EMPIRICAL ANTIBIOTIC THERAPY OF SEPSIS IN SURGICAL INTENSIVE CARE UNIT

Ljiljana Mihaljević[1*], Slobodan Mihaljević[2], Ivan Vasilj[3], Semra Čavaljuga[4], Fadila Serdarević[4], Ivan Soldo[5]

1 Clinical Department for Clinical and Molecular Microbiology, Clinical Hospital Center Zagreb, Kišpatićeva 12, 10000 Zagreb, Croatia
2 Clinic for Anesthesiology, Reanimatology and Intensive Care Unit, Clinical Hospital Center Zagreb, Kišpatićeva 12, 10000 Zagreb, Croatia
3 Institute of Public Health, West Hercegovina Canton, Kraljice Katarine bb, 88340 Grude, Bosnia and Herzegovina
4 Institute of Epidemiology, Faculty of Medicine, University of Sarajevo, Čekaluša 90, 71000 Sarajevo, Bosnia and Herzegovina
5 Ministry of Health, West Hercegovina Canton, Kraljice Katarine bb, 88340 Grude, Bosnia and Herzegovina

* Corresponding author

Abstract

Retrospective study was conducted in surgical intensive care unit (ICU) in Clinical Hospital Center Zagreb in 2005. The aim of study was to create guidelines for empirical antibiotic therapy of sepsis in ICU for unknown causative agent based on antimicrobial susceptibility of causative bacteria.

Thirty-two patients with severe sepsis were included in study and from medical records their clinical and microbiological data were analyzed. Antimicrobial susceptibility of the strains isolated from the blood-culture was tested by disk diffusion method according to CLSI (Clinical Laboratory Standard Institution). We used APACHE II score to predict the severity of illness. Mann-Whitney test and χ^2 test were used to test statistical significance difference between results.

Acinetobacter baumannii and *Pseudomonas aeruginosa* were the predominant causative agent. *Acinetobacter baumannii* was displaying excellent susceptibility to ampicillin+sulbactam and carbapenems, whereas *Pseudomonas aeruginosa* was showed good susceptibility on ceftazidim and carbapenems.

Methicillin-resistant *Staphylococcus aureus* (MRSA), third predominant causative agent exhibiting good susceptibility to vancomycin and linezolide.

The recommended therapy is empirical antibiotic therapy and should cover all important pathogens.

KEY WORDS: empirical antibiotic therapy, sepsis, surgical ICU, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus* (MRSA)

Introduction

The International Sepsis Forum was published in 2001 guidelines for the management of patients with severe sepsis and septic shock, which were including an evidence-based review on antibiotic therapy (1). These guidelines have been updated and extended in 2003, under the auspices of the Surviving Sepsis Campaign, critical care and infectious disease experts representing 11 international organizations (2). Criteria for sepsis definition and antibiotic therapy pattern are recommended until now. Sever sepsis (infection-induced organ dysfunction or hypo-perfusion abnormalities), septic shock (hypotension not reversed with fluid resuscitation and associated with organ dysfunction or hypo- perfusion abnormalities) and mortality of sepsis remains unacceptably high in most ICU (3, 4). Infection in sepsis can occur at any site, most commonly in the respiratory tract, abdomen and bloodstream, and in more than 90% were caused by bacteria (4, 5). Thus, it is very important to find a precise microbiological diagnosis in patients with sepsis and to ensure effective antimicrobial therapy (5). The appropriate empirical antibiotic therapy depends on following factors: patient's history (including drug intolerance), underlying diseases and susceptibility patterns of microorganisms in the hospital environment (6). Choice of appropriate empirical antibiotic therapy in sepsis is one of the most important factors for the better outcome of patients in sepsis (7). The initial empirical antimicrobial regimen should be broad enough to cover likely pathogens; for mixed (polymicrobial) or one causative agent infection. Mixed sepsis has been a more serious therapeutic problem. The aim of this study was to define and recommend the appropriate empirical antibiotic therapy for sepsis in surgical intensive care unit (ICU) in Clinical Hospital Center Zagreb.

Patient and Methods

Study population

32 patients with positive blood-culture (BC) in surgical ICU in Clinical Hospital Center Zagreb in 2005 were identified from clinical microbiology laboratory records. Epidemiological, clinical and microbiological data was analyzed from the medical records of these 32 patients.

Identification and antimicrobial susceptibility testing

Blood cultures were processed with the BACTEC system and organisms were identified using Vitek system. Results were interpreted according to the guidelines of the Clinical Laboratory Standard Institution (CLSI). Intermediate susceptibility to the antibiotics was considered as resistance.

Study design and data collection

The medical records of patients were retrospectively reviewed. The data collected included: age, gender, severity of illness (as calculated by acute physiology and chronic health evaluation-APACHE II score at a time of bacteriemia), antimicrobial therapy regimen at admission in ICU, changing of the therapy according to disk diffusion test (antibiogram), *in vitro* effectiveness of empirical antimicrobial agents, *in vitro* effectiveness of definitive antimicrobial agents and antimicrobial susceptibility of causative agents, type of infection (caused by one agent or polymicrobial), type of agents causing infection and outcome of patients.

Antibiotic therapy

Blood culture had been taken first, and than empirical antimicrobial therapy was initiated. Initiated therapy was changed to definitive therapy according to the results of culture and susceptibility testing within 3 days after the bacteriemia episode. The attending physician was decided about definitive therapy, mono-therapy vs. combined therapy.

Definitions

Positive blood-culture (BC) was defined as the isolation of the bacterial species from one or more blood cultures, and by the presence of clinical features consistent with sepsis. The standard definition for sepsis (severe sepsis and septic shock) provided by the Internal Sepsis Forum were used to determine septic patients. Severe sepsis was defined as sepsis associated with evidence of at last one organ dysfunction and positive blood-culture. Mixed sepsis was defined as the presence of two or more causative bacteria in the blood-culture.

Statistical analysis

Statistical significance difference between results was tested by Mann-Whitney test and χ^2 test.

Results

In a study 32 patients with severe sepsis were included. The mean age for all patients was 59 (range 22-85), 20 male and 12 female. Sepsis caused by one agent were present at 18 (56%) patients, and sepsis caused by more than one agent, polymicrobial (mixed) sepsis, were present at 14 (44%) patients (Chart 1). Nine different causative agents were isolated, 6 in mono-agent sepsis, and 8 in mixed sepsis (Chart 2, 3, 4).

CHART 1. Types of sepsis

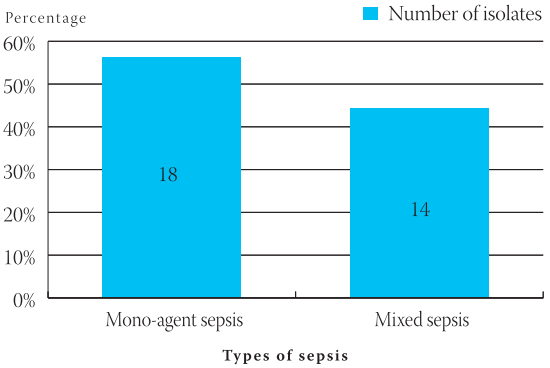
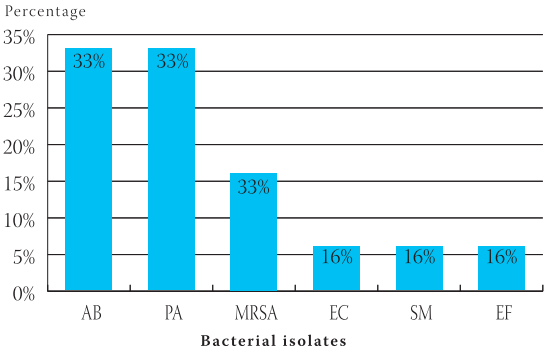


CHART 2. Bacterial isolates in mono-agent sepsis



Abbrevations: AB-*Acinetobacter baumannii,* PA-*Pseudomonas aeruginosa,* MRSA-methilicin-resistant *Staphylococcus aureus,* EC-*Escherichia coli,* SM-*Serratia marcescens,* EF-*Enterococcus faecalis.*

Acinetobacter baumannii was the predominant causative agent in both type of sepsis, it was found in 33% patients with mono-agent sepsis and in 23% patients showing mixed sepsis, whereas *Pseudomonas aeruginosa* was also presented as predominant causative agent in mono-agent sepsis, it was found at 33% patients, but only at 15% patients having mixed sepsis. Methicilin-resistant *Staphylococcus aureus* (MRSA) was identified at 16% patients showing mono-agent sepsis and at 18% patients with mixed sepsis. *Escherichia coli, Serratia marcescens* and *Enterococcus faecalis* were detected with equal frequency in one (6%) patient with mono-agent sepsis, respectively (Chart 2). *Escherichia coli* were found in 4 (11%) patients with mixed sepsis (Chart 3).

Klebsiella pneumoniae, Enterobacter spp., Staphylococcus epidermidis were detected with equal frequency in 3 (9%) patients with mixed sepsis. *Enterococcus faecalis* was found at 1 (3%) patient with mixed sepsis. The initial (empirical) antibiotic therapy was changed in 22 (70%) patients, four of them died. Initial antibiotic therapy was not changed in 10 (30%) patients, six of them died. Average value of APACHE II score in patients who died was 22 and was higher than in patients who were survived their APACHE II score was 16. Total mortality of 30% correlated with the predicted value of APACHE II score for mortality, which is 40% for APACHE II score of 22.

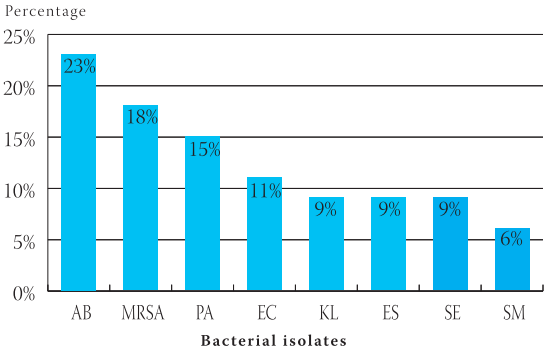
Prevalence of bacterial isolates

The most prevalent bacterial isolate from the blood-culture was *Acinetobacter baumannii* (26%) followed by *Pseudomonas aeruginosa* (21%), methicilin-resistant *Staphylococus aureus MRSA* (17%) and *Escherichia coli* (9%). There was 6% of *Klebsiella pneumoniae, Enterobacter spp. , Staphylococcus epidermidis* and *S.marcescens, Enterococcus faecalis* was the least prevalent (3%). (Chart 4).

Antimicrobial susceptibility

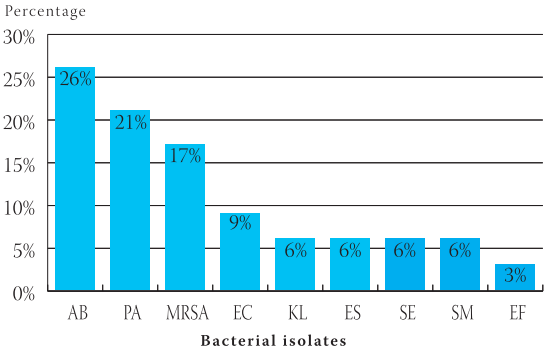
All *Acinetobacter baumannii* strains were susceptible to ampicillin+sulbactam, imipenem, meropenem. Among *Pseudomonas aeruginosa* no resistance to ceftazidim, meropenem, colistin was observed. 100% of methicillin-resistant *Staphylococcus aureus*

CHART 3. Bacterial isolates in mixed sepsis



Abbrevations: AB-*Acinetobacter baumannii,* MRSA-methicillin-resistant *Staphylococcus aureus,* PA-*Pseudomonas aeruginosa,* EC-*Escherichia coli,* KL-*Klebsiella pneumoniae,* ES-*Enterobacter spp.,* SE-*Staphylococcus epidermidis,* SM-*Serratia marcescens.*

CHART 4. Prevalence of bacterial isolates



Abbrevations: AB-*Acinetobacter baumannii,* PA-*Pseudomonas aeruginosa,* MRSA-methilicin-resistant *Staphylococcus aureus,* EC-*Escherichia coli,* KL-*Klebsiella pneumoniae,* ES-*Enterobacter spp.,* SE-*Staphylococcus epidermidis,* SM-*Serratia marcescens,* EF-*Enterococcus faecalis*

(MRSA) strains were susceptable to vancomicin and rifampicin.

All *Enterobacteriaceae* (*Klebsiella pneumoniae, Escherichia coli* and *Enterobacter spp.*) strains were sensitive to ceftazidim, gentamicin, imipenem and meropenem.

Staphylococcus epidermidis was sensitive to ampicillin and cloxacillin.

Enterococcus spp. was sensitive to ampicillin, vancomycin and rifampicin.

Statistical analysis

There was statistically significant difference in APACHE II score between patients who were survived and those who died ($p<0,05$). No significant difference was found in APPACHE II score between patients who died with mono-agent sepsis and mixed sepsis ($p>0,05$). According to antibiogram antimicrobial therapy was significantly more often changed for younger patients compared to the older patients ($p<0,05$). Correction of the therapy, related to a causative agent, was more often necessary for mixed sepsis than mono sepsis ($p<0,05$).

Discussion

Sepsis is still associated with significant mortality and high health-care costs in spite of the all known guidelines and recommendation for treating (6). The many recent studies report high frequency mortality rates of sepsis, from 27% of patients dying in the ICU, rising to >50% in patients with severe sepsis and septic shock (5,6). There are also recent studies reports where mortality rate is not so high, for example, the EPISEPSIS study in France reported that 15% of patients had severe sepsis and UK study reported a rate of 27% (8). This study included patients admitted for routine postoperative surveillance who are likely to have lower rates of complications. Many of our patients were admitted in emergency, so that higher mortality rate of 31% is in concordance with the present bibliographic data. Furthermore, this proportion remains high in spite of the new antimicrobial agents (1, 7). Type of sepsis is another important problem: mono-agent sepsis (sepsis caused with one agent) presents less therapeutic problem than mixed sepsis (sepsis caused with two or more agent). There was 44% mixed sepsis and 56% mono-agent sepsis in our study. This is also correlated with the data published by other authors (2, 6, 7). There was no significant difference between patients who died due to the mono-agent sepsis and mixed sepsis ($p>0,05$). APACHE II score remains reliable predictive data for patient's outcome (8, 9, 10, 11). Therapeutic approach for intraabdominal infection, pneumonia (ventilator associated pneumonia – VAP) or catheter-associated infection is different, so identification of sepsis's source (focus) could be very helpful, especially for the empirical therapy (12). Intraabdominal infection, followed by VAP was the predominant source of sepsis in our surgical ICU. Some authors suggested flucloxacillin + amikacin like empirical therapy for unknown causative agent (13). Paul-Erlich-Gesellschaft recommended cephaslosporine third generation and aminoglicoside (14, 15). According to the antibiograms of the strains isolated in our surgical intensive care unit ICU, we would suggest cephalosporine third generation and ampicillin+sulbactam for the empirical therapy of the sepsis with the unknown causative agent. Since staphylococci were isolated from blood-culture in some of our patients, in our opinion beta-lactamase stable penicillin (flucloxacillin) should be added to empirical therapy (16). *Acinetobacter baummanii* and *Pseudomonas aeruginosa* often require administration of carbapenems, due to their multiple antibiotic resistances (17, 18). Carbapenems remains antibiotic of choice for the treatment of infections caused by *Klebsiella pneumoniae* and *Escherichia coli.* Sepsis caused with methicillin-resistant *Staphylococcus aureus* (MRSA) should be treated with vancomycin or linezolide (19, 20).

Conclusion

Surveillance of antibiograms for all causative agents of sepsis *is condition sine qua non*. Redefinition of present antibiotic therapy according to the antibiograms is necessary for empirical antibiotic therapy of sepsis for unknown causative agent.

Acinetobacter baumannii, Pseudomonas aeruginosa and methicillin-resistant *Staphylococcus aureus* (MRSA) were the predominant causative agent of sepsis in surgical intensive care unit (ICU) in Clinical Hospital Center Zagreb.

References

(1) Dellinger R.P., Carlet J.M., Masur H., Gerlach H., at al. Surviving Sepsis Campaign for management of severe sepsis and septic shock. Crit. Care Med. 2004; 30:536-555

(2) Bochud P.Y., Bonten M., Marchetti O., Calandra T. Antimicrobial therapy for patients with severe sepsis and septic shock: An evidence-based review. Crit. Care Med. 2004; 32(Suppl.):S495-S512

(3) Friedman G., Silva E., Vincent J.L. Has the mortality of septic shock changed with time? Crit. Care Med. 1998; 26:2078-2086

(4) Angus D.C., Linde-Zwirble W.T., Lidicker J. et al. Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. Crit. Care Med. 2001; 29:1303-1310

(5) Laupland K.B., Zygun D.A., Doig C.J., Bagshaw S.M., Svenson L.W., Fick G.H. One-year mortality of blood-stream infection –associated sepsis and septic shock among patients presenting to a regional critical care system. Intensive Care Med. 2005; 31:213-219

(6) Alberti C., Brun-Buisson C., Burchardi H. et al. Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. Intensive Care Med. 2002; 28:108-121

(7) Buising K.L., Thursky K.A., Bak N., Skull S., Street A., Presneill J.J. Antibiotic prescribing in response to bacterial isolates in the intensive care unit. Anesth. Intensive Care. 2005; 33(5): 571-577

(8) Brun-Buisson C., Meshaka P., Pinton P., at al: EPISEPSIS: a reappraisal of the epidemiology and outcome of severe sepsis in French intensive care units. Intensive Care Med. 2004; 30:580-588

(9) Weycer D., Akhras K.S., Edelsberg J. et al. Long-term mortality and medical care charges in patients with severe sepsis. Crit. Care Med. 2003; 31:2316-2323

(10) Le Gall J.-R. The use of severity scores in the intensive care unit. Intensive Care Med. 2005; 31:1618-1623

(11) Knaus W.A., Draper E.A. et al. APACHE II: A severity of disease classification system. Crit. Care Med. 1985; 13:818-829

(12) Jimenez M.F., Marshall J.C. Source control in the management of sepsis. Intensive Care Med. 2001; 27:S49-S62

(13) Trampuz A., Zimmerli W. Pathogenese un Therapie der Sepsis. Schweiz. Med. Forum. 2003; 35:811-818

(14) Rosenthal E.J.K. und Studiengruppe: Antibiotika-Empfindlichkeit von Sepsis-Erregern 2000-2001. Chemoth. J. 2003; 12:71-78

(15) Leone M., Bourgoin A., Cambon S., at al. Empirical antimicrobial therapy of septic shock patients: Adequacy and impact on the outcome. Crit. Care Med. 2003; 31:462-467

(16) Garnacho-Montero J., Garcia-Garmendia J.L., Barrero-Almodovara L., at al. Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. Crit. Care Med. 2003; 31:2742-2751

(17) Micek S.T., Lloyd A.E., Ritchie D.J., Reichley R.M., Fraser V.J., Kollef M.H. Pseudomonas aeruginosa bloodstream infection: Importance of appropriate initial antimicrobial treatment. Antimicrob. Agents Chemother. 2005; 49:1311-1325

(18) Choi J.Y., Park Y.S. Kim C.O., Park Y.S., Yoon H.J., Shin S.Y. at al. Mortality risk factors of Acinetobacter baumannii bacteriemia. Intern. Med. J. 2005; 35.599-603

(19) Guilarde A.O., Turchi M.D., Marteli C.M.T., Primo M.G.B. Staphylococcus aureus bacteriemia: incidence, risk factors and predictors for hospital death in a Brasilian teaching hospital. J. Hosp. Infect. 2006; 63:330-336

(20) Hurley J.C. Risk of death from methicillin-resistant Staphylococcus aureus bacteriemia, a meta-analysis. Med. J. Aust. 2002; 176:188-189