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# Changes in the serum levels of clusterin in children with sepsis

## *Stężenie klusteryny u dzieci z posocznicą*

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ABSTRACT

**Aim:** The first aim of this study was to determine levels of clusterin in pediatric patients with systemic inflammatory response syndrome or septic state, comparing these levels with a healthy population. The second objective was to compare levels of clusterin within individual septic conditions, influence of levels of these proteins on mortality. **Background:** Clusterin is a highly conserved protein which is expressed at increased levels by many cell types in response to a broad variety of stress conditions. **Methods:** Fifty-seven children aged 0–19 years (30 boys and 27 girls) hospitalized from June 2009 to March 2011, with expected or proven SIRS and septic condition. The degree of severity was evaluated according PELOD Score. Blood tests to determine levels of clusterin were taken throughout the patient meets the criteria of SIRS or sepsis. Control group to determine the serum levels of clusterin has been taken from patients undergoing elective surgery. **Results:** We found lower concentrations of clusterin in patients with SIRS or septic state, than in the control group. Clusterin cut-off for first day – D1 was 91.04 μg/ml; AUC 0.900; *p*-value <0.001; for third day – D3 was cut-off 86.73 μg/ml; AUC 0.849; *p*-value <0.001; for fifth day – D5 cut-off was 105.26 μg/ml; AUC 0.755; *p*-value <0.001. Effect of clusterin levels on mortality in the dynamics was recorded significant for 5 days in groups non-survivors/survivors, *p*-value 0.004. **Conclusion:** We have demonstrated a decrease clusterin levels in pediatric patients with septic state, and its effect on mortality.



## Introduction

Sepsis is the most common cause of death in infants and children in the world [1]. The incidence of pediatric sepsis has been recently estimated to be 0.56/1000 children with the highest incidence in infancy at 5.6/1000; overall mortality is 10.6% [2]. Sepsis is a complex, highly variable, multiple system, clinical process induced by pathogens that causes a deleterious, systemic host response [3]. Organ dysfunction is the final tissue sequelae in response to severe sepsis and the ultimate determinant of survival. It has been amply demonstrated that septic hosts who have progressive multiple organ failure are much more likely to succumb to severe sepsis than those who develop a single or no organ dysfunction in response to sepsis [4, 5].

The diagnosis of sepsis and evaluation of its severity is complicated by the highly variable and non-specific nature

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of the signs and symptoms of sepsis [6]. However, the early diagnosis and stratification of the severity of sepsis is very important, increasing the possibility of starting timely and specific treatment [7]. Biomarkers can have an important place in this process since they can indicate the presence/absence or severity of sepsis [8]. One of the potential biomarkers with the chaperone-like activity is clusterin.

### *Clusterin*

The clusterin protein was first discovered more than 25 years ago in rat testis fluid because of its ability to facilitate clustering of a variety of cell types in culture [9]. It is a 75–80-kDa disulfide-linked heterodimeric protein with about 30% of the mass of the molecule comprised of *N*-linked carbohydrate which is branched, complex, and rich in sialic acid [10].

Clusterin is an enigmatic molecule, implicated in diverse biological processes, and has additionally been associated with opposing functions in regard to apoptosis [11]. Possible protective mechanisms are considered by blockage of the terminal complement cascade (C5b-9) or by protecting against oxidative stress [12, 13]. More recent studies show that clusterin may be a secreted chaperone molecule, inhibiting stress-induced precipitation of a very broad range of structurally divergent protein substrates and binding irreversibly *via* an ATP-independent mechanism to stressed proteins to form solubilized high molecular weight complexes [14, 15].

The first aim of this study was to determine levels of clusterin in pediatric patients with systemic inflammatory response syndrome (SIRS) or septic state, comparing these levels with a healthy population. The second objective was to compare levels of clusterin within individual septic conditions, and influence of levels of this protein on mortality.

## Materials and methods

Prospective observational study occurred during the period from June 2009 to March 2011. The study protocol and informed consent approach were approved by the Ethics committee of the University Hospital, Brno. Parents provided informed written consent for their children to participate in this trial. Data were collected and analyzed from fifty-seven consecutive patients with SIRS or septic state who were admitted to the Department of Anesthesia and Intensive Care of the University Children's Hospital Brno, Czech Republic. The most common sources of infection that led to sepsis were the lungs – bacterial and viral infections, and central nervous system – bacterial infections of the brain. Infections, sepsis, severe sepsis, septic shock and multiple organ dysfunction syndrome (MODS) were defined according to commonly used criteria – by International pediatric sepsis consensus conference. The criteria for adult SIRS were modified for pediatric use. Age-specific norms of vital signs and laboratory data were incorporated into the definitions of SIRS. Sepsis was defined as SIRS associated with suspected or proven infection [16]. Patients were categorized into five groups according to their clinical data and to the described definitions: (a) SIRS, (b) sepsis, (c) severe sepsis, (d) septic shock, (e) MODS. In these groups, we compared the difference in the levels of clusterin. The samples from 70 children undergoing elective surgery were used as controls (strabismus surgery, umbilical and inguinal hernia repair), *i.e.* samples from patients without signs of infection. Blood samples were collected before surgery.

Patient data were recorded at the time of diagnosis of SIRS or sepsis, severe sepsis, septic shock and multiple organ dysfunction syndrome and consisted of age, sex, Pediatric Logistic Organ Dysfunction (PELOD), length of hospitalization [17]. PELOD score is a tool which is used to characterize severity of organ dysfunction in critically ill child. Score which is given to each organ will increase according the severity of organ dysfunction so PELOD score can be used to predict severity of organ dysfunction. The PELOD scoring system consists of physical and laboratory variables representing 6 organs, namely nervous, cardiovascular, renal, respiratory, hematologic, and hepatic system [17]. Value of PELOD 12 was taken as the average of the whole set.

Specimens for the diagnosis of infection were obtained as early as possible.

Complete medical history and clinical examination, laboratory parameters, and disease-specific examinations were evaluated.

Blood samples were obtained from a central venous catheter during the first 12 h after the diagnosis SIRS or septic state, or at the beginning of surgery in the control group. For the evaluation of clusterin dynamics, samples were collected at all times when patients meet the criteria SIRS or septic state.

Samples were allowed to clot at room temperature and were centrifuged at 3000 rpm for 10 min. Separated serum was stored at −80 °C until further analysis. Samples were

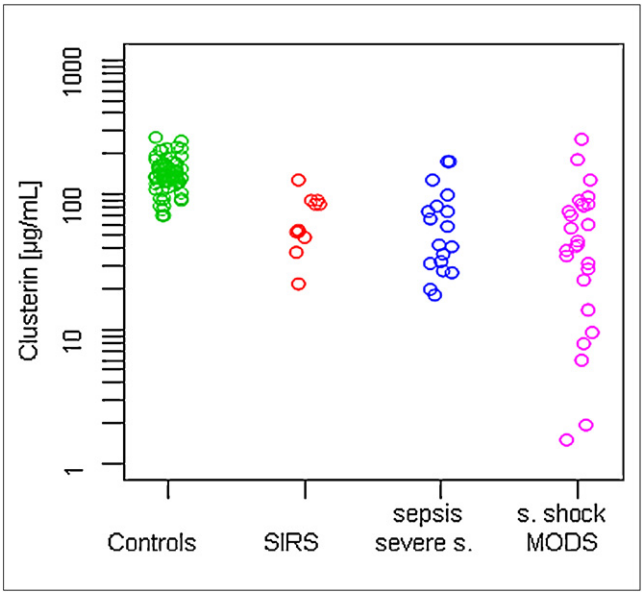


**Fig. 1 – Distribution of clusterin levels in individual septic states. SIRS – systemic inflammatory response syndrome; MODS – multiple organ dysfunction syndrome**