

Sepsis epidemiology and outcome in the paediatric intensive care unit of Vilnius University Children's Hospital

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Research was carried out at the paediatric intensive care unit (paediatric ICU) of the Children's Hospital, affiliate of Vilnius University Hospital Santariškių klinikos.

Background. Being the most common cause of children's death, sepsis is a challenge for most physicians. In order to improve the outcomes, it is important to know the aetiology and peculiarities of sepsis in a particular region and hospital. The aim of this study was to analyse the outcomes of sepsis in a paediatric intensive care unit and their relation with patients' characteristics and causative microorganisms.

Materials and Methods. A retrospective analysis of the Sepsis Registration System in Vilnius University Children's hospital was started in 2012. From 2012 to 2015, we found 529 sepsis cases in our hospital, 203 of which were found to be fulfilling all of the inclusion criteria (patient's age >28 days on admission, taken blood culture/positive PCR test, need for paediatric ICU hospitalization) and were included in the final analysis.

Abbreviations:

ICD – international disease classification

PCR – polymerase chain reaction

Results. Sepsis made 4% of all patients of the paediatric ICU in the period from 2012 to 2015 and caused 32% of deaths in the unit. Paediatric mortality reached 14% of all sepsis cases in our analysis, the majority of them due to hospital-acquired sepsis that occurred in patients suffering from oncologic or hematologic diseases. Another significant part of the patients that did not survive were previously healthy with no co-morbidities. The most common microorganism in lethal community-acquired cases was *N. meningitidis* and in hospital-acquired sepsis – *Staphylococcus* spp. Multi-drug resistance was observed, especially in the cases of hospital-acquired sepsis.

Conclusions. A large percentage of lethal outcomes that occur in the paediatric ICU are due to sepsis. The majority of lethal cases of sepsis occur in patients suffering from chronic co-morbidities, such as oncologic, hematologic, neurologic, and others.

Keywords: sepsis, children, paediatric ICU, outcome, epidemiology

INTRODUCTION

Sepsis is one of the greatest world health problems with the prevalence and death rates increasing every year despite the achievements of intensive care, vaccination, and the abilities of antibacterial therapy, and despite the definition or guidelines being revised or improved (1). In Sepsis-3 International Consensus definitions for sepsis and septic shock, sepsis was described as a life-threatening organ dysfunction due to abnormal body response to infection. Score systems for organ dysfunction (qSOFA and SOFA) were introduced making it easier to identify sepsis as a life-threatening disease in adults (2).

Being the most vulnerable part of the population, paediatric patients require special attention as sepsis is one of the most common causes of children's death due to infection (3). Worldwide escalation of the awareness of sepsis is the key point to early detection and timely antibacterial treatment, which leads to better survival with both good early and late-term outcomes (4).

Sepsis survival depends on timely, appropriate, and optimal antibacterial treatment. In the intensive care unit, the term "the golden hour" was applied as the treatment of critically ill children with sepsis and septic shock and was based upon early recognition and early administration of appropriate antibiotics (5). It is known that a delay in the first antibiotic administration is associated with increased morbidity and mortality (6).

Co-morbidities are another important aspect in surviving sepsis as affected organs are more susceptible to injuries, leading to a worse prognosis. In addition to that, children undergoing chemotherapy or any other immunosuppressive therapy are more prone to opportunistic infections (7). There is a growing evidence for global spread of antimicrobial resistance (8) and it is known that mortality is strongly associated with the growth of bacteria resistance and various co-morbidities (9).

Globally, antimicrobial resistance to Gram-negative microbes is rising faster than resistance to Gram-positive bacteria, and there are no new effective antibiotics against Gram-negative bacteria in the immediate pipeline (10).

Depending on the level of development and healthcare system, different countries have different sepsis tendencies, therefore it is important to

know not only universal, but also local problems and issues regarding the prevalence of microorganisms, especially of multidrug resistant forms as well as the other factors important to sepsis survival (1, 11). This facilitates the optimization of antibacterial and other treatment, which leads to better survival and better late-term outcomes (12).

Supposedly, sepsis-related paediatric deaths are underestimated and it is very important to put more effort to ascertain a more accurate impact of sepsis on childhood mortality worldwide (13). Mortality in paediatric ICUs is not the same in different countries. It may reach values above 50% and varies across geographical regions: 21% in North America, 29% in Europe, 32% in Australia/New Zealand, 40% in Asia, 11% in South America, and 40% in Africa (14, 15).

Our aim was to analyse the outcomes of sepsis in the paediatric ICU of Vilnius University Children's Hospital and their relation with patient's characteristics and causative microorganisms. One-third of critically ill children in Lithuania are treated in the paediatric ICU of Vilnius University Children's Hospital, and all bone-marrow transplantations for children are performed in this hospital.

MATERIALS AND METHODS

We launched the Sepsis Registration System at Vilnius University Children's Hospital in 2012. A total number of 529 sepsis cases were registered using ICD-10 codes during the period of 2012 to 2015.

This study is a retrospective analysis of information found in patients' records (both paper and electronic). Prior to analysis, patient records/information was anonymised and de-identified.

Our inclusion criteria for the final analysis were:

- Patient's age above 28 days on admission;
- Taken blood culture or a positive PCR test;
- Need for paediatric ICU hospitalization.

In total, 203 cases fulfilled all the inclusion criteria and were retrospectively analysed. The paediatric ICU of our hospital provides care for patients with various pathologies, with the exception of cardio-surgical patients. This needs to be noted when analysing differences and similarities of sepsis tendencies in other hospitals.

All statistical analyses were conducted using SPSS for Windows 10.0. Statistical significance was defined as a *p* value <0.05.

RESULTS

There were 5,075 admissions and 91 death cases in the period of 2012 to 2015 in the paediatric ICU. Four percent of all the paediatric ICU admissions were due to sepsis and even 32% of deaths that occurred in the paediatric ICU were due to sepsis. About 70% of cases treated in the paediatric ICU were cases of community-acquired sepsis in previously healthy children (Fig. 1). In comparison, most of the hospital-acquired sepsis cases were a complication of immunosuppressive therapy in oncologic or hematologic patients (24% of all the paediatric ICU sepsis cases), whereas other patients with hospital-acquired sepsis were suffering from such neurologic co-morbidities as cerebral palsy, from congenital abnormalities, or others (Fig. 2).

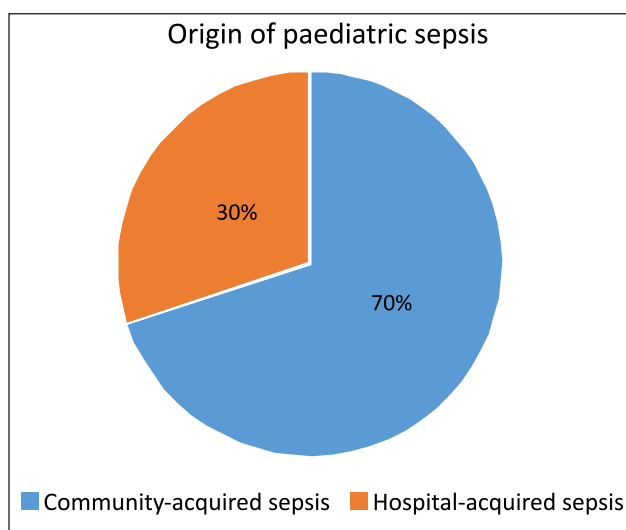


Fig. 1. Sepsis in the paediatric ICU

The median age for septic patients treated in paediatric ICU was 2.4 years (due to uneven distribution, average value was not measured), most of them being male. The average length of hospitalization was 16.1 days, while 2.25 days were averagely spent in the paediatric ICU. More characteristics of sepsis patients can be seen in the Table.

Blood culture samples and PCR tests helped confirming the aetiology of 61%, or 126, of sepsis cases. A total number of 34 different species of microorganisms were identified. A number of blood culture tests contained several microorganisms, especially in the blood culture samples of the hospital-acquired-sepsis group. Due to that the average number of 1.1 and 1.56 microorganisms per one community-acquired sepsis and hospital-acquired sepsis blood culture test were found.

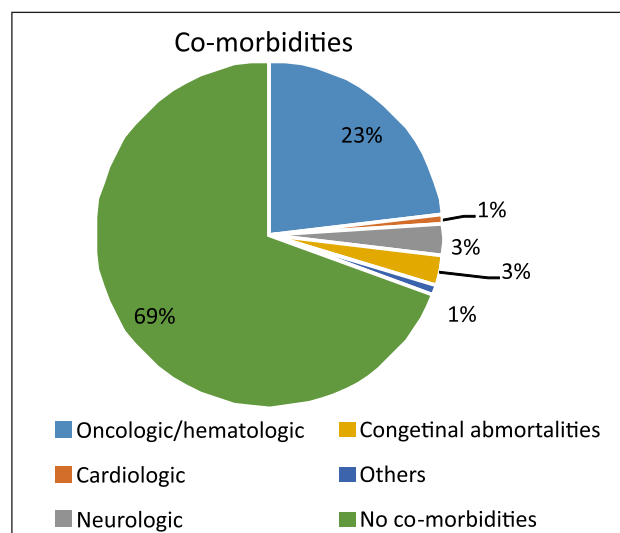


Fig. 2. Co-morbidities

Table. Characteristics of sepsis patients

	All patients	Community-acquired sepsis	Hospital-acquired sepsis	Lethal cases
Total	203	142	61	29
Age, median (years)	2.4	1.4	2.2	3.7
Sex, M:F	1.5:1	1:0.7	1:1	1.2:1
Length of stay in-hospital mean, days	16	13.5	50.2	15
Length of stay in the paediatric ICU mean, days	2.2	1.7	8.5	4
Lethal cases, N	29	13	16	
Case fatality, %	14	9	28	100

The most common sepsis-causing microorganism was *Staphylococcus* spp., as well as *N. meningitidis*, *Streptococcus* spp., and others. Some differences were noticed in different patient groups when it came to causative microorganisms. *Staphylococci* and other *cocci* were responsible for most of the cases of hospital-acquired sepsis (Fig. 3), whereas *N. meningitidis* was the most common bacteria causing community-acquired sepsis (Fig. 4). Gram-negative rods were responsible for minority of sepsis cases in both patient groups. Significant resistance to antibacterial drugs was noticed in *Staphylococci* and *N. meningitidis*. Almost 37% of all *Staphylococci* were resistant to Meticillin, 18% in community-acquired-sepsis group and 62% in hospital-acquired-sepsis group, respectively; 13% of all of them were resistant to Vancomycin. Only 9% of *N. meningitidis* were susceptible to Penicillin.

About 86% of sepsis cases in the paediatric ICU were treated successfully with good outcomes. A statistically significant difference was found when analysing sepsis outcomes in different patient groups ($p < 0.05$). Almost 91% of patients with community-acquired sepsis survived, in comparison with 82% of patients with hospital-acquired sepsis (Fig. 5).

A total number of 29 lethal outcomes of sepsis were registered during this period, most of them (38%) at the age of 1–8 years with median age of 3.75 years (the average value was not measured due to uneven distribution), male being the dominant sex.

More than half of lethal cases were seen in patients with hospital-acquired sepsis, the majority of them suffering from oncologic or hematologic co-morbidities (45%). Other patients were also

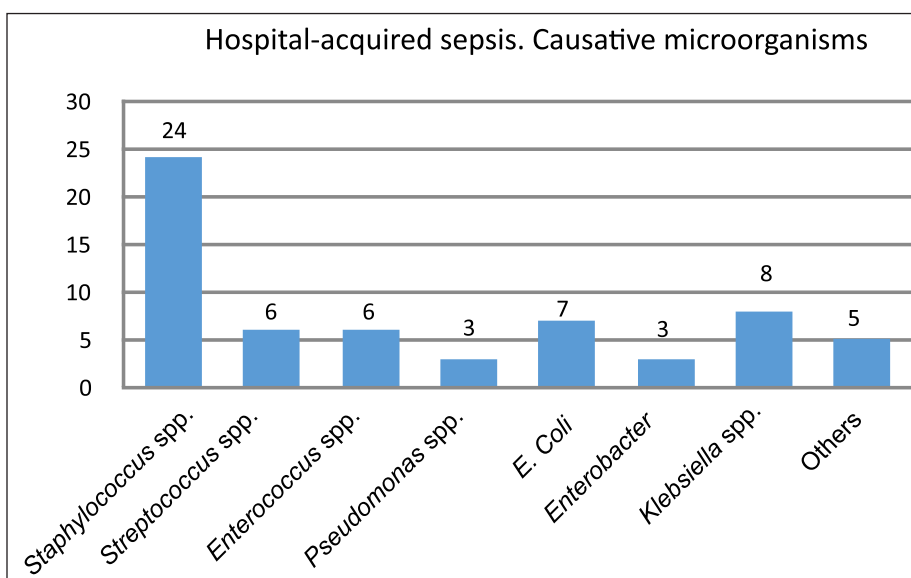


Fig. 3. Hospital-acquired sepsis. Causative microorganisms

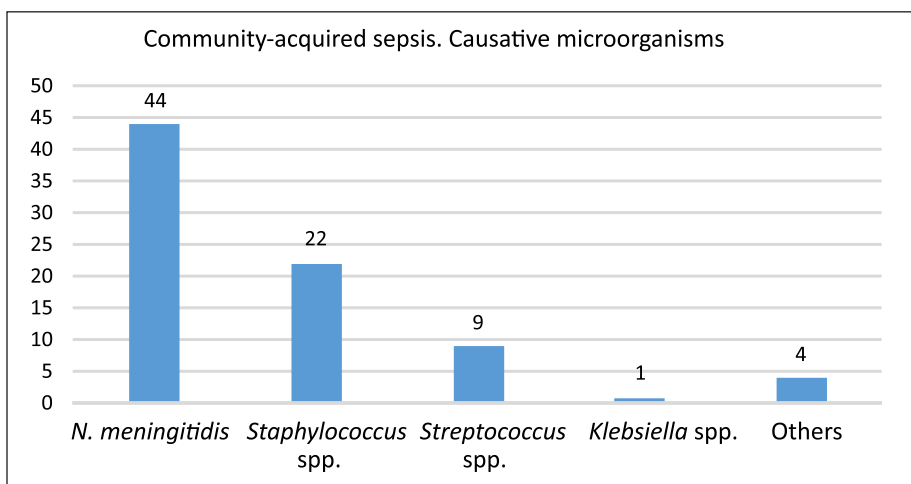


Fig. 4. Community-acquired sepsis. Causative microorganisms

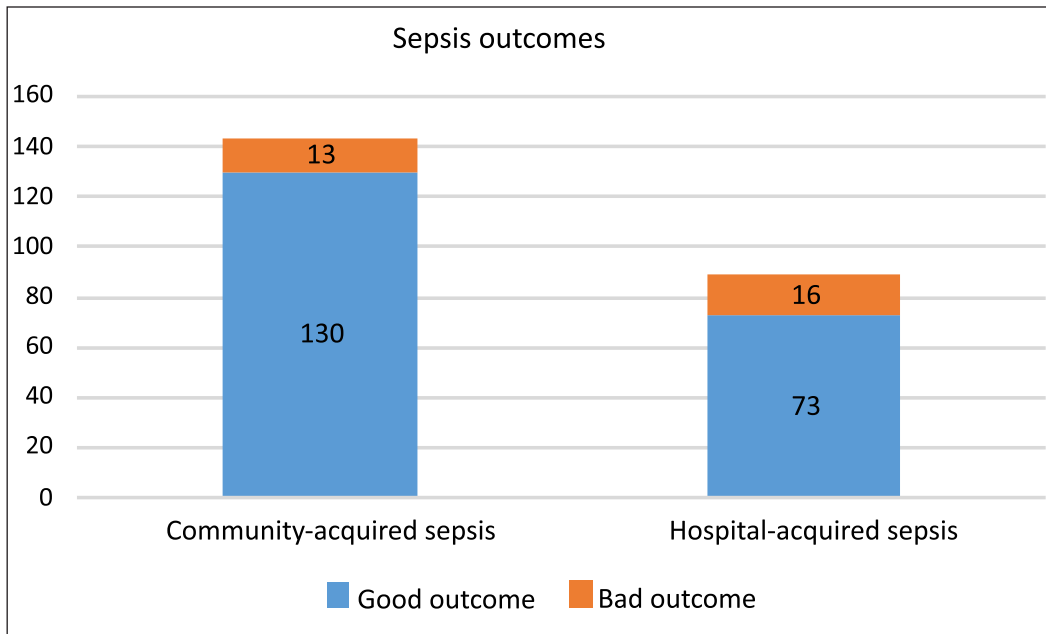


Fig. 5. Sepsis in the paediatric ICU. Outcomes

suffering from different neurological conditions or had various congenital abnormalities. More than 40% of lethal outcomes occurred in previously healthy children with no co-morbidities (Fig. 6). The average length of hospitalization in lethal cases was 15 days, 4.0 days were averagely spent in the paediatric ICU.

The most common causative microorganisms in the cases of lethal sepsis were *Staphylococcus* spp. and *N. meningitidis*; 12% of the cases were found to be caused by multiple microorganisms. Most of lethal outcomes in the community-acquired-sep-

sis group were due to fulminant meningococemia, whereas the most common causative microorganism of lethal sepsis was *Staphylococcus* spp. in the hospital-acquired-sepsis group.

Significant resistance to antibacterial drugs was observed. A great number of *Staphylococci* were seen to be Meticillin- or even Vancomycin-resistant. Even 40% of all lethal cases caused by *Staphylococcus* spp. were resistant to Meticillin: 0% in the cases of community-acquired sepsis and 50% in the cases of hospital-acquired sepsis, respectively.

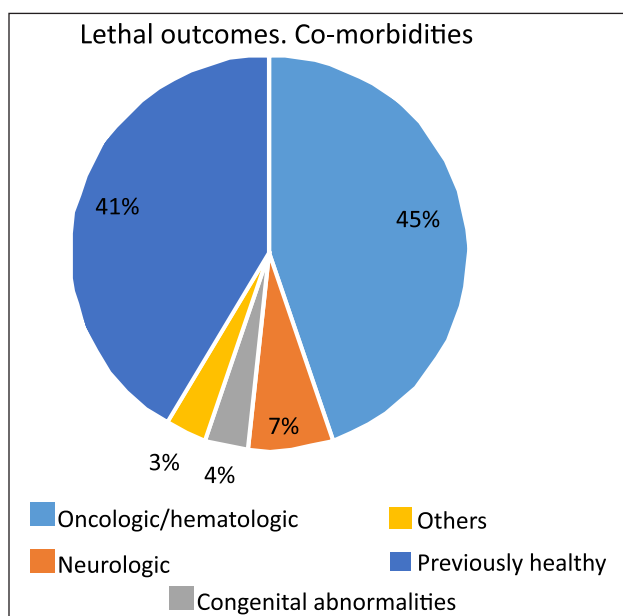


Fig. 6. Lethal outcomes. Co-morbidities

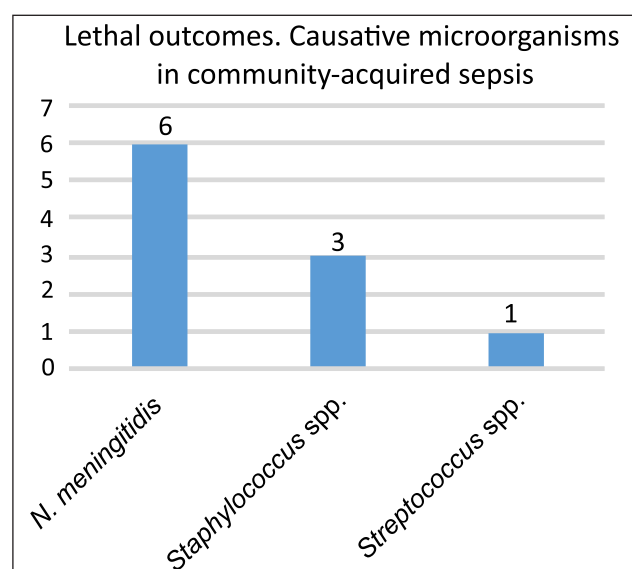


Fig. 7. Lethal outcomes. Causative microorganisms in hospital-acquired sepsis

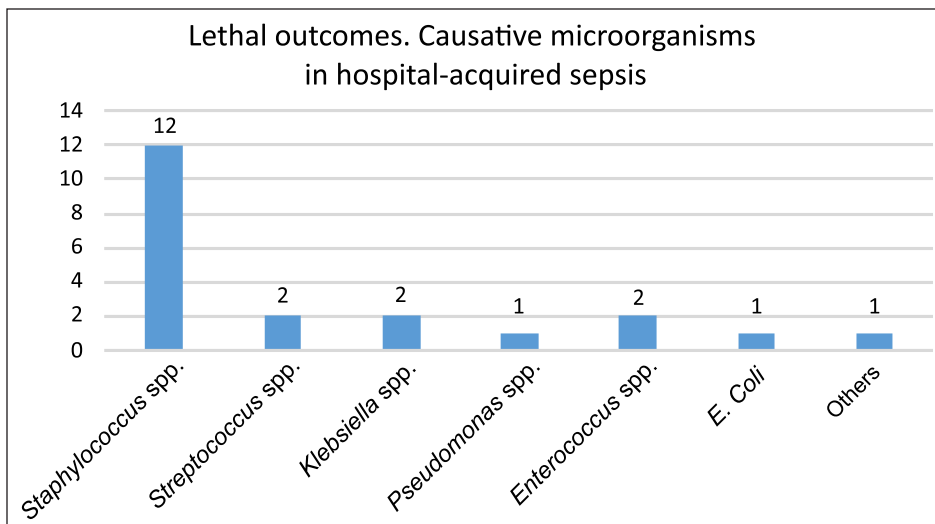


Fig. 8. Lethal outcomes. Causative microorganisms in community-acquired sepsis

DISCUSSION

Sepsis was diagnosed in 4% of all the patients in the paediatric ICU and was responsible for 32% of deaths. Paediatric mortality reached 14% of all the sepsis cases in our analysis. The outcomes of paediatric sepsis are seen to be of great variability, ranging from 3% to 29% (16).

The majority of lethal outcomes were due to hospital-acquired sepsis that occurred in patients suffering from oncologic or hematologic diseases, similarly to the data from Weiss et al., where the highest mortality (37.7–48.2%) was seen in patients with solid organ/stem cell transplants, malignancies, renal diseases, and hematologic/immunologic conditions (17). Another significant part of the patients that did not survive were previously healthy with no co-morbidities, mostly due to fulminant meningococemia, where mortality reached 13%. The age of the patients with lethal outcomes is also seen to be younger in most studies (18).

In our study, the most common microorganism causing hospital-acquired sepsis was *Staphylococcus* spp., whereas *N. meningitidis* was most common in community-acquired sepsis. At this time, Gram-positive infections are more frequent than Gram-negative sepsis in most prospective studies (19). The meningococcal disease remains a devastating cause of epidemic meningitis and sepsis worldwide, especially among children and young adults (20). Our findings were similar to the data from Ruth et al., where *Staphylococcus* species were the most commonly coded causative organisms for paediatric sepsis (21).

Significant multi-drug resistance was observed, especially in hospital-acquired sepsis cases. Most of the *N. meningitidis* were non-susceptible or resistant to the Penicillin group antibiotics, whereas most of *Staphylococci* were seen to be Meticillin- or even Vancomycin-resistant.

The most frequent sepsis-causing pathogens *Escherichia coli* and *Staphylococcus aureus* are characterized by the development of increasing antibiotic resistance for which initial empirical antibiotic therapy might fail (22). Our analysis has some limitations, for instance, paediatric patients from the cardio-surgical paediatric ICU ward were not included in our analysis which makes our data incomplete.

CONCLUSIONS

Sepsis accounted for about 4% of all the patients of the paediatric ICU in the period of 2012 to 2015 and caused 32% of deaths. Paediatric mortality reached 14% of all sepsis cases in our analysis, the majority due to hospital-acquired sepsis that occurred in patients suffering from oncologic or hematologic diseases. Another significant part of the patients that did not survive were previously healthy with no co-morbidities. The most common microorganism in lethal community-acquired cases was *Neisseria meningitidis* and in hospital-acquired sepsis *Staphylococcus* spp. Significant drug resistance was observed, especially in the cases hospital-acquired sepsis.

Received 23 March 2017

Accepted 1 June 2017

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SEPSIO EPIDEMIOLOGIJA IR IŠEITYS VILNIAUS UNIVERSITETINĖS VAIKŲ LIGONINĖS VIT SKYRIUJE

Santrauka

Tikslas. Sepsis – viena dažniausių vaikų mirties priežasčių dėl infekcijos. Tai yra iššūkis kiekvienam gydytojui. Diagnozuojant ir gydant sepsį svarbu žinoti ne tik bendras šios ligos ypatybes, bet ir atskirų rajonų, ligoninių, skyrių ypatumus. Mūsų tyrimo tikslas – išanalizuoti VIT skyriuje gydytų vaikų sepsio atvejus bei jų išeičių sąsajas su pacientų charakteristikomis ir sukėlėjais.

Medžiaga ir metodai. Atlikome retrospektyvią Sepsio registravimo sistemos, įkurtos 2012 m., analizę. Užfiksuoti 529 sepsio atvejai, registruoti naudojant TLK-10 kodus 2012–2015 m. Atvejai (203), atitikę įtraukimo kriterijus (amžius per 28 dienų, paimtas

kraujo pasėlis ar teigiamas PGR tyrimas, hospitalizacija į VIT), dalyvavo galutinėje analizėje.

Rezultatai. Dėl sepsio į VIT skyrių 2012–2015 m. hospitalizuoti asmenys sudarė 4 % visų VITS pacientų, tačiau šis susirgimas buvo priežastis net 32 % VITS mirčių. Mirtingumas dėl sepsio siekė 14 %, daugiausia dėl LŠ atvejų, nustatytų pacientams, sergantiems sunkiomis gretutinėmis onkologinėmis ir hematologinėmis ligomis. Dažniausiai mirtimi pasibaigusius sepsio atvejus BŠS pacientų grupėje sukėlė *N. Meningitidis*, o LŠ grupėje – *Staphylococcus* spp. Matomas ryškus atsparumo antimikrobiniams vaistams didėjimas, ypač – LŠ atvejais.

Išvada. Sepsis nulemia didelę dalį mirties atvejų VIT. Didžiausią dalį sudaro pacientai, sergantys lėtinėmis gretutinėmis ligomis: onkologinėmis, hematologinėmis, neurologinėmis ir kt.

Raktažodžiai: sepsis, vaikai, VIT, išeitys, epidemiologija