miyoka *et al*., 2005; Silveira *et al*., 1999; Oda *et al*., 2005; Pan *et al*., 2003; Riche *et al*., 2000). The median IL6 level for sepsis patients in our study is similar to the median IL6 levels from Gaini *et al.* (2006) as is the median IL6 for patients with SIRS without sepsis (21 pg/ml and 20 pg/ml, respectively). We found a moderate correlation between IL 6 and LBP which is consistent with findings from the study by Gaini *et al*. (2006). We obtained a cut-off level of 44.5 pg/ml for IL-6, which is relatively close to the results by Silveira *et al*. (1999), who recorded a cut-off of 32 pg/ml for neonatal sepsis diagnosis. In ROC analysis, IL-6 performed the best from our markers, with an AUC 0.79 which is close to results of Groselj-Grenc *et al*. (2007) — AUC 0.776 for acute appendicitis diagnosis in children, and marginally different from AUC results in Pavcnik-Arnol *et al.* (2004) study — 0.67 (mainly the neonatal age group was studied), and their results from the adult population — AUC 0.65 (Gaini *et al.*, 2006).

IL-6 and LPB levels increased significantly in sepsis patients on the second day of study, confirming that IL-6 and LBP are early inflammatory markers, the levels of which decreases sharply if appropriate therapy is initiated (Pan *et al.*, 2003).

In our study, 39% (n = 25) of the SIRS patients and 84% (n = 16) in the sepsis group had elevated PCT levels. Several studies suggest that PCT provides less diagnostic accuracy than previously supposed (Pavcnik-Arnol *et al*., 2004; Thayyil *et al*., 2005; Gaini *et al*., 2006). Our results match the literature data in respect to the correlation between PCT level and the intensity of inflammation. The extent to which the PCT concentration is elevated could possibly be a useful laboratory tool for recognising sepsis patients, because 48% (n = 9) of the sepsis patients, even at the beginning of the illness, had concentrations > 2 ng/ml compared with the SIRS group in which only 14% (n = 9) had a concentration

> 2 ng/ml. These results correspond with those of Hatherill *et al.* (1999) and Rey *et al*. (2007) (patients with localised bacterial infections and sepsis had PCT > 2 ng/ml) and with the data of Guven *et al*. (2002) (significantly elevated changes in PCT in the early stages of disease were indicative of a greater probability that sepsis would develop). In conclusion, the method chosen for PCT detection in our study (for financial reasons) did not fulfill our expectations, the data were difficult to analyse statistically compared with similar data from other studies.

The statistically significant differences in CRP that we observed between SIRS and sepsis patients were also found in other studies (Gaini *et al*., 2006; Kocabas *et al.*, 2007).

During the study for all patients two separate blood cultures were performed, the pathogen was recognised in the blood of only 16% (n = 3) of sepsis patients. We did not further analyse these data.

The strength of our study is the possibility of examining a children population where to date only few studies are done. The study focussed on early sepsis diagnosis in children population using inflammatory markers that have been intensively investigated during recent years. The patients included in our study represented the average population admitted to the Children's Hospital which was in accordance with the aim of our study: to obtain the research results that may be useful in future clinical practice for early sepsis diagnosis by using effective diagnostic markers.

Summarising the above discussion, we can conclude that in early sepsis diagnosis in children, LBP, IL-6, PCT and CRP are probably the superior diagnostic markers, with the best performance by IL6. LBP and IL-6 are the superior markers for monitoring of sepsis patients in dynamics and could be used as indicators for evaluation of initiated empiric therapy. The role of HMGB as an inflammatory cytokine in children has not been thoroughly explored. Our results suggest that HMGB1 does not have a diagnostic value in differentiating sepsis patients from those in the SIRS group. In view of the relatively small number of subjects in the sepsis group, current evidence only allows us to suggest that particular attention should be paid to SIRS patients with elevated levels of the above-mentioned inflammatory indicators. There is a need to find new, specific and sensitive inflammatory markers, as well as combinations of markers, in SIRS patients that will enable sepsis to be diagnosed early.

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DIAGNOSTISKIE MARĶIERI AGRĪNAI SEPSES NOTEIKŠANAI BĒRNIEM AR SISTĒMISKĀ IEKAISUMA ATBILDES SINDROMU

Infekcijas izraisīta sepses joprojām ir viens no vadošiem mirstības cēloņiem bērniem. Liela nozīme sepses mirstības mazināšanā ir prasmei to savlaicīgi atpazīt un agrīni uzsākt terapiju. Jaunākie pētījumu rezultāti liecina, ka tieši sensitīviem un specifiskiem bioķīmiskiem marķieriem ir aizvien pieaugoša loma agrīnā sepses diagnostikā. Pētījuma mērķis – izpētīt *high–mobility group box-1 protein* (HMGB1), lipopolisaharīdus saistošā olbaltuma (LBP), interleikīna 6 (IL-6), prokalcitonīna (PCT), C reaktīvā proteīna (CRP) noteikšanas lietderīgumu agrīnai sepses diagnostikai bērniem ar sistēmiskā iekaisuma atbildes sindromu (SIRS). Prospektīvā pētījumā tika iekļauti 84 bērni ar sistēmiskā iekaisuma atbildes sindromu (SIRS). Sepse tika konstatēta 23% (n = 19) pētījuma pacientu. LBP, IL-6, CRP un PCT līmeņi statistiski ticami bija augstāki sepses pacientu grupā ($P < 0.05$). HMGB1 līmenis abām pacientu grupām nebija statistiski ticami atšķirīgs. Sepses pacientu ROC analīžu rezultāti iekaisuma marķieriem LBP, IL6 un CRP bija pietuvināti($P < 0.001$), tomēr IL6 uzrādīja labāko rezultātu. Mūsu rezultāti norāda, ka iekaisuma indikatorus LBP, IL-6, PCT un CRP var izmantot agrīnai sepses pacientu identificēšanai, IL6 uzskatāms par precīzāko no šiem marķieriem. Sepses pacientu slimības procesa monitorēšanai precīzāki ir LBP un IL-6. Iekaisuma marķierim HMGB1 netika konstatēta diagnostiska nozīme sepses pacientu identificēšanas procesā.