Acute Renal Failure in Septic Children

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Abstract. *Background and objective: Researchers discuss the influence of acute kidney failure on outcomes of septic pediatric patients. The aim of our study was to determine the pathogens of sepsis, prevalence of acute kidney failure (AKF) in septic children, and outcomes depending on the severity of sepsis.*

Materials and methods: Retrospective analysis of medical records data of 206 pediatric patients treated for sepsis at the Hospital of Lithuanian University of Health Sciences Kauno klinikos Department of Children Diseases during the period 2013–2016 years was performed. The patients were divided into 2 groups: group 1 – patients with sepsis, and group 2 – patients with severe sepsis. Patients in the sepsis group had generalized infection complicated by one organ dysfunction. Severe sepsis was diagnosed when sepsis was associated with cardiovascular dysfunction, acute respiratory distress syndrome (ARDS), or dysfunction in two or more other organ systems [1].

Results: 206 pediatric patients (92 girls, 44.7%; 114 boys, 55.3%) aged from 1 month to 18 years were included into the study. N. meningitidis was the prevalent pathogen in blood cultures in both patients groups. Acute kidney failure (AKF) was diagnosed in 22 patients (10.7%): 5 (2.7%) in the sepsis group and 17 (70.8%) in the severe sepsis group ($P < 0.001$). Renal replacement therapy was administered to 9 patients (40.1%). The mortality rate in the study cohort was 10 (4.9%), while the mortality rate in the AKF and severe sepsis group was 7 (41.2%). Patients in the severe sepsis group statistically significantly more frequently were admitted to pediatric intensive care unit (PICU) (95% CI 5.337–306.196, OR 40.424) and had longer duration of hospitalization in PICU (95% CI 1.079–1.299, OR 1.184). The duration in PICU was >5 days (95% CI 4.272–34.956, OR 12.22), causative microorganism N. Meningitidis (95% CI 2.058, 4.272-34.956, OR 2.058).

Conclusions: Streptococcus and Staphylococcus were the leading causative factors in the sepsis group, while N. meningitidis was in the severe sepsis group. Acute kidney failure was more common in the severe sepsis group. The mortality rate in the AKF and severe sepsis group was 41.2% and the mortality rate in the study cohort was 4.9%.

Introduction

Sepsis is an infection complicated by one or more organ dysfunctions [2]. It is a very severe problem among hospitalized children. Prevalence of sepsis in children is still increasing. Bacterial pathogens that cause sepsis are different depending on epidemiology in the country. It has been estimated that 8% of children in pediatric intensive care units (PICU) have severe sepsis [3]. Mortality rates of sepsis in pediatric patients reaches 9.8–30% [4,5]. Early sepsis therapy is associated with reduced mortality [6]. According to the data of Vilnius University Children's Hospital, sepsis was diagnosed in 4% of PICU patients and was responsible for 32% of deaths [7]. A large international study with participation of Kaunas PICU showed overall 8.2% prevalence of severe sepsis in PICU (North America 7.7%, Europe 6.2%, Australia/New Zealand 6.8%, Asia 15.3%, South America 16.3%, and Africa 23.1%) with different mortality rates in this group of patients (21% in North America, 29% in Europe, 32% in Australia/New Zealand, 40% in Asia, 11% in South America, and 40% in Africa) [3]. One of the most common complications in septic children is acute kidney injury (AKI) and one-third of these patients need renal replacement therapy [8, 9]. Sepsis and AKI was observed in 25–71.03% of patients admitted to PICU, depending on the severity of sepsis [5,10]. AKI in septic patients elevates the mortality rate by 6–11 times [5, 11, 12].

The aim of our study was to determine the pathogens of sepsis, prevalence of AKF in septic children, and outcomes depending on the severity of sepsis.

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Materials and Methods

Study Population

Retrospective analysis of medical records data of 206 pediatric patients treated for sepsis at the Hospital of Lithuanian University of Health Sciences Kauno klinikos Department of Children Diseases during the period 2013–2016 was performed. All the patients included into the study had a diagnosis of sepsis defined by the third international consensus for sepsis and septic shock (sepsis-3) [2].

Analyzed Data

The analyzed data were as follows: demographic data (age, gender), hospitalization day after the onset of the disease, percentage of patients admitted to PICU, duration of hospitalization and days in PICU, site of infection and causative microorganisms, comorbidities, and clinical data, i.e., the need for vasoactive drugs, renal function (diuresis, urea, creatinine), number of affected systems, need for renal replacement therapy and its duration and outcomes.

Definitions

Patients included into the study had a diagnosis of sepsis defined by the third international consensus for sepsis and septic shock (sepsis-3) [2]. Kidney function was evaluated by estimated GFR (eGFR) using Schwartz's formula. AKF was defined by decreased of eGFG <90 mL/min/1.73 m^2. Oliguria was defined as diuresis 1–0.5 mL/kg/h, anuria <0.5 mL/kg/h or as complete cessation of diuresis (in normovolemic patient) for a period of 24 h. The patients were divided into 2 groups: group 1 consisted of patients with sepsis, and group 2 consisted of patients with severe sepsis.

Statistical Analysis

The data of the study were processed using SPSS 22.0 (*Statistical Package for Social Science*) software. The significance level of 0.05 was chosen. Parametric Student *t* and nonparametric Mann–Whitney test was used for the comparison of means in independent groups. To evaluate the dependence between qualitative features, χ^2 criterion was used. Depending upon the sample size, accurate and asymptomatic χ^2 criterion was used. For the prognosis, binary logistic regression analysis was performed. ROC (receiver operating characteristics) and AUC (area under the curve) were calculated.

Results

Comparison of Various Characteristics in Sepsis and Severe Sepsis Groups

During the study period, 25 215 children were treated at the Department of Children Diseases. In total, 206 pediatric patients (92 girls, 44.7%; 114 boys, 55.3%) aged 1 month to 18 years were included into the study. Sepsis was diagnosed in 182 patients, severe sepsis in 24 patients. Sepsis patients accounted for 0.72% of all children treated at the Clinic. Severe sepsis patients accounted for 0.01% of all patients. The main characteristics of patients with sepsis and severe sepsis are listed in Table 1.

The patients of the severe sepsis group were admitted to the hospital earlier. For the prognosis of severe sepsis, we calculated that the duration of hospitalization in PICU of 5 days was the limit (ROC test: area under the curve – 79.7%, specificity – 56.5%, sensitivity – 90.4%). The patients in the severe sepsis group statistically significantly more frequently were admitted to PICU and had a longer duration of hospitalization in PICU (Table 2).

Table 1. Characteristics of pediatric patients in sepsis and severe sepsis groups

Variable	Sepsis (n/*n = 182/58)	Severe sepsis (n = 24)	*P* value
Age M ± SD, years	4.3 ± 5.0/3.8 ± 4.8	4.8 ± 5.9	0.662/0.403
Female, n (%)	84 (46.2)/23 (39.7)	8 (33.3)	0.235/0.591
Comorbidities, n (%)	51 (28.0)/16 (27.6)	8 (33.3)	0.589/0.603
Days of hospitalization after the onset of the disease, M ± SD	1.9 ± 2.7/2.0 ± 2.6	0.8± 1.0	0.009/0.044
Admitted to PICU, n (%)	66 (36.3)/30 (51.7)	23 (95.8)	< 0.001/< 0.001
Duration of hospitalization in PICU M ± SD, days	2.3 ± 4.0/2.5 ± 2.3	9.6 ± 14.18/10.0 ± 14.3	< 0.001/0.001
Total duration of hospitalization M ± SD, days	12.0 ± 10.0/14.5 ± 13.2	38.3 ± 55.7	0.117/0.317
Septic schock, n (%)	7 (3.8)/2 (3.4)	23 (95.8)	< 0.001/< 0.001
Need of vasopressors, n (%)	5 (2.7)/2 (3.4)	23 (95.8)	< 0.001/< 0.001
Outcomes (died), n (%)	0	10 (41.7)	< 0.001/< 0.001

*n – in order to increase reliability of the investigation, randomly selected 58 patients from the sepsis group.
M, mean; OR, odds ratio; CI, confidence interval.

Table 2. Logistic regression for association of variables between sepsis and severe sepsis groups

Variable	OR	95% CI	*P* value
Admitted to PICU	40.424	5.337–306.196	< 0.001
Duration of hospitalization in PICU	1.184	1.079–1.299	< 0.001
If duration of hospitalization in PICU > 5 days	12.22	4.272–34.956	< 0.001
N. meningitidis	2.058	1.537–16.651	0.008

Table 3. Site of infection in patients in sepsis and severe sepsis groups

Source of infection	Sepsis (n = 182)	Severe sepsis (n = 24)	*P*
Respiratory tract	35 (19.2%)	4 (16.7%)	0.814
Urinary tract	10 (5.5%)	0 (0.0%)	0.240
Skin	9 (4.9%)	0 (0.0%)	0.264
Neuroinfection	11 (6.0%)	3 (12.5%)	0.270
Gastrointestinal tract	7 (3.8%)	1 (4.2%)	0.645
Bone and joint	2 (1.1%)	0 (0.0%)	0.623
Unclear	108 (59.3%)	16 (66.7%)	0.453

Table 4. Causative microorganism in blood cultures of patients with sepsis and severe sepsis

Microorganism	Sepsis (n = 182)	Severe sepsis(n = 24)	*P*
S. aureus	14 (7.7%)	1 (4.2%)	0.486
Staphylococcus plasma non coagulative	11 (6.0%)	1 (4.2%)	0.693
Streptococcus pneumoniae	15 (8.2%)	0 (0.0%)	0.152
Str. pyogenes	3 (1.6%)	0 (0.0%)	0.623
N. meningitidis	9 (4.9%)	5 (20.8%)	0.004
Other	37 (20.3%)	4 (16.7%)	0.726
No microorganisms	93 (51.1%)	13 (54.2%)	0.783

We did not find any significant difference between 2 groups according to the site of infection (Table 3).

N. meningitidis was the prevalent pathogen in blood cultures in both groups of patients (Table 4). More than 50% of the patients had negative blood cultures.

Comparison of Various Characteristics in Children With Acute Renal Failure in Sepsis and Severe Sepsis Groups

Acute kidney failure was diagnosed in 22 patients (10.7%): 5 (2.7%) in the group of patients with sepsis and 17 (70.8%) in the group of patients with severe sepsis ($P < 0.001$). Causative microorganisms of sepsis in children with ARF are listed in Table 5.

The main characteristics of the patients with acute renal failure (AKF) in sepsis and severe sepsis groups are listed in Table 6. The results show that patients with acute renal failure and severe sepsis statistically significantly earlier were admitted to the hospital, had longer hospitalization, and a higher mortality rate.

AKF correlated with diuresis on the first day in hospital. Diuresis was normal in 8 patients (36.4%) who developed AKF, while 8 (36.4%) had oliguria and 6 (27.3%) anuria ($P < 0.0001$). Nine patients (40.1%) needed renal replacement therapy (RRT): 1 patient needed HD, and 8 patients needed HF. The majority of these patients – 8 (88.9%) – re-

Table 5. Causative microorganisms in blood cultures of children with ARF in sepsis and severe sepsis groups

Microorganism	Sepsis (n = 5)	Severe sepsis (n = 17)	*P*
Staphylococcus plasma noncoagulative	0 (0.0%)	1 (5.9%)	0.58
N. meningitidis	1 (20.0%)	5 (29.4%)	0.69
Other	3 (60.0%)	3 (17.6%)	0.08
No microorganism	1 (20.0%)	8 (47.1%)	0.29

Table 6. Characteristics of patients with acute renal failure in sepsis and severe sepsis groups

Variable	Sepsis (n = 5)	Severe sepsis (n = 17)	*P* value
Gender (female), n (%)	1 (20.0)	6 (35.29)	1.0
Age M ± SD, years	8.4 ± 5.8	4.9 ± 5.9	0.147
Comorbidities, n (%)	3 (60.0)	3 (17.6)	0.1
Hospitalization days after the onset of the disease M ± SD, days	2.0 ± 1.4	0.9 ± 1.1	0.042
Duration of hospitalization in PICU M ± SD, days	1.2 ± 1.6	7.2 ± 7.0	0.031
Total duration of hospitalization M ± SD, days	15.0 ± 9.0	32.5 ± 42.4	0.906
Outcomes (died), n (%)	0 (0%)	7 (41.2%)	0.082

ceived renal replacement therapy on the first day after admission, and 1 (11.1%) on the second day after admission to the hospital. The mean duration of RRT was 5.78 ± 3.90 days. One patient who received RRT died. The common mortality rate in the study cohort was 10 (4.9%), while the mortality rate in the AKF and severe sepsis group was 7 (41.2%) ($P < 0.001$). During the study period, 77 children died in the Clinic, which accounted for 0.3% of all patients treated in the Clinic.

Discussion

There is a lack of information about the influence of acute kidney failure on outcomes of septic pediatric patients. Most of the studies are retrospective and the data vary widely. Our data showed that 10.7% of all septic patients and 70.8% of severe sepsis patients developed AKF. According to Schneider et al., 16% of children in PICU have AKI, but the true prevalence of sepsis with AKI is unknown [13]. A few studies have shown that sepsis is one of the most common causes of AKI, accounting for 11–27% of cases [9,14,15]. AKI has been diagnosed in 19% of septic patients, 23% of severe sepsis patients, and 51% of septic shock patients [16]. Other authors conclude that sepsis and AKI was observed in 25–71% of patients admitted to PICU, depending on the severity of sepsis [5,10]. The results among the studies vary in a high range; thus, it is very hard to find out the true prevalence, and a large well designed multicenter prospective study could answer this question.

We did not find significant differences between sepsis and severe sepsis groups according to gender as other investigators [3].

The most common microorganisms that caused sepsis were *Streptococcus* and *Staphylococcus*. This corresponds to the works of other authors [3, 17]. We noticed a higher incidence of *N. meningitidis* in the severe sepsis group (vs. the sepsis group). According to our colleagues from Vilnius University Children's hospital, *N. menigitidis* was the most common bacteria causing community-acquired severe sepsis [7]. We hope that the vaccination programme could improve this situation in Lithuania. No microorganism was isolated from the blood in more than 50% of septic patients in our study. The extraction of microorganisms from the blood is a great challenge all over the world in pediatric population. A large study performed in 26 countries in 126 PICU (including Kaunas PICU) showed an infection microorganism as a cause of infection in 65% of severe sepsis patients, but only 26% of blood cultures were positive [3]. A multicenter study in Australia and New Zealand showed similar results: in 46.2–50.1% of septic patients, no infectious microorganism was identified [17]. The most common primary site of infection was a respiratory tract infection in our cohort, what is common in other authors' works [3, 5].

Our investigation shows no predominant source of infection in sepsis with AKF. No one microorganism predominated in this group. Riyuzo et al.'s data show that the main cause of sepsis with AKI (84%) was diarrhea and/or pneumonia [18]. Our cohort was not so large to get statistically significant results in this group of patients. The predominant site of infection could be explained by infections and epidemiological peculiarities of the country and the region.

Comorbidities were diagnosed in 28.1–33.3% of children in our study. According to literature, comorbidities such as chronic renal disease, diabetes mellitus, heart failure, malignancy and liver disease increase sepsis-associated AKI [19–22]. Weis et al. diagnosed comorbidities in 47.5% of children with severe sepsis [3]. Other authors found comorbidities in 44–55.8% patients with sepsis and severe sepsis [17]. According to Weiss, comorbidities did not affect PICU mortality, but noticed a higher mortality in patients with solid organ/stem cell transplant, malignancy, renal disease and hematologic/immunologic conditions [3].

Children with sepsis had shorter duration of treatment in PICU and at the hospital than those with severe sepsis. That shows a better condition of these children. The mean duration of treatment in children with sepsis (1.3 days) was shorter than in the cohort of Schlapbach (6.04), but the duration of treatment of severe sepsis was higher in our patients' group (9.6 vs 7.3) [17].

Our data show that 40.1% of children with sepsis and AKF need dialysis. This percentage is comparable with the data of other authors (31.4%) [23]. On the first day after admission to the hospital, 8 of 9 patients received renal replacement therapy; and one patient received it on the second day. Gellespie RS et al's data show that using RRT earlier in the group of patients with sepsis and persisting anuria or oliguria by 24 h may lead to a better survival rate [17]. Thus, we speculate that early initiation of the treatment and renal replacement therapy could be the cause of a better survival of our patients.

According to our data, no one patient died in the groups of sepsis or sepsis with AKF, but in the AKF and severe sepsis group, 41.2% of children had lethal outcomes. Multiple studies show a high incidence of mortality in patients with sepsis and AKI (57–66%), which is much higher comparing with children who have sepsis or AKI alone [24, 25]. Early sepsis diagnosis and therapy are the key for the reduction of mortality [6,7]. Our patients were hospitalized on day 1.9 in the sepsis group, day 2.0 in the severe sepsis group and day 0.9 in the severe sepsis and AKF group. Less than one-third of the patients had comorbidities. Better outcomes of patients could be associated with early sepsis diagnosis and treatment. Better outcomes could be a consequence of fewer comorbidities in our cohort.

Our data show that overall the mortality of children in the severe sepsis group is comparable and reaches 41.7%, while in the uncomplicated sepsis group no children died. A large prospective SPROUT study performed at 128 sites in 26 countries showed that the prevalence of severe sepsis in children who were admitted to PICU was 6–8% in North America, Europe, Australia, and New Zealand, 15.3% in Asia, 16.6% in South America and 23.1% in Africa [3]. The PICU mortality rate in the severe sepsis group varied from 21 to 32% in North America, Europe, Australia, and New Zealand, and was 40% in Africa [3].

Sepsis doubles and triples the odds of death in children [11]. The association of sepsis and AKI increases the risk of death by 11 times [12]. We noticed that the mortality rate in the AKF and severe sepsis group was 41.2% and the mortality rate in the study cohort was 4.9%. We did not evaluate the disability of children that survived. Improving medical care in the world, prevention of septic children against AKI development, and current best-evidence strategies for sepsis treatment may help to decrease the mortality rate in this group.

Conclusions

Streptococcus and *Staphylococcus* were the leading causative factors in the sepsis group, while *N.meningitidis* was the causing factor in the severe sepsis group. Acute kidney failure was more common in the severe sepsis group. The mortality rate in the AKF and severe sepsis group was 41.2% and the mortality rate in the study cohort was 4.9%.

Conflict of Interest

The authors report no conflict of interest.

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