

Retrospective study of the incidence and outcomes of sepsis in a Center

Retrospektivna studija o učestalosti i uzrocima sepse u jednom centru

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Summary

Background: sepsis is the common cause of death in immunocompromised patients and those suffering from malignant diseases. The mortality can be significantly reduced when early and correct diagnosis is given and the appropriate therapy is administered. Here we set to determine the incidence, sources and outcomes of sepsis and to resolve which bacteria, based on Gram staining, are more often the cause of sepsis.

Patients and methods: we conducted a retrospective study of medical history in a two-year period, from April 2014 to April 2016. Diagnosis was given based on patients' blood culture findings or their clinical presentation.

Results: during a two-year period 1663 patients were treated. Sepsis was diagnosed in 35 patients (2.10%). The median age was 73 years and 22 patients (63%) were male. Sepsis was the primary cause of death in 10 patients (29%). Gram-positive bacteria were isolated in 21 patients (60%), and Gram-negative bacteria in 10 patients (31%).

Conclusion: in our retrospective study, the gastrointestinal tract had the highest frequency of identified sepsis source. The incidence of sepsis caused by Gram-positive bacteria found in blood cultures was higher than by Gram-negative bacteria. However, due to small sample size, no difference in mortality was found based on Gram status.

Key words: sepsis, malignant disease, Gram-positive, Gram-negative

Sažetak

Uvod: Sepsa je česti uzrok smrti u imunokompromitiranih bolesnika i onih koji boluju od malignih bolesti. Mortalitet može biti značajno snižen kada se rano uspostavi točna dijagnoza i aplicira odgovarajuća terapija. U ovom radu ćemo odrediti učestalost, izvore i ishode sepse, te utvrditi koje bakterije, s obzirom na Gram bojanje, su češći uzročnik sepse.

Bolesnici i metode: Proveli smo retrospektivnu studiju povijesti bolesti u razdoblju od dvije godine, od travnja 2014. do travnja 2016. Dijagnoze su uspostavljene na temelju hemokultura ili kliničke slike.

Rezultati: tijekom dvije godine na odjelu se liječilo 1663 bolesnika. Sepsa je bila dijagnosticirana u njih 35 (2,10%). Medijan godina je bio 73, a muških bolesnika bilo je 22 (63%). Sepsa je bila primarni uzrok smrti u 10 bolesnika (29%). Gram-pozitivne bakterije su bile izolirane u 21 bolesnika (60%), a Gram-negativne u njih 10 (31%).

Zaključak: U našoj retrospektivnoj studiji, gastrointestinalni trakt je bio najčešći identificirani izvor sepse. Učestalost sepse uzrokovane Gram-pozitivnim bakterijama je bila veća od učestalosti i zaraze Gram negativnim bakterijama, no međutim, zbog malog uzorka bolesnika, nismo ustanovili razliku u mortalitetu na temelju Gram-statusa (chi-kvadrat test, $p = 0,48$).

Ključne riječi: sepsa, maligna bolest, Gram-pozitivne, Gram-negativne

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Introduction

Sepsis is a life-threatening condition that arises when the body's response to infection injures its own tissues and organs.¹ The incidence of sepsis is affected by a variety of patient-specific factors. We have long recognized that age is an important component of someone's risk for developing sepsis, as are a variety of comorbid medical conditions. Perhaps most obvious are conditions like HIV, cancer and diabetes, each of which may alter the immune system.² The mortality caused by sepsis in these patients can be significantly reduced when early and correct diagnosis is given and the appropriate antibiotics therapy is administered.

The purpose of this study is to evaluate the epidemiology of sepsis, with particular attention to the incidence, sources and outcomes in the Department of Hematology and Oncology (DHO) of General Hospital "Dr. Josip Benčević", Slavonski Brod, Croatia. We have also set to determine which bacteria, based on Gram staining, are more often the cause of sepsis. We present the most common sources of sepsis, which gives a useful tool in predicting which empirical therapy to administer.

Patients and methods

We conducted a retrospective study of medical history in a two-year period, from 15 April 2014 to 15 April 2016. Patients on DHO were treated for solid tumors, lymphomas and leukemia (excluding childhood acute conditions) with intense chemotherapy. No sterile units are present at the DHO. Diagnosis was given based on the patient's blood culture findings. Diagnosis of patients with negative blood cultures was made based on the next clinical findings: axillary temperature higher than 38.5°C or lower than 36.0°C, and two or more from the next set of criteria: hypotension (systolic pressure lower than 100 mmHg), tachycardia (heart rate higher than 120/min), tachypnea (respiratory rate higher than 30/min), signs of tissue hypoperfusion (altered level of consciousness, peripheral cyanosis, marmorated skin), and if these signs and symptoms didn't have any other clear cause, e.g. myocardial infarction.

Regarding the standard diagnostic procedures that can be performed in our hospital, the following next parameters were analyzed in all of our patients: complete blood count, electrolytes, glucose in blood, acid-base status, bilirubin and liver enzymes, coagulogram, inflammatory markers, fibrinogen, troponin, creatinine, cortisol, hemoculture and urino-culture. Procalcitonin values, as potential sepsis

indicator, were also measured as part of the laboratory diagnostic tests performed during our study. However, this was measured only in a dozen of individuals and, therefore, we couldn't observe it as a relative indicator. Some of the parameters were taken as part of standard diagnostic procedures for sepsis while other parameters were required to exclude other diseases which could have had similar clinical presentation. All parameters analyzed were the results from the day that sepsis was diagnosed or the first following day.

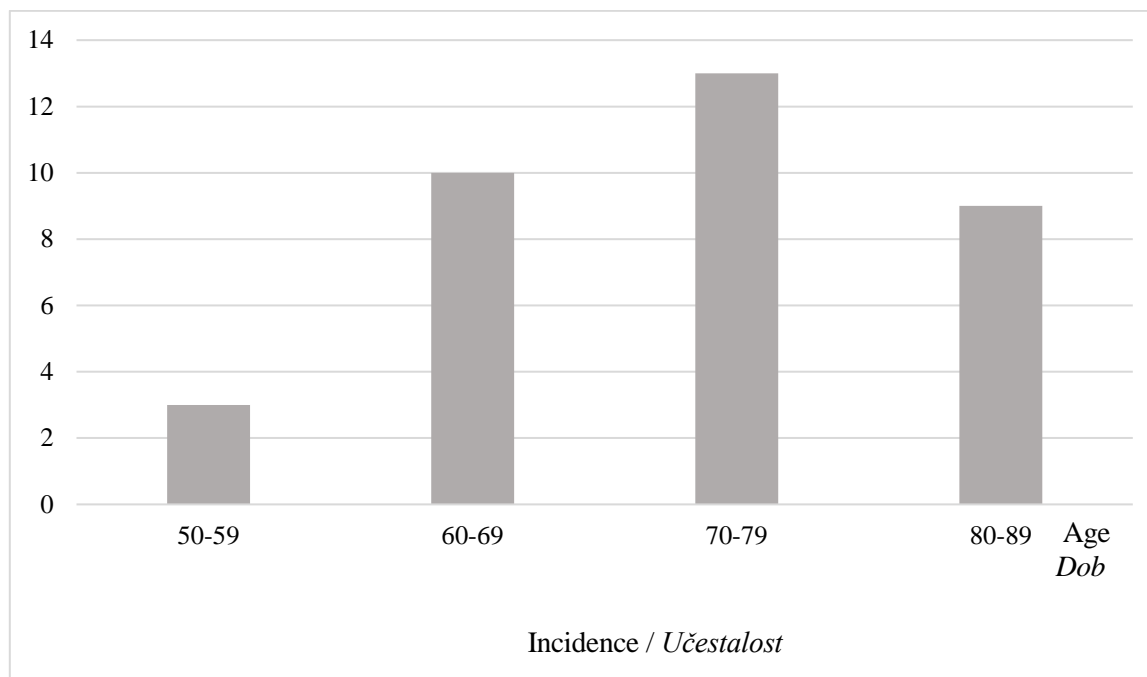
The first antibiotic regimen that our patients received was part of an empirical therapy where the second antibiotic regimen was based on antibiogram results. Therefore, some of our patients were administered with multiple antibiotics. As soon as the antibiogram results were known, empirical therapy was stopped and new antibiotic regimen was introduced. If the patient remained febrile 48 hours after the administration of empirical therapy and no bacteria was isolated nor antibiogram results were known, the second antibiotic was introduced.

The data for this study was gathered from the patients' medical history, both in written form and abstracted from the electronic database. MS Office Excel was used for storing and analyzing our data, as well as for designing the Pictures and Tables. In this study, we used the Chi-square test to determine whether there is a statistically significant difference in mortality based on Gram-status.

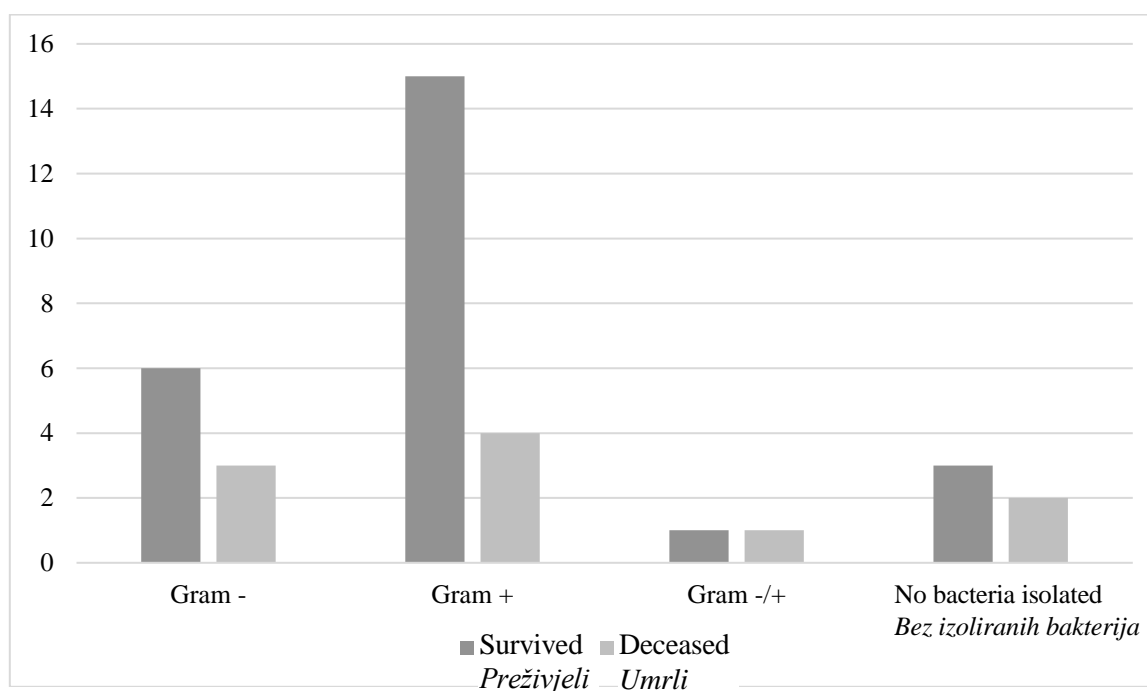
Results

During the two-year period, 1663 patients were treated, out of which 1190 patients suffered from malignant disease and 46 had lymphoma or leukemia. Sepsis was diagnosed in 35 patients (2.10%). In that group, 28 were diagnosed with cancer, 18 with solid tumor and 10 with lymphoma or leukemia. The median age was 73 (Picture 1), and 22 patients (63%) were men. Sepsis was a primary cause of death in 10 patients, hence mortality was 29%, 10 out of 35 patients.

Thirty (86%) patients had positive blood culture findings. Only gram positive (G+) bacteria were isolated in 19 patients (57%), and only gram negative (G-) bacteria in 9 patients (31%). Out of 19 patients, from which only G+ bacteria were isolated, 4 died. On the contrary, out of 9 patients from which were isolated only G-bacteria, 3 died. No significant difference in mortality was found based on Gram status ($p=0.48$). Both G+ and G- bacteria were isolated in 2 patients. (Picture 2)



Picture 1 Patient age distribution. Median age is 73.
 Slika 1. Raspored godina starosti bolesnika. Srednja dob je 73 godine



Picture 2 Incidence and outcomes based on Gram staining. Due to small sample size, no difference in mortality was found based on Gram status (chi-square test, $p=0.48$).

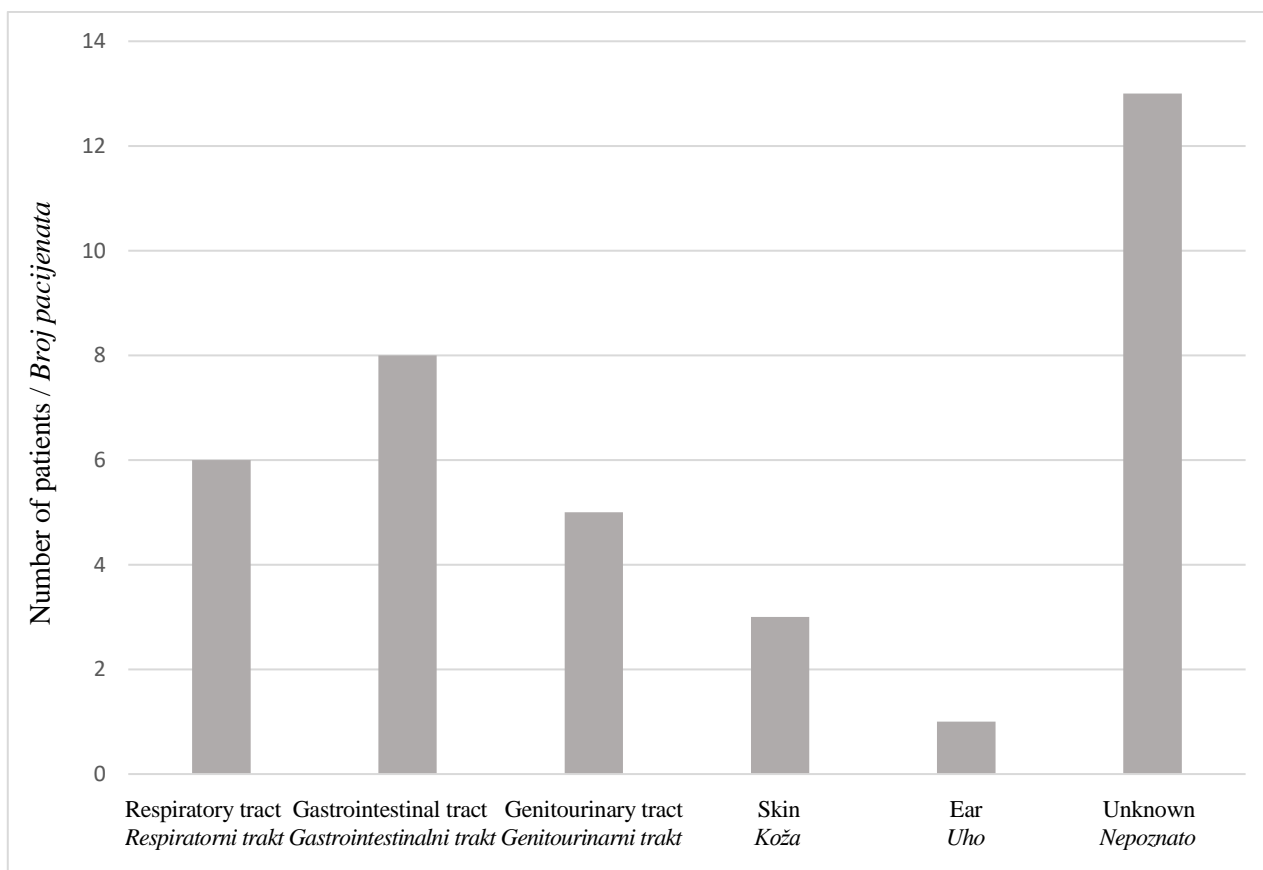
Slika 2. Učestalost i ishodi na temelju Gram bojanja. Uslijed malog broja uzoraka nije pronađena razlika u mortalitetu na temelju Gram bojanja (hi-kvadrat testiranje, $p = 0,48$).

In 5 patients (14%) no bacteria were isolated despite symptoms being present, out of which one was admitted to the Intensive Care Unit (ICU), and was later diagnosed with the Systemic Immune Response Syndrome (SIRS). Two other patients died in hospital, one within two and a half hours and the other within sixteen hours from admission in hospital. 4 out of 5 patients were diagnosed with malignant diseases. 3 patients were treated with chemotherapy and 2 of those patients were diagnosed with neutropenia.

The source of sepsis was unknown in 13 patients (36%), gastrointestinal tract in 8 patients (22%), respiratory tract in 6 patients (17%), genitourinary tract in 5 patients (14%), skin in 3 patients (8%) and ear in 1 patient (3%). (Picture 3) Some of the most common microbes isolated in the blood cultures in our study were *S. epidermidis* (G+) isolated in 11 patients (24%), *E. coli* (G-) in 9 patients (20%), *S. aureus* (G+) in 6 patients (13%) and *S. pneumoniae* (G+) in 6 patients (13%) (Table 1).

Table 1 Cause of sepsis isolated from blood culture
 Tablica 1. Uzrok sepsa izoliran iz kulture krvi

Bacterium <i>Bakterija</i>	No. (%) patients <i>Broj (%) bolesnika</i>
<i>S. epidermidis</i>	11 (24)
<i>E. coli</i>	9 (20)
<i>S. aureus</i>	6 (13)
<i>S. pneumoniae</i>	6 (13)
<i>E. faecalis</i>	3 (8)
<i>E. faecium</i>	2 (4)
<i>S. oralis</i>	2 (4)
<i>Yersinia spp.</i>	2 (4)
<i>A. baumannii</i>	1 (2)
<i>C. amalonaticus</i>	1 (2)
<i>K. pneumoniae</i>	1 (2)
<i>P. mirabilis</i>	1 (2)



Picture 3 Distribution of sources among patients
 Slika 3. Raspored izvora među bolesnika

Empirical therapy was successful in 9 patients (26%). Two most commonly used antibiotics in our study as empirical therapy regimen were amoxicillin/clavulonic acid combination used in 10 patients (28%) and meropenem in 5 patients (13%). Others are shown in Table 2. In 26 patients (74%) one or more antibiotics were used alongside the empirical antibiotic. In these patients, the most commonly used antibiotics were ciprofloxacin (30%), vancomycin (23%) and metronidazole (15%).

Table 2 Empirical therapy distribution among patients
Tablica 2. Distribucija empirijske terapije između pacijenata

Antibiotic <i>Antibiotik</i>	No. (%) patients <i>Broj bolesnika</i>
Amoxicillin/clavulanic acid	10 (28)
Meropenem	5 (13)*
Ceftriaxone	4 (11)
Metronidazole	4 (11)
Piperacillin/tazobactam	4 (11)
Ciprofloxacin	3 (8)*
Azithromycin	1 (3)
Cefepime	1 (3)
Cefuroxime	1 (3)
Gentamicin	1 (3)
Imipenem/cilastatin	1 (3)
Vancomycin	1 (3)

* in 1 patient both meropenem and ciprofloxacin were administered

* kod jednog bolesnika dat je meropenem i ciprofloxacin

In our study, we have used standard sets of diagnostic procedures to assess our patients. We have determined the minimum and maximum measured values as well as the median for each diagnostic parameter.

Discussion

Originally, sepsis was described and strongly considered to be a disease specifically related to Gram-negative bacteria.³ However, as time went by epidemiological studies started showing evidence that Gram-positive bacteria were becoming a more common cause of sepsis in the past 35 years. According to the most recent estimates in sepsis, there are approximately 200,000 cases of Gram-positive sepsis each year, compared with approximately

150,000 cases of Gram-negative sepsis.⁴ The incidence of G+ bacteria found in blood cultures in our study was higher than that of G- bacteria, 21 versus 11, respectively. In our study no difference was found in mortality based on Gram status ($p=0.48$). The reason for this is due to a relatively small sample size (Picture 2).

Sepsis tends to occur from specific and consistent sources. Respiratory infections are invariably the most common cause of sepsis, severe sepsis and septic shock. Overall, respiratory infections account for approximately half of all cases of sepsis. The next most common causes are genitourinary and abdominal sources of infection with primary bacteremia and unknown sources being the next most common causes.⁴⁻⁶ Our study has shown different results. Unknown sources take first place, then gastrointestinal tract, being the most common identified source of sepsis. After that, as in other researches, come the respiratory and genitourinary tract. Precise distribution can be seen in Picture 3.

S. epidermidis, *E. Coli* and *S. aureus* were the most commonly isolated bacteria in the blood cultures of our patients (Table 1). Empirical therapy regimen is a result of epidemiological parameters for our hospital. Just as a comparison, in one other Croatian study in Zagreb the most common isolated organisms were *E. coli* (28.6%), *S. aureus* (12.3%), *S. pneumoniae* (8.4%), *K. pneumoniae* and *P. mirabilis* (4.5%).⁷

More recently it has been recognized that race, ethnicity and gender may also contribute to the differential risk for developing sepsis.^{5,8,9} In general, males have a higher risk for developing sepsis than females, regardless of age.^{5,8,10} Out of 35 septic patients in our study, 22 were men.

Appropriate antimicrobial therapy and its early application is essential in treating the septic state. Mortality significantly increases in patients with pneumonia that got into septic shock if the antibiotic administration was delayed.^{8,11} Nevertheless, the therapy of sepsis still remains as one of the biggest problems. In our study, amoxicillin/clavulanic acid is the most commonly administered antibiotic for empirical therapy, which matches with the presumption that the respiratory infection is the most common source of sepsis and therefore G+ bacteria most common cause. An early combination of antibiotic therapy is associated with decreased mortality in septic shock compared with monotherapy.¹² In our study 74% of our patients were treated alongside the empirical therapy with one or more antibiotics: ciprofloxacin, vancomycin and metronidazole being the most common.

All in all, we believe that our study could have implicated some important epidemiological parameters (like mortality based on Gram status) if our sample size had been higher. This study is limited in the number of cases due to the size of the health care institution and research duration. Nevertheless, this data can be used with epidemiological data from other health care institutions and then cumulatively show better results.

Conclusion

In this retrospective study of medical history in a two-year period, the incidence of sepsis was 2.16% (N = 35), out of which 78% had malignant disease. 10 patients died, and 8 suffered from malignant disease. The most commonly identified source of sepsis was the gastrointestinal tract. The incidence of G+ sepsis was higher than G-sepsis.

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