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SEVERE SEPSIS – CLINICAL MANIFESTATIONS AND PHARMACO-ECONOMIC ANALYSIS IN AN INTENSIVE CARE UNIT IN LATVIA

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Sepsis is widespread among hospitalised patients worldwide. In fact, severe sepsis and septic shock is a major cause of patient admission and mortality in intensive care units and the difficulty in diagnosing the initial stage of the disease is a major obstacle to the reduction of mortality from sepsis. Retrospective analysis of medical records of 72 patients was carried out within the framework of the study. The study included patients of both sexes and all ages, who were hospitalised at the stationary "Gaiļezers" of the Rīga East Clinical University Hospital from 2011 to 2014. The study aim was to determine the clinical course of treated septic patients and conduct a pharmaco-economic analysis. In the course of the disease, almost half of the patients — 34 (48.6%) showed development of septic shock. Mortality in these patients exceeded a half (60.0%; 21 patients). Artificial lung ventilation during hospitalisation was received by 43 (59.7%) of patients. Artificial lung ventilation had been required in a significantly larger number of cases in the dead patient group (75%, p *= 0.01). The average costs per one patient day (including bed-day price and manipulation costs) was 383 euros. Septic shock was associated with high mortality. Severe sepsis is an expensive diagnosis, as the average cost of one patient exceeds costs of other departments by 4.5 times.*

Key words: *septic shock, antibiotic therapy, Surviving Sepsis Campaign guidelines, sepsis mortality.*

INTRODUCTION

Sepsis is a global problem and carries a high risk of mortality. Studies have shown that more than one-third of sepsis patients treated in an intensive care unit die. The primary cause of death due to infection is sepsis, despite the advances made in medicine, such as vaccination, antibacterial treatment options, and acute patient care.

A. Kumar's survey shows that each hour without antibacterial therapy for patients with septic shock increases mortality by 7.6% (Kumar *et al*., 2006). When a patient enters the emergency department with severe sepsis diagnosis, the risk of mortality for the patient is 6 to 10 times greater than in those with acute myocardial infarction.

The number of patients hospitalised with sepsis has exceeded the number of cases of myocardial infarction (Yeh *et al*., 2010). Also, the number of death cases of sepsis exceeds the total number of death cases due to prostate cancer, breast cancer, and the acquired immune deficiency syndrome (AIDS).

The increase in incidence of sepsis might be due to poor socio-economic conditions, greater awareness of the diagnosis, its detection, aging of the population, and the presence of chronic diseases. A great role is played by surgical intervention, widely useable invasive procedures, immunosuppressive and chemotherapeutics, and the expansion of microorganisms resistant to anti-bacterial therapy.

Sepsis is also one of the most expensive diagnoses in the world, representing a significant health burden; the annual costs in the USA in 2011 were more than 20 billion dollars. And the costs are rising on average by 11.9% each year (Torio and Andrews, 2011). In Germany, the average direct costs/patient amounted to 27 467 euros; the total costs are estimated at approximately 7.7 billion euros. In the United States it is estimated that early diagnosis of sepsis and evidence-based therapy could reduce the number of deaths by 92 000 per year and reduce hospital costs by more than 1.5 billion (Shorr *et al*., 2007).

The aim of the study was to determine the clinical course of treated septic patients and conduct a pharmaco-economic analysis.

MATERIALS AND METHODS

Retrospective analysis of medical records of 72 patients was carried out, stratified by year of treatment outcome (dead/alive). The study included both sexes and all ages of patients who were hospitalised at the Rīga East Clinical University Hospital "Gaiļezers" in the period 2011 to 2014. All patients involved in the study had severe sepsis and at least one organ dysfunction. In all cases the included medical history was validated.

The patient costs were calculated according to data obtained by the Statistics Department of the Rīga East Clinical University Hospital "Gaiļezers", which included the price of bed days and manipulation costs. The bed-day price was calculated according to the therapeutic department rate of 57 euros per one bed-day/24 hours. However, on average one patient of 72 patients involved in the study spent 9.4 days in the intensive therapy unit (sepsis clinic), where the price of one bed-day is 259 euros. Therefore, the standard bed-day price should be multiplied by at least 4.5. The bed-day price includes the necessary medication minimum set by Regulation No. 220 of the Cabinet of Ministers of the Republic of Latvia (Anonymous, 2007).

The medication costs were calculated from the medical records of each patient, which documented medication received at the sepsis clinic. The medication costs were obtained from the closed-type pharmacy Rīga East Clinical University Hospital "Gaiļezers".

The research has been carried out with the approval of the Ethics Committee of the Rīga East Clinical University Hospital "Gaiļezers".

Statistical methods. Data was described using means with standard deviations (SD) and median with interquartile range (IQR) for continuous variables and percentages for categorical variables. Non-parametric methods were used for the comparison of data: Mann-Whitney U for continuous data and chi-square tests for categorical data. A p value less than 0.05 was accepted as statistically significant. The statistical analysis was conducted using the SPSS (Statistical Package for the Social Sciences) (22.0 version) software.

RESULTS

Of the patient group, 40 (55.6%) were men and 32 (44.4%) were women. The age of patients ranged from 22 to 90. Patient data on admittance to the main hospital are summarized in Table 1.

Distribution of age groups is given in Figure 1. The average age was 63.4 years (Table 1).

The average duration of patient illness and hospitalisation time was 5.6 days or median 3.0 (IQR 2.0 to 5.0) days (Table 1).

In the prehospital stage, no patients had received antibiotic therapy.

Average procalcitonine levels at admittance to the hospital was 35.4 ng/ml, and only 3 (4%) patients had a normal level (norm 0 to 0.05 ng/ml).

Upon admittance to the hospital, the procalcitonine rate for patients who died was greater than in the survivors, respectively, 44.5 ng / ml and 29.1 ng / ml ($p = 0.018$). (Fig. 2)

The average duration of treatment at the sepsis clinic was 9.4 days; median 7.5 (IQR 4.0 to 13.8) days. The clinical course of severe sepsis patients is summarised in Table 2.

Respiratory system dysfunction was the most common (48 patients, 66.3%), followed by renal dysfunction (25 pa-

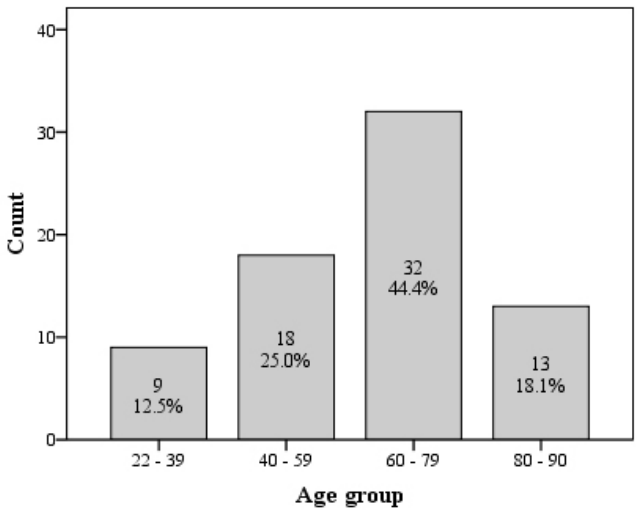

Fig. 1. Severe sepsis development in relation to age.

Table 1

PATIENT DATA IN THE EVENT OF A HOSPITAL

Parameter	Total n = 72	Treatment outcome		*p*
		dead n = 36	alive n = 36	
Send to the hospital, n (%)				
medical emergency	65 (90.3%)	34 (52.3%)	31 (47.7%)	0.429
referral	7 (9.7%)	2 (28.6%)	5 (71.4%)	
Sex, n (%)				
men	40 (55.6%)	17 (42.5%)	23 (54.5%)	0.155
women	32 (44.4%)	19 (59.4%)	13 (40.6%)	
Age, years				
average (SD)	63.4 (15.9)	67.8 (14.4)	59.0 (16.3)	0.012
median (IQR)	65.0 (56.0–75.0)	72.0 (60.3–78.8)	58.5 (49.0–71.7)	
Disease duration before hospitalization, days				
average (SD)	5.6 (8.2)	7.0 (11.0)	4.2 (3.0)	0.864
median (IQR)	3.0 (2.0–5.0)	3.0 (2.0–5.0)	4.0 (2.0–5.0)	
Procalcitonine occurrence, ng/ml				
average(SD)	35.4 (49.8)	43.3 (51.8)	27.5 (47.2)	0.018
median(IQR)	16.0 (4.4–42.4)	23.9 (6.9–59.4)	12.5 (1.0–36.2)	

SD, standard deviation IQR, interquartile range

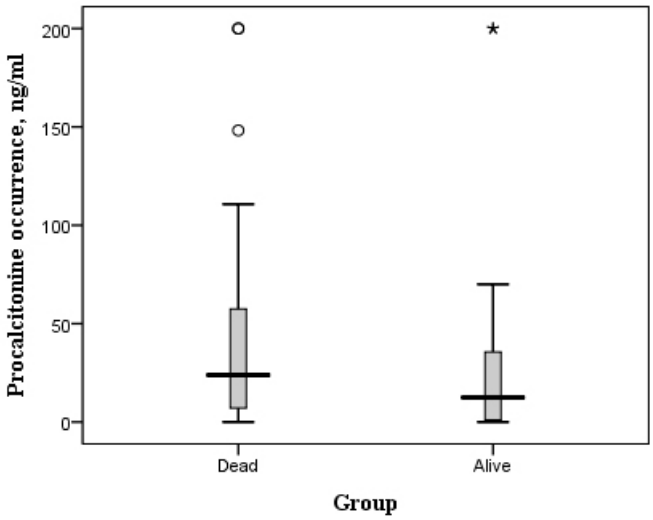

Fig. 2. Procalcitonine concentration in association with the outcome of the disease.

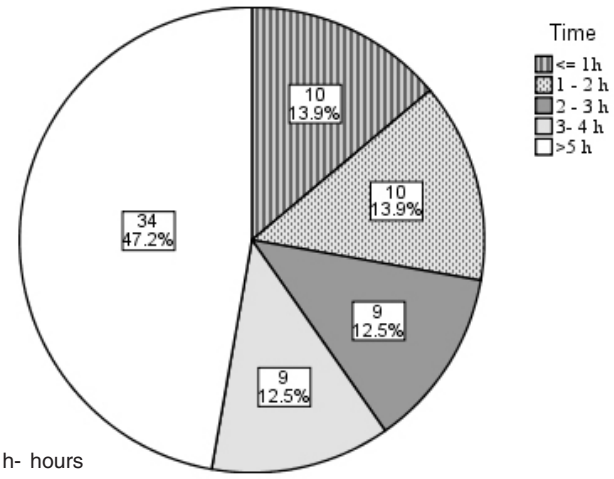

Fig. 3. Antibacterial therapy start-up time (h) since admittance to the stationary.

tients, 34.4%). This organ dysfunction developed in the intensive care unit.

Artificial lung ventilation during hospitalisation was received by 43 (59.7%) of patients, and the renal replacement therapy by 13 (18.1%) patients. Both mechanical ventilation and renal replacement therapy were needed for 11(15.2%) patients. In the dead patient groups, artificial lung ventilation was required significantly more cases, (75%, $p = 0.01$); renal replacement therapy was received by 25% ($p = 0.12$) (Table 2).

Septic shock was observed in 34 (48.6%) patients and 21 (60.0%) of them died (Table 2).

Microbiological plating of urine was positive in 11 (15.3%) patients; the most common agents in plating was *E. coli* and Staphylococci. Plating of blood was positive in 32 (44.4%) patients. The *Streptococcus pneumoniae* Ag test was positive in 17 (23.6%) patients (Table 2).

During the first hour of admittance in the hospital, antimicrobial therapy was received by 10 (13.9%) of the patients (Fig. 3). Among patients receiving antibiotic therapy after 5 hours, 19 (55.9%) died (Fig. 4).

The most common final clinical diagnosis was pneumonia (34 patients, 47.2%), followed by intra-abdominal infection (16 patients, 22.2%), sepsis of unspecified aetiology (6 patients, 8.3%), complex soft tissue infections (5 patients,

Table 2

SEPTIC PATIENT CLINICAL COURSE

Parameter	Total n = 72	Treatment outcome		*p*
		dead n = 36	alive n = 36	
The number of bed days ITU (sepsis clinic)				
average(SD)	9.4 (6.9)	9.9 (8.5)	9.0 (4.8)	0.607
median (IQR)	7.5 (4.0–7.5)	7.0 (2.0–16.5)	8.0 (5.0–11.5)	
Artificial lung ventilation, n (%)				
yes	43 (59.7%)	27 (62.8%)	16 (37.2%)	0.008
no	29 (40.3%)	9 (31.0%)	20 (69.0%)	
Artificial lung ventilation, days				
Average(SD)	7.4 (7.4)	8.2 (8.6)	6.1 (4.8)	0.830
median (IQR)	6.0 (2.0–12.0)	6.0 (2.0–12.0)	5.5 (2.3–8.5)	
Renal replacement therapy, n (%)				
yes	13 (18.1%)	9(69.2%)	27 (45.8%)	0.126
no	59 (81.9%)	4 (30.8%)	32 (54.2%)	
Renal replacement therapy, days				
average(SD)	3.1 (1.7)	2.9 (1.6)	3.6 (1.9)	0.518
median (IQR)	3.0 (1.8–5.0)	3.0 (1.5–4.0)	5.0 (1.5–5.0)	
Septic shock, n (%)				
yes	35 (48.6)	21 (60.0%)	14 (40.0%)	0.099
no	37 (51.4)	15 (40.5%)	22 (59.5%)	
Plating of urine, n (%)				
positive	11 (15.3)	4(36.4%)	7(63.6%)	0.326
negative	61 (84.7)	32 (52.5%)	29 (47.5%)	
Blood plating n (%)				
positive	32 (44.4)	15 (46.9%)	21 (52.5%)	0.635
negative	40 (55.6%)	17 (53.1%)	19 (47.5%)	
Streptococcus pneumonia Ag test, n (%)				
positive	17 (23.6%)	8(47.1%)	9(52.9%)	0.781
negative	55 (76.4%)	28 (50.9%)	27 (49.1%)	
A/b initiation, hours				
average(SD)	8.2 (21.8)	9.1 (20.3)	4.6 (7.8)	0.564
median (IQR)	3.5 (1.7–5)	4.0 (2.0–5.0)	12.5 (1.0–36.2)	

SD, standard deviation
IQR, interquartile range
A/b, antibacterial therapy

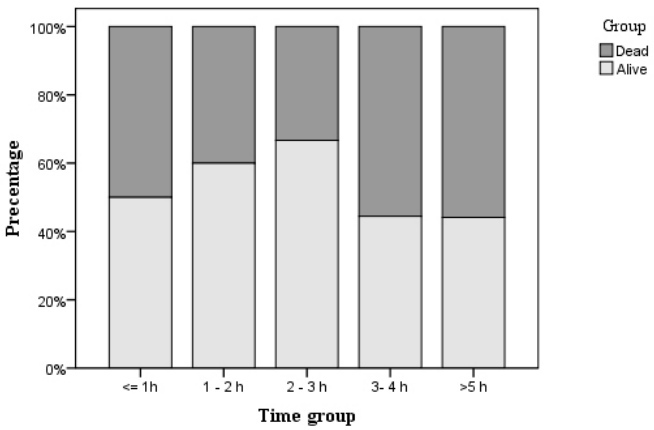

Fig.4. Antibacterial therapy in association with mortality.

7.0%), tumour (3 patients, 4.2%), endocarditis (3 patients, 4. 2%), meningoencephalitis (3 patients, 4.2%), and urinary tract infection (2 patients, 2.7%).

According to data obtained by the Statistics Department of the Rīga East Clinical University Hospital "Gaiļezers" the total costs for 72 patients was 160 236 euros which included 71 494 euros for bed-day price, manipulation costs of 70 742 euros and medication costs of 18 000 euros.

The average hospitalisation costs per patient were 2226 (SD 1830) euros, which included 993 (SD 772) euros for bed-days, manipulation costs of 983 (SD 1179) euros and medication costs of 250 euros.

We did not find any significant association between cost and survival (Fig. 5).

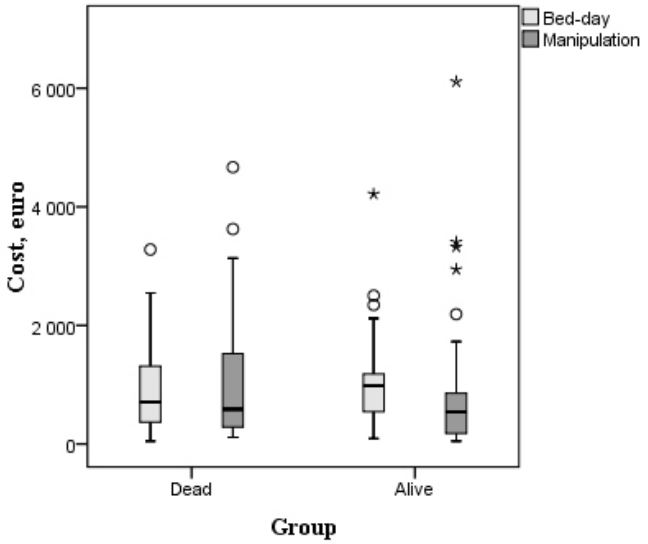

Fig. 5. Costs associated with antibacterial therapy outcome.

The average costs for a one patient day (included bed-day price and manipulation costs) was 383 euros, median 198 (IQR 136 to 378).

DISCUSSION

Sepsis is one of the most frequent reasons for hospitalisation in intensive care units worldwide. Early sepsis detection and timely treatment administration with appropriate antibiotics are the most important factors in improving the outcome of sepsis. However, the initial sepsis clinical signs and symptoms are non-specific, creating the risk of late diagnosis.

Epidemiology. In all countries where the registration of hospital sepsis patients exists, the number is growing. Sepsis is a serious clinical condition resulting from severe infections. In the United States, the annual incidence of sepsis was reported to be 750 000 cases in 2005 and over 1 665 000 cases were reported with high mortality rates as high as 20 to 50 per cent in 2009. In Spain the incidence of severe sepsis and septic shock is 104/100 000 adults and 31/100 000 adults per year with 20.7% and 45.7% hospital mortality, respectively. In the Netherlands, 15 500 cases with severe sepsis and 6000 patients with the septic shock were admitted to hospitals annually. In Asia, in Taiwan a severe sepsis incidence rate was reported — 507/1000 with 45% mortality in 2008. In German hospitals, in the period 2007–2013, sepsis incidence increased by overall 5.7% annually from 200 535 to 279 530 cases. Mortality was 24.3%, resulting in 67 849 deaths per year. Sepsis now ranks third among the causes of deaths in Germany. Sepsis is diagnosed in 1.54% of hospital admissions (Reinhart, 2015). In China (2010), the sepsis mortality rate was 67.5 deaths per 100 000 population, its ranks fourth among the causes of deaths in China (Bin, 2015).

Surviving Sepsis Campaign. The Surviving Sepsis Campaign (SSC) is an international programme that develops guidelines to improve the management of this serious clinical condition and to reduce the high mortality rates. The first SSC guidelines, which were published in 2004, classified the recommendations as a resuscitation bundle including elements for first six hours, and a resuscitation and management bundle including elements for first 24-hour management. The guidelines were renewed in 2008. Many studies revealed that clinical implementation of these bundle elements improve the quality of sepsis care and reduce hospital mortality. In 2012, the SSC 2008 guidelines were updated, and again in 2015; recommendations were classified as ones to be completed within three hours and others to be completed within six hours (Tufan *et al*., 2015). Of note, the 6-hour bundle was updated; the three-hour SSC bundle was not changed.

Elements to be implemented within three hours since the time of presentation were:

1. Measure lactate level;

2. Obtain blood cultures prior to administration of antibiotics;

3. Administer broad spectrum antibiotics;

4. Administer 30 ml/kg crystalloid for hypotension or lactate ≥ 4mmol/L.

The time of presentation is defined as the time of triage in the emergency department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of severe sepsis or septic shock ascertained through chart review.

Elements to be implemented within six hours since the time of presentation were:

5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mmHg;

6. In the event of persistent hypotension after initial fluid administration (MAP 65 mm Hg) or if initial lactate was ≥ 4 mmol/L, re-assess volume status and tissue perfusion and document reassessment of volume status and tissue perfusion with: Repeat focused exam (after initial fluid resuscitation) by licensed independent practitioner including vital signs, cardiopulmonary, capillary refill, pulse, and skin findings. Or two of the following: measure central venous pressure (CVP), measure central venous oxygen saturation (ScvO2), bedside cardiovascular ultrasound, dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge;

7. Re-measure lactate if initial lactate elevated (Dellinger *et al*., 2012; Anonymous, 2014; Levy *et al*., 2014; Yealy *et al*., 2014; Mouncey *et al*., 2015).

Several studies show that, consistent with the guidelines, early initiation of antimicrobial therapy has reduced the duration of hospitalisation of patients and limited the develop-

ment of resistance to antibiotics (Angus and van der Poll, 2013; Van den Bosch *et al*., 2014).

Our study showed that mean antimicrobial therapy start-up time from admittance to the hospital was 8.2 (SD 21.8) hours. During the first hour after admittance to the hospital, antimicrobial therapy was received by 10 (13.9%) of the patients. The gold standard according to the guidelines is the initiation of antimicrobial therapy within one hour from the moment of diagnosing severe sepsis. It should be taken into account that at the time of hospitalisation, sepsis was not developed or proven in all of the patients, since by definition, diagnosis of sepsis is based on a number of physiological indicators and the results of laboratory investigations, as well as the identification of the focuses of infection that caused these modifications. Early initiation of antimicrobial therapy reduces bacterial load and hence the mortality of septic patients.

The role of micro-organisms. Respiratory tract infections, in particular pneumonia, are a major cause of the sepsis, and it is related to higher mortality. Our data showed that in patients with pneumonia (34.5%), the mortality rate was 55.9% (19 patients). Currently, gram-positive microorganisms more frequently suggest sepsis than gram-negative microorganisms. However, a large meta-analysis study reported that gram-negative bacteraemia is associated with higher mortality than gram-positive bacteraemia. Coagulase-negative *Staphylococcus* and *E. coli* were most commonly found in the bloodstream, and were associated with a low mortality rate (20% and 19%), in comparison with Candida species, where the mortality rate was 43% and Acinetobacter species 40%. However, pneumoniae caused by *Staphylococcus aureus* is associated with higher mortality (41%), in comparison with pneumonia caused by *Streptococcus pneumonia* (13%). The highest mortality was associated with *Pseudmonas aeruginosa* (77%). However, more than a half of blood culture from patients with severe sepsis were not positive (Cohen *et al*., 2004). In our study, 55.6% of cases were negative on bacterial plating of blood.

Studies have indicated that older patients, male gender, African Americans, and patients with chronic health problems are particularly prone to the development of severe sepsis, and therefore prevention strategies should be targeted to these groups (Mayr *et al*., 2014). Our data showed that most of the patients were in the age group of 60 to 79 (n = 32.4%) and 20 (62.5%) died. Severe sepsis occurs more often in patients with chronic obstructive pulmonary disease, tumours, chronic kidney, liver diseases, and diabetes. Other risk factors that increase the risk of developing sepsis are long-term care at care establishments, malnutrition, use of immunosuppressive medications, and immunocompromised patients. There have also been reports on the relationship between socioeconomic status and blood stream infection (Mendu *et al*., 2012).

Causes of the severe sepsis and their relative frequency. The most common cause of sepsis is pneumonia (50 to 60% of patients, which is comparable to our data — 34 patients, 47.2%; 95% CI (confidence interval) 36.1% to 58.6%), intra-abdominal infections are found in 20 to 25% (our data — 16 patients, 22.2%; 95% CI 14, 2% to 33.1%), urinary tract infection in 7 to 10% (our data — 2 patients, 2.7%; 95% CI 0.7% to 10.0%), soft tissue involvement, bones, joints in 5 to 10% (our data — 5 patients, 7.0%; 95% CI 3, 0% to 15, 3%), endocarditis in % (our data — 3 patients, 4.2%; 95% CI 1.4% to 11.6%), and meningitis in 5% (our data — 3 patients, 4.2%; 95% CI 1.4% to 11.6%) (Vincent *et al*., 2006). Similar results also were shown in the SOAP study (Sepsis Occurrence in Acutely Ill Patients), which was conducted among 198 intensive care units in 24 European countries; the most common infectious cause of sepsis patients was in the pulmonary system (68%), followed by the localisations in the abdominal cavity (22%), blood (20%) and urinary tract (14%) (Barochia *et al*., 2010).

Diagnostic options. Recently, a number of publications have shown that genetic variation, particularly single nucleotide polymorphism of cytokines in the innate immune system, may affect risk of sepsis. Among these cytokines, interleukin-6 (IL-6) is one of the most important members that may be associated with sepsis risk and outcome. Some studies have indicated that IL-6 may play a key role in the inflammatory response to microbial invasion (Gao *et al*., 2015).

Previous studies showed that a high IL-6 level was associated with increased severe sepsis mortality and risk (Palmiere and Augsburger, 2014).

Extensive investigations into the efficacy of lactate kinetics as a marker for response to resuscitative therapies in septic patients have demonstrated a clear association with clinical outcomes including mortality. However, the majority of studies have focused on the utility during the early phase of sepsis management, with little attention regarding later time periods. Future studies should focus on lactate as a potential prognostic tool for late sepsis management and treatment duration, as increased knowledge in this direction has the potential to direct physicians in their care for septic patients during this understudied time period and improve patient outcomes (Yeh *et al*., 2010).

Procalcitonine also may be associated with sepsis risk and outcome. Our study showed that procalcitonine concentration for the dead patients was greater than for the survivors.

The detection of early sepsis patients is very important. There are a variety of scales that can help to detect early septic patients, such as the modified early warning score (MEWS, Modified Early Warning Score) used for the evaluation of the patient. The criteria are based on evaluation of deviation from the physiological norm. This scale has demonstrated its importance as a screening method in sepsis / severe sepsis diagnostics. In Latvia such scales have not been introduced yet.

If the patient has 4 or more points according to the MEWS, or suspicion of infection, then the probability of the Sys-

temic Inflammatory Response Syndrome (SIRS) should be considered and due to possible accession of sepsis the patient should be evaluated every 30 minutes to provide early diagnosis of possible sepsis (Zavatti *et al*., 2010). Application of this scale would be very useful in the outpatient prehospital stage, as well as at reception, as it would allow to differentiate the potential septic patients. However, there is need of further studies to introduce the following scales. They need to be easy to use and widely applicable before introduction.

A study limitation was the small number of patients, which made it difficult to assess the cost differences and effects of antibacterial treatment.

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SMAGA SEPSE — KLĪNISKĀS IZPAUSMES UN FARMAKOEKONOMISKĀ ANALĪZE INTENSĪVĀS TERAPIJAS NODAĻĀ LATVIJĀ

Pētījuma mērķis bija izvērtēt Rīgas Austrumu klīniskās universitātes slimnīcas stacionārā "Gaiļezers" ārstēto septisko pacientu slimības gaitu un farmakoekonomisko analīzi. Tika veikta retrospektīva 72 pacientu slimību vēsturu analīze, stratifikācija tika veikta pēc terapijas gada un saslimšanas iznākuma. Pētījumā tika iekļauti abu dzimumu un visu vecumu pacienti, kas tika stacionēti Rīgas Austrumu klīniskās universitātes slimnīcas stacionārā "Gaiļezers" no 2011. līdz 2014. gadam. Visas pētījumā iekļautās slimības vēstures tika atzītas par derīgām. Pacientu izmaksas tika aprēķinātas pēc Rīgas Austrumu klīniskās universitātes slimnīcas "Gaiļezers" iegūtajiem statistikas daļas datiem. Dati tika aprakstīti, pielietojot standartnovirzes (SD) un mediāno ar starpkvartiļu amplitūdu. Pētījuma datu salīdzināšanai izmantoja *Mann-Whitney U* un *chi-square* testus. Datu statistiskā analīze tika veikta ar SPSS (22.0 versiju). Apkopojot rezultātus, biežākā pamatdiagnoze pacientiem bija pneimonija — 34 (47.2%). Prehospitālā etapā antibakteriālo terapiju nebija saņēmis neviens pacients. Pirmās stundas laikā no stacionēšanas brīža antibakteriālo terapiju saņēma 10 (13,9%) pacientu. Vairāk kā pusei pacientu 43 (59,7%) bija nepieciešama mākslīgā plaušu ventilācija. Novēroja augstu mirstību — 21 (60, 0%) — pacientiem ar septisko šoku (34; 48,6%). Kopējās 72 pacientu izmaksas sastādīja 160 236 eiro. Smaga sepse un septisks šoks ir biežs iemesls pacientu uzņemšanai un mirstībai intensīvās terapijas nodaļās. Tādēļ ir ļoti nozīmīga agrīna šo pacientu atklāšana un adekvātas terapijas uzsākšana. Sepse ir viena no dārgākajām diagnozēm pasaulē, kas veido nozīmīgu veselības aprūpes slogu.