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PATIENTS WITH SEPSIS IN INFECTIOUS DISEASES DEPARTMENT IN YEARS 1997-2010 – EPIDEMIOLOGY AND CLINICAL FEATURES

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ABSTRACT

INTRODUCTION. Sepsis is a clinical syndrome that complicates severe infection. The incidence of sepsis is increasing worldwide.

AIM of the study was evaluation of demographic data and clinical picture of patients hospitalized in Infectious Diseases Ward with a diagnosis of sepsis and severe sepsis.

MATERIAL AND METHODS The retrospective study included 107 patients with sepsis and severe sepsis hospitalized in 1997-2010.

RESULTS. Sepsis was diagnosed in 48.6% of patients and severe sepsis - in 51.4% of patients. The mortality rate in patients with severe sepsis was 30.9%. Blood cultures were positive in 55.1% cases. Gram-positive bacteria were isolated most frequently – 71.7%. The most common source of infection overall was pneumonia (21.5%). Odontogenic infections (25%) and urinary tract infections (21.2%) dominated in patients with sepsis. 25.2% of patients developed bacterial meningitis.

CONCLUSIONS. Despite advances in diagnostics and treatment sepsis is still a major medical problem with high mortality. Patients with severe sepsis and meningitis should be treated in ICU setting. Decayed teeth should be considered as a potential source of sepsis of unknown origin.

Key words: *sepsis, epidemiology, clinical features, decayed teeth*

INTRODUCTION

Sepsis is a clinical syndrome that complicates severe infection. It is characterized by the cardinal signs of inflammation occurring in tissues that are remote from the infection. The incidence of sepsis is increasing worldwide (1).

In USA the current incidence of sepsis is at least 240 patients per 100,000 people, whereas for severe sepsis it is between 51 and 95 patients per 100,000 people (1).

In Poland it is estimated that ca 53 patients per 100,000 develop severe sepsis annually (2). Severe sepsis remains a serious medical problem and is one of the main causes of death with mortality rate of 30-50%. Patients who survive sepsis also appear to have a persistent decrement in the quality of their life (3).

The main risk factors of sepsis development are age, concomitant diseases (diabetes, malignancy, alcoholism), immunoincompetency (4).

In Poland patients with sepsis are hospitalized either in Infectious Diseases Wards or in ICU in dependence on patients clinical status.

The aim of the study was evaluation of demographic data and clinical picture of patients hospitalized in Infectious Diseases Ward with a diagnosis of sepsis and severe sepsis.

CHARACTERISTICS OF ANALYZED PATIENTS AND METHODS

The retrospective study included 107 patients diagnosed with sepsis and severe sepsis and hospitalized in the Department of Infectious Diseases and Neuroinfections of Medical University in Białystok in years 1997-2010. The Department is a regional reference centre for Central Nervous System infections including bacterial meningitis.

Medical documentation of patients was analyzed with regard to demographic information, physiological variables, comorbidities, laboratory measurements, suspected source of infection and previous antibiotic use. Basing on the available data severity of illness in the form of the sequential organ failure assessment (SOFA) score and Acute Physiology and Chronic Health Evaluation II (APACHE II) score in the moment of patient's admission were counted. In the cases of individual patients referred to the department from other medical centers, available results of basic laboratory tests and cultures received from the medical institution of the prior hospitalization were used.

Sepsis was defined as presence of two or more SIRS criteria: 1) a body temperature greater than 38 °C or lower than 36 °C; 2) a heart rate greater than 90 beats per minute; 3) tachypnea, manifested by a respiratory rate greater than 20 breaths per minute, or hyperventilation, as indicated by a PaCO₂ of less than 32 mm Hg; 4) an alteration in the white blood cell count, such as a count greater than 12 000/cu mm, a count less than 4 000/cu mm, or the presence of more than 10 percent immature neutrophils) and a infectious process (5,6).

Severe sepsis was defined as sepsis complicated by organ dysfunction such as arterial hypoxemia (PaO₂/FIO₂ <300), acute oliguria (urine output <0.5 mL/kg/hr or 45 mmol/L for at least 2 hrs, creatinine increase <0.5 mg/dL, coagulation abnormalities (INR >1.5 or APTT >60 secs), ileus (absence of bowel sounds), thrombocytopenia (platelet count <100,000 /L), hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 mmol/L) (5).

Septic shock was defined as a state of acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes. Hypotension is defined by a systolic arterial pressure below 90 mm Hg, MAP <60 or a reduction in systolic blood pressure of >40 mm Hg from baseline, despite adequate volume resuscitation, in the absence of other causes for hypotension (5).

Statistical analysis was performed using Statistica 8.0 software. Normality was evaluated using Shapiro-Wilk test. Groups were compared by Mann-Whitney test and Chi-squared test. P value <0.05 was considered statistically significant.

The ethics committee approval to conduct this study was not required.

RESULTS

In the total group of 107 patients with sepsis, 64 (59.8%) were male and 43 (40.2%) - female; the mean age was 48.9 years (range: 18-87); 80 patients (74.8%) were inhabitants of towns and 27 patients (25.2%) – in-

habitants of country (tab. I- Demographic and clinical data of analyzed patients).

Sepsis was diagnosed in 52 patients (48.6%) and severe sepsis - in 55 patients (51.4%). In 6 patients the disease was complicated by septic shock (5.6%); 21 patients (19.6%) required ICU treatment. The mortality rate in patients with severe sepsis was 30.9%. None of the patients with sepsis died. In the age group <20 years sepsis was diagnosed in 2 patients (66.6%) and severe sepsis – in 1 patient (33.3%), in the age group 20-40 years – in 14 (48.3%) and 15 (51.7%) patients respectively, in age group 41-60 years – in 21 (45.7%) and 25 (54.3%) patients, in age group >60 years – in 15 (51.7%) and 14 (48.3%) patients. In the age group <20 years none of the patients died, in age group 20-40 years – 3 patients died (10.3%), in age group 41-60 years – 8 patients died (17.4%), in age group >60 years – 5 patients died (17.2%).

Mean duration of hospital stay was 22.7±11.3 days.

The mean SOFA score was 2. In the sepsis group the score ranged from 0 to 2 points, while in severe sepsis group – from 0 to 9 points. The mean APACHE II score at admission was 9.7±6.4. It was significantly higher in the severe sepsis group 13.1±7.2 vs 6.2±2.4.

74 patients (78.72%) had a body temperature higher than 38°C, and 7 patients (7.44%) were hypothermic <36°C. A heart rate greater than 90 beats per minute was observed in 46 cases (48.9%). Leukocytosis greater than 12 000/mm was detected in 68 cases (63.6%), and leucopenia <4 000/mm in 6 episodes (5.6%), the presence of immature neutrophils was detected in 9 cases (8.4%). Mean WBC count was 13,400 cells/mm³ and it was significantly higher in severe sepsis. Mean CRP level was 178.8 mg/l and it was significantly higher in patients with severe sepsis. Mean albumin concentration was 2.9 g/dl and it was significantly lower in patients with severe sepsis. The mean concentration of glucose was 120.1 mg/dl and was nonsignificantly higher in patients with severe sepsis. Aminotransferases activity was significantly higher in patients with severe sepsis.

Mean hemoglobin concentration was 11.1 g/dl and it was significantly lower in patients with severe sepsis.

In 96 patients (89.7%) the infection was community acquired while in 11 (10.3%) it was nosocomial.

Pathological organisms were isolated from blood cultures in 60 cases (55.1%). Gram-positive bacteria were isolated most frequently – 43 (71.7%) followed by Gram-negative bacteria – 16 (26.7%). *Staphylococcus aureus* was the most common pathogen overall – 23 (38.3%); methicillin-resistant *S. aureus* (MRSA) accounted 26% of staphylococcal sepsis.

In 3 cases more than 1 pathogen was isolated. Among 47 patients with negative blood cultures 13 (27.6%) received antibiotics before hospitalization. Table II shows the pathogens isolated from blood cultures of patients with sepsis and severe sepsis.

Table I. Demographic and clinical data of analyzed patients (n=107)

	overall	Sepsis n=52	severe sepsis n=55	p
Mean age (years)	48,9 ±17.5	48,3±17.2	49,4±18.0	0.8
Male	64(59.8%)	34	30	0.34
Female	43(40.2%)	18	25	
Country	27(25.2%)	14	13	0.69
Town	80(74.8%)	38	42	
Community acquired	96(89.7%)	47(90.4%)	49(89.1%)	0.89
Nosocomial	11(10.3%)	5(9.6%)	6(10.9%)	0.89
Response to empiric treatment	66 (61.7%)	42(80.8%)	24(43.6%)	<0.05
Mean duration of hospital stay (days)	22.7±11.3	21.7±10	23.7±12.6	0.29
Duration of fever >38 C (days)	12.9±8.8	13.3±8.2	12.4±9.6	0.55
SOFA score	2.1±2.4	0.5±0.6	3.5±2.6	<0.05
APACHE II	9.7±6.4	6.2±2.4	13.1±7.2	<0.05
Mortality	17(15.8%)	0	17(30.9%)	<0.05
Glucose concentration	120.1±37.4	111.4±25.9	128.5±44.8	0.08
Median WBC count (thousand cells/mm ³)	13.4 (2.34-103)	11.7 (3.8-102)	16.1(2.34-103)	<0.05
Mean HGB (g/dl)	11.1±2.1	11.9±2	10.5±2	<0.05
Mean CRP levels(mg/l)	178.8±121.8	132.4±95.0	226.2±128.7	<0.05
Mean albumin concentration (g/dl)	2.9±0.6	3.1±0.6	2.7±0.7	<0.05
Median ALAT (U/l)	41.0 (7-449)	32 (7-355)	49.5 (12-449)	0.07
Median AspAT (U/l)	39.5 (9-2833)	27 (9-455)	59.5 (13-2833)	<0.05
chronic comorbidities				
Hypertension	22 (20.6%)	11(21.2%)	11(20%)	0.73
Heart diseases	19(17.8%)	8(15.4%)	11(20%)	0.5
Autoimmunological diseases	9 (8.4%)	3(5.8%)	6(11%)	0.32
Alcoholism	8(7.5%)	2(3.8%)	6(10.9%)	0.15
Diabetes mellitus	6(5.6%)	1(1.9%)	5(9.1%)	0.1
Cancer	5(5.6%)	2(3.8%)	3(5.5%)	0.68
Thyroid diseases	5(5.6%)	3(5.8%)	2(3.6%)	0.61
Cholelithiasis	6(5.6%)	3(5.8%)	3(5.5%)	0.42
Chronic cholecystitis	4(3.7%)	1(1.9%)	3(5.5%)	0.75
Urolithiasis	4(3.7%)	2(3.8%)	2(3.6%)	0.96

ALAT – Alanine transaminase
CRP – C-reactive protein
HGB – haemoglobin

AspAT - Aspartate transaminase
WBC – White blood cell
SOFA score – organ failure assessment score

The empiric treatment was adequate in 61.7% of cases (45.5% in nosocomial infections and 63.5% in community-acquired infections).

The most common source of infection overall was pneumonia (23 cases – 21.5%). It was the main source of infection in patients with severe sepsis (16 cases – 29.1%) while odontogenic infections (13 patients – 25%) and urinary tract infections (11 patients – 21.2%) dominated in patients with sepsis (tab. III).

27 patients (25.2%) developed bacterial meningitis. It was significantly more frequent in patients with severe sepsis (23 cases – 41.8%) than in patients with sepsis (4 cases – 7.7%). Waterhouse-Friderichsen syndrome was observed in 2 cases (1.8%).

Chronic comorbidities were present in 85% of patients. The most common comorbidities were: hypertension 22 (20%), heart diseases 17 (15.95%), autoimmunological diseases 14 (13.1%) and alcoholism 10 (9.3%) (tab. I).

The group of patients who died consisted of 11 men and 6 women in the mean age of 54±17.9 years.

The median time of hospitalization in this group was 4 days (range 1-36 days). At admission 5 of these patients fulfilled all 4 SIRS criteria, 8 patients – 3 criteria and 4 patients – 2 criteria. The mean APACHE II score in this group was 19.9±6.4. 12 patients had positive blood culture: S.aureus MSSA – 3 patients, S.aureus MRSA – 2 patients (other pathogens are listed in Table II).

8 patients in this group developed bacterial meningitis, 4 patients – septic shock, 2 patients - DIC. 2 patients had a history of chemotherapy due to neoplastic disease, 2 patients had autoimmunological diseases, 3 patients – diabetes, 6 patients – heart diseases and 6 patients – hypertension.

After development of respiratory or/and circulatory failure the patients were transferred to ICU.

DISCUSSION

According to some authors over 40% of sepsis cases never require intensive care (7,8).

Table II. Blood culture results of patients with sepsis and severe sepsis (n=60)

Pathogens	Overall n=60	%	sepsis n=29	%	severe sepsis n=31	%	p
Gram-positive	43	71.7	21	72.4	22	71.0	0.73
<i>Staphylococcus aureus</i> (MSSA)	17	28.3	8	27.6	9	29.0	0.9
<i>Staphylococcus aureus</i> (MRSA)	6	10.0	2	6.9	4	12.9	0.44
Coagulase-negative staphylococci (CoNS)	7	11.7	5	17.2	2	6.5	0.2
<i>Streptococcus pneumoniae</i>	2	3.3	1	3.4	1	3.2	0.96
Streptococcus group A	2	3.3	0	0.0	2	6.5	0.16
Streptococcus group Viridans	3	5.0	3	10.3	0	0.0	0.07
<i>Listeria monocytogenes</i>	1	1.7	0	0.0	1	3.2	0.33
<i>Enterococcus spp</i>	4	6.7	2	6.9	2	6.5	0.95
<i>Bacillus cereus</i>	1	1.7	0	0.0	1	3.2	0.33
Gram-negative	16	26.7	8	27.6	9	29.0	0.9
<i>Escherichia coli</i>	5	8.3	2	6.9	3	9.7	0.7
<i>Stenotrophomonas maltophilia</i>	3	5.0	1	3.4	2	6.5	0.59
<i>Neisseria meningitidis</i>	2	3.3	1	3.4	1	3.2	0.96
<i>Klebsiella pneumoniae</i>	3	5.0	2	6.9	1	3.2	0.51
<i>Klebsiella oxytoca</i>	1	1.7	1	3.4	0	0.0	0.3
<i>Ochrobactrum anthropi</i>	1	1.7	1	3.4	0	0.0	0.3
<i>Acinetobacter baumani</i>	1	1.7	0	0.0	1	3.2	0.33
<i>Pseudomonas aeruginosa</i>	1	1.7	0	0.0	1	3.2	0.33
Fungi	1	1.7	0	0.0	1	3.2	0.33
<i>Cryptococcus neoformans</i>	1	1.7	0	0.0	1	3.2	0.33

In Poland patients with sepsis are usually treated in Infectious Diseases Wards and only patients with circulatory and/or respiratory failure are admitted to ICU. Patients analyzed in our study, at least at the moment of admission, generally were in better condition than those usually treated in ICU. However patients who died had APACHE II score of 19.9 ± 6.4 .

In many studies performed in non-ICU settings the reported mortality of patients with severe sepsis was high and varied from 20 to 29.5% (9-11). The mortality in our study for severe sepsis patients was 30.9% which is in accordance with aforementioned studies. Wang *et al* showed that patients who were admitted to ICU from ER had significantly lower APACHE II score and mortality than patients who were previously treated in hospital wards (12).

A study of Kübler *et al* showed that average mortality of patients with severe sepsis in polish ICU was ca 55%. Authors concluded that the probable reason for such high mortality were late referrals of seriously ill patients to the ICU, which may be associated with too low availability of intensive care beds. In Poland ICU beds account for 2–5% of all hospital beds, whereas in Western Europe - 8–10% (2).

According to Martin *et al*. case fatality rates increases linearly by age. Also elderly patients present with more severe course of sepsis and require longer hospitalization (13).

In our study the highest mortality was in patients 41-60 years old (17.4%), while in older patients (>60 years old) the mortality was 17.2%. It has to be underlined that, although younger, patients in group 41-60 suffered

from many chronic diseases including neoplastic processes and chronic alcoholism. Also in this age group meningitis, septic shock and DIC were more frequent than in patients >60 years old.

The average age of our patients (48.9 ± 17.5 years) was lower than in the study from United States (1).

The majority of patients in our study were males. This is in accordance with other studies (6, 13, 14). Martin *et al*. reported that the risk of sepsis development is ca 30% higher in men than in women (1).

Almost 90% of examined patients had a community-acquired infection. This is in accordance with results acquired by Esteban *et al*. (83%) (9).

As far as source of sepsis is concerned pneumonia dominated in the group with severe sepsis while in the group with sepsis odontogenic and urinary tract infections were the most common sources. Pneumonia was also reported as the most common source of infection by Esteban *et al*. (56% of community-acquired infections vs 21.5% in our study) followed by urinary tract infections (20% vs 15.9%) (9).

According to Padkin *et al*. respiratory infections as a cause of severe sepsis appear to be increasing over time, whereas urinary sources are decreasing (14). Kübler *et al*. reported that in polish ICU the most common source of infection is abdominal cavity (47%) followed by respiratory tract infections (28%) (2).

Odontogenic infections are interesting as they are only rarely considered as a potential source of sepsis. Some authors state that there is no scientific evidence of relationship between inflammation in oral cavity (e.g. periapical) and internal organ infections (15).

Table III. Potential sources of infection (n=107)

Potential sources of sepsis	Total n=107	%	sepsis n=52	%	severe sepsis n=55	%	p
Pneumonia	23	21.5	7	13.5	16	29.1	<0.05
Urinary tract infection	17	15.9	11	21.2	6	10.9	0.15
Odontogenic infection	16	15.0	13	25.0	3	5.5	<0.05
Internal abscesses	7	6.5	2	3.8	5	9.1	0.27
Abdominal	7	6.5	3	5.8	4	7.3	0.75
Skin infection	5	4.7	3	5.8	2	3.6	0.6
i.v. catheters/injections	4	3.7	1	1.9	3	5.5	0.34
Infectious endocarditis	4	3.7	4	7.7	0	0.0	<0.05
Vertebral osteomyelitis	3	2.8	2	3.8	1	1.8	0.53
Other/Unknown	21	19.6	6	11.5	15	27.2	<0.05

However it was proven that intensive toothbrushing and dental extractions cause bacteremia as bacteria enter the circulation through gingival tissue the surrounds the teeth (16).

The median number of teeth with caries in our patients in which odontogenic infection was suspected was 7 (range 2-19) and a median of teeth extracted during hospitalization in this group was 2 (range 1-5). In most cases the teeth that were the source of infection had received a root canal therapy in the past. There was no other potential source of infection and extraction of decayed teeth resulted in rapid improvement of these patients' clinical status.

High percentage of meningitis in our patients may be explained by the specificity of the Department which is a regional reference center for neuroinfections.

Comparison of group of patients with severe sepsis and meningitis and group with severe sepsis but without meningitis showed that deaths were more frequent in the first group than in the latter ($p < 0.05$). Therefore development of meningitis may be considered a negative prognostic factor.

In other studies patients suffering from CNS dysfunction in the course of sepsis are also reported to have significantly higher risk of death (4,17,18).

The most common chronic comorbidities were hypertension, autoimmune diseases, heart diseases, alcoholism, diabetes, cancer and thyroid diseases (Table I). Among these, heart diseases and alcoholism were more frequent in the non-survivors group in comparison to other patients with severe sepsis, although it was on the edge of statistical significance ($p = 0.05$ for alcoholism and $p = 0.06$ for heart diseases).

Other comorbidities had little effect on patients mortality.

Forsblom et al. and *Laupland et al.* reported chronic alcoholism as one of the factors influencing fatal outcome of severe bacteraemia (19,20). According to *Schuetz et al.* diabetes is not a negative prognostic factor for mortality in sepsis (21).

In 55.1% of examined patients blood cultures were positive. In both analyzed groups Gram positive bacteria dominated with *S.aureus* as the most common pathogen.

This is in contrast to results reported by *Esteban et al.* which showed dominance of Gram negative bacteria (*E.coli* was the dominant pathogen responsible for ca 36% of infections) (9). Another non-ICU based study performed by *Sundararajan* showed dominance of Gram positive bacteria (10). In largest polish epidemiologic study (3800 blood cultures) Gram positive bacteria dominated (63% vs 27%) (22).

In many ICU based studies Gram positive bacteria were more common (1,8,13) although polish study of *Kübler et al.* showed slight dominance of Gram negative bacteria (48.2%) (2).

The comparison between sepsis and severe sepsis group showed that patients with severe sepsis had statistically significantly higher CRP concentration. It is in accordance with a study of *Suprin et al.* who showed that CRP concentration depends on severity of sepsis (23).

The hemoglobin concentration in patients with severe sepsis was significantly lower. Anemia in patients with severe sepsis may be caused either by hemolysis or by inflammatory process. The pathophysiology of anemia of inflammation is complex and includes reduced production of erythropoietin, impaired bone marrow response to erythropoietin and decreased red blood cell survival (24).

Also the albumin concentration was lower in severe sepsis. *Li et al.* reported that hypoalbuminemia in patients with severe sepsis is caused by the increased distribution rate from vessel to tissue and the improved decomposition rate (25).

CONCLUSIONS

- Despite advances in diagnostics and treatment sepsis is still a major medical problem with high mortality.
- Because of high mortality, patients with severe sepsis and meningitis should be treated in ICU setting even if no circulatory or respiratory failure is present.
- Decayed teeth should be considered as a potential source of sepsis of unknown origin.

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