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Original scientific paper

Microbiological Surveillance of the Surgical Intensive Care Unit in Zagreb – a Pivot for Guideline-based Therapy of Severe Sepsis

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A B S T R A C T

The aim of this retrospective study was to create guidelines for therapy of severe sepsis in surgical intensive care unit (ICU) for unknown causative agent based on antimicrobial susceptibility of causative bacteria. Seventy-four patients with severe sepsis from surgical ICU in 2003.–2005. were included in study. Their clinical and microbiological data were analyzed from the medical records. Antimicrobial susceptibility of the strains isolated from the blood-culture was tested by disk diffusion method according to CLSI (Clinical Laboratory Standard Institution). APACHE II score was used to predict the severity of illness. Statistical significance difference between results was tested by Mann-Whitney test and x^2 test. Important problem remained type of sepsis: mono-agent sepsis presented less therapeutic problem than sepsis caused with two or more agents (mixed sepsis). Methicillin-resistant Staphylococcus aureus *(MRSA),* Pseudomonas aeruginosa *and* Acinetobacter baumannii *were predominant causative agents in both type of sepsis. There was remarkable increase of* A. baumannii *prevalence in 2005 compared to 2004 and to 2003. There was also decrease of MRSA prevalence in 2004 and 2005 compared to 2003. P.aeruginosa were the predominant causative agents in 2004. MRSA displayed good susceptibility to vancomycin and linezolide, whereas* P. aeruginosa *showed excellent susceptibility to ceftazidime and carbapenems.* A. baumannii*, third predominant causative agent, exhibited excellent susceptibility to ampicillin+ sulbactam and carbapenems. The recommended therapy is empirical and should cover all important pathogens.*

Key words*: severe sepsis, empirical antibiotic therapy, surgical ICU*

Introduction

The mortality of sepsis, sever sepsis (infection-induced organ dysfunction or hypoperfusion abnormalities) and septic shock (hypotension not reversed with fluid resuscitation and associated with organ dysfunction or hypoperfusion abnormalities) in most ICU remains unacceptably high[1,2]. In 2001, the International Sepsis Forum published guidelines on the management of patients with severe sepsis and septic shock, including an evidence-based review on antibiotic therapy[3]. In 2003, under the auspices of the Surviving Sepsis Campaign, critical care and infectious disease experts representing 11 international organizations, the International Sepsis Forum published guidelines have been updated and extended[4]. Criteria for sepsis definition and antibiotic therapy pattern are recommended until now.

Infection is *sine qua non* of sepsis and can occur at any site, most commonly the respiratory tract, abdomen and bloodstream[3,4]. More than 90% of cases of sepsis are caused by bacteria, and Gram-negative and Gram-positive organisms occur with approximately equal frequency[5]. There are several reasons why it is important to obtain a precise microbiological diagnosis in septic patients. One, and most important, is to ensure that effective antimicrobial therapy is given[6].

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Choice of empirical antibiotic therapy depends on several factors related to the patient's history (including drug intolerance), underlying diseases and susceptibility patterns of microorganisms in the hospital environment[7]. The initial selection of an empirical antimicrobial regimen, monotherapy or combination therapy, should be broad enough to cover likely pathogens; for mixed (polymicrobial) or one causative agent infection. Mixed infections have been shown to pose a more serious therapeutic problem[6,8]. Choice of appropriate empirical antibiotic therapy in sepsis is one of the most important factors for the better outcome of patients in sepsis[3,8].

The aim of this paper is to define and suggest the appropriate empirical antibiotic therapy in surgical intensive care unit (ICU) in Clinical Hospital Center Zagreb.

Patients and Methods

Study population

The retrospective study was conducted in an 8-bed surgical ICU at University hospital Center Zagreb, Croatia. The study was included patients with sepsis treated at ICU between January 1, 2003 and December 31, 2005. Of 2349 surgical ICU patients admitted during study period, 74 had confirmed diagnosis of severe sepsis with positive blood-culture (BC) in the records from the clinical microbiology laboratory. Epidemiological, clinical and microbiological data were analyzed from the medical records of these 74 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 clinical data collected included: age, gender, severity of illness (as calculated by acute physiology and chronic health evaluation – APACHE II score within the first 24h of admission in ICU[9]), 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

Empirical antimicrobial therapy was initiated immediately after diagnosis of sepsis was confirmed and blood culture had been taken, and was changed to definitive therapy according to the results of culture and susceptibility testing within 3 days after the bacteriemia episode. The choice of monotherapy vs. combined therapy which was administered as definitive therapy was made by attending physician.

Definitions

The standard definition for sepsis (severe sepsis and septic shock) provided by the Internal Sepsis Forum were used to determine sepsis[3,4]. 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. 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.

Statistical analysis

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

Results

A total of 74 patients with severe sepsis were included in the present study. The mean age for all patients was 58 (range 22–85), 52 were male and 22 female. Forty-eight (65%) patients had sepsis caused by one agent and 26 (35%) patients had polymicrobial (mixed) sepsis (Figure 1). Ten different causative agents were isolated, 9 agents in mono-agent sepsis, and 10 agents in mixed sepsis (Figure 2 and 3). MRSA, *P. aeruginosa* and *A.baumannii* were the predominant causative agents in both type of sepsis. *P.aeruginosa* was found in 27% (11) patients with mono- agent sepsis and in 22% (14) patients showing mixed sepsis whereas *MRSA* was found in 30% (12) patients showing mono-agent sepsis and 22% (14) patients having mixed sepsis.

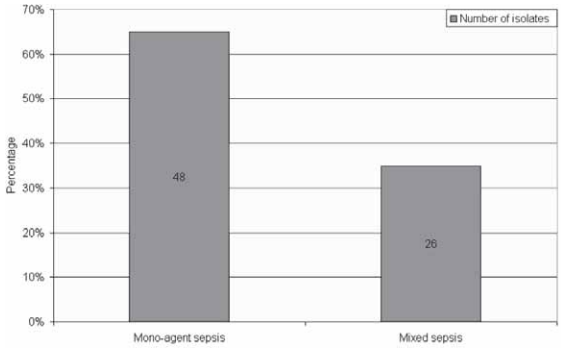

Fig. 1. Types of sepsis.

A. baumannii was identified at 10% (4) patients showing mono-agent sepsis and at 18% (12) patients with mixed sepsis.

Coagulase-negative *Staphylococcus, Staphylococcus aureus, Klebsiella pneumoniae* and *Serratia marcescens* were detected with equale frequency in 3% (1) patient

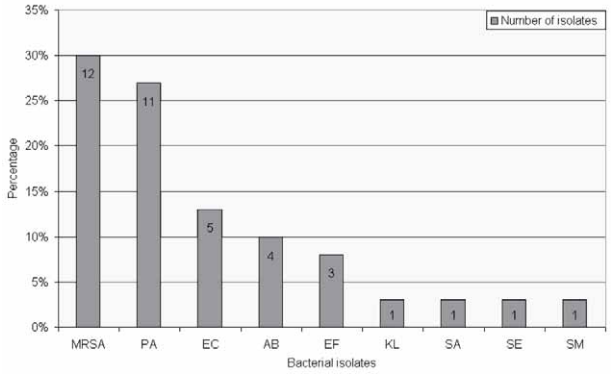

Fig. 2. Bacterial isolates in mono-agent sepsis. AB – Acinetobacter baumannii, *EC* – Escherichia coli, *EF* – Enterococcus faecalis, *ES* – Enterobacter *spp, KL* –Klebsiella pneumoniae, *MRSA* – *Methicillin-resistant* Staphylococcus aureus, *PA* – Pseudomonas aeruginosa, *SA* – Staphylococcus aureus, *SE* – *coagulase- negative* Staphylococcus, *SM* – Serratia marcescens.

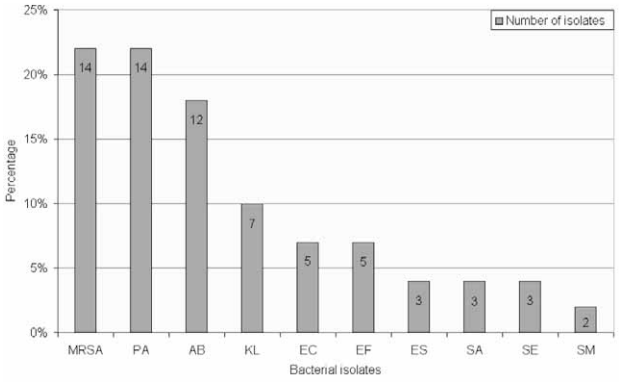

Fig. 3. Bacterial isolates in mixed sepsis. AB – Acinetobacter baumannii *EC* – Escherichia coli, *EF* – Enterococcus faecalis, *ES* – Enterobacter *spp, KL* –Klebsiella pneumoniae, *MRSA* – *Methicillin-resistant* Staphylococcus aureus, *PA* – Pseudomonas aeruginosa, *SA* – Staphylococcus aureus, *SE* – *coagulase-negative* Staphylococcus, *SM* – Serratia marcescens.

with mono-agent sepsis. At mixed sepsis coagulase-negative *Staphylococcus* and *S. aureus* were detected also at 4% (3) patients respectively, same as *Enterobacter species,* whereas *S. marcescens* was at 2% (2) patients. *K. pneumoniae* was identified at 10% (7) patients showing mixed sepsis. *Escherichia coli* was found in 5(13%) patients with mono-agent sepsis and also at 5 (7%) patients with mixed sepsis. *Enterococcus faecalis* was found in 8% (3) patients with mono-agent sepsis and in 7% (5) patients with mixed sepsis.

The initial (empirical) antibiotic therapy was changed in 52 (70%) patients, in spite of that 9 patients died. Initial antibiotic therapy was not changed in 22 (30%) patients 13 of them died. Total mortality rate was 30% (22 of 74 patients).

Average value of APACHE II score was 16, average value of APACHE II score for patients who died was 22, APACHE II score was higher in patients who died.

The predicted value of APACHE II score for mortality was 40%, which correlated with total mortality of 30%.

Statistical analysis

There was statistically significant difference in APACHE II score between patients who were successfully treated and those who died (Mann-Whitney U-test, $p=0.002$). No significant difference in APACHE II score was found between patients who died with mono-agent sepsis and mixed sepsis ($p>0.05$).

Antimicrobial therapy was significantly more often changed according to antibiogram for younger patients compared to the older patients (Mann-Whitney U-test, $p=0.027$).

According to a causative agent correction of the therapy was more often necessary for mixed sepsis (χ^2 test, $p=0.019$).

Prevalence of bacterial isolates and temporary trends

MRSA (25%) and *P. aeruginosa* (23%) were the most prevalent bacterial isolates from the blood-culture followed by *A. baumannii* (15%) and *E. coli* (9%) (Figure 4). There were 7% isolates of *E. faecalis* and *K. pneumoniae* and were 4% of coagulase-negative *Staphylococcus* and *S. aureus*.

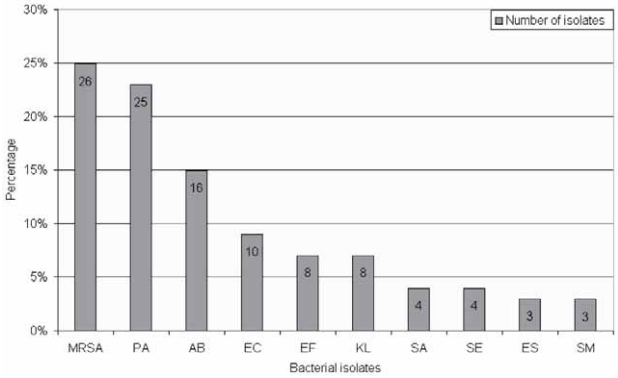

Fig. 4. Prevalence of bacterial isolates. AB – Acinetobacter baumannii, *EC* – Escherichia coli, *EF* – Enterococcus faecalis, *ES* – Enterobacter *spp, KL* –Klebsiella pneumoniae, *MRSA* – *Methicillin-resistant* Staphylococcus aureus, *PA* – Pseudomonas aeruginosa, *SA* – Staphylococcus *aureus, SE* – *coagulase-negative* Staphylococcus, *SM* – Serratia marcescens.

The least prevalent were *Enterobacter* spp. and *S. marcescens* (3%). There was remarkable increase of *A. baumannii* prevalence in 2005 (11 isolates) compared to 2004 (4 isolates) and to 2003 (1 isolate).There was also decrease of MRSA prevalence in 2004 and 2005 (7 isolates) compared to 2003 (12 isolates, Figure 5).

Antimicrobial susceptibility

100% of MRSA strains were susceptible to vancomycin and rifampicin. Among *P. aeruginosa* no resistance

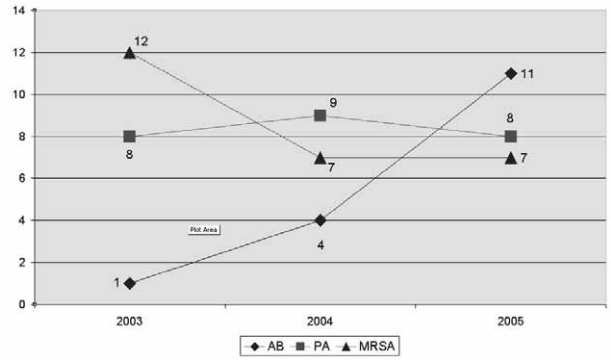

Fig. 5. Major causative agents of sepsis. AB – Acinetobacter baumannii*, MRSA – Methicillin-resistant* Staphylococcus aureus*, PA* – Pseudomonas aeruginosa.

to ceftazidime, meropenem, colistin was observed. All *A. baumannii* strains were susceptible to ampicillin+sulbactam, imipenem, meropenem. All *Enterobacteriaceae* (*K. pneumoniae, Enterobacter spp.* and *E. coli)* strains were sensitive to ceftazidime, gentamicin, imipenem and meropenem. Coagulase-negative *Staphylococcus* was sensitive to ampicillin and cloxacillin. *Enterococcus spp.* waere sensitive to ampicillin, vancomycin and rifampicin.

Discussion

The many recent studies report high frequency of sepsis, mortality rates, with 27% of patients dying in the ICU, rising to more than 50% in patients with severe sepsis and septic shock[5,10]. We report higher mortality rate of severe sepsis than in some other recent study; for example, the EPISEPSIS study in France reported that 15% of patients had severe sepsis and UK study reported a rate of 27%[11]. However, this study included patients admitted for routine postoperative surveillance who are likely to have lower rates of complications. In contrast, in our study more patients were admitted in emergency.

In spite of the all known guidelines and recommendation for treating, sepsis is still associated with significant mortality and health-care costs[1,12,13]. Mortality rate according to our results was 30%, which is in concordance with the bibliographic data.

Furthermore, this proportion remains high in spite of the new antimicrobial agents[1,14].

Another important problem remained the type of sepsis: mono-agent sepsis presented less therapeutic problem than sepsis caused with two or more agent (mixed sepsis). There was 35% mixed sepsis and 65% mono-agent sepsis in our study. This is also correlated with the data published by other autors[6,14,15]. We found 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[9,16,17].

Identification of the sepsis's source (focus) could be very helpful, especially for the empirical therapy. There is difference in therapeutic approach between intraabdominal infection, pneumonia, (ventilator associated pneumonia – VAP) or catheter-associated infection[18]. The predominant source of sepsis in our surgical ICU was intra-abdominal infection, followed by VAP.

We observed an increasing trend on *A. baumannii* sepsis in contrast to MRSA sepsis.

Trampuz and Zimerlli[19] suggested flucloxacillin + amikacin like empirical therapy for unknown causative agent. Paul-Erlich-Gesellschaft recommended cephalosporine III generation and aminoglicoside[20].

According to the antibiograms of the strains isolated in our surgical ICU, we would suggest cephalosporine III 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 β-lactamase stable penicillin (flucloxacillin) should be added to empirical therapy[15,21].

A.baumannii and *P.aeruginosa* often require administration of carbapenems, due to their multiple antibiotic resistence[22–24]. Carbapenems remains antibiotic of choice for the treatment of infections caused by ESBL *K. pneumoniae* and *E.coli*. Vancomycin or linezolide we would recommend for the therapy of sepsis caused by MRSA[25,26].

Carbapenems and ampicillin+sulbactam could be considered as an option for the treatment of sepsis caused by *A. baumannii*, which is a pathogen of growing importance nowadays.

Surveillance of antimicrobial susceptibility of the causative agents and their trends could be very useful to create guidelines for the empirical therapy of the sepsis with the unknown causative agent.

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MIKROBIOLOŠKI NADZOR U KIRURŠKOJ JEDINICI INTENZIVNOG LIJEČENJA KBC-a ZAGREB – PILOT-STUDIJA ZA SMJERNICE TERAPIJE TEŠKE SEPSE

S A Ž E T A K

Retrospektivnom studijom od 01.01.2003. godine do 31.12.2005. godine kod 74 bolesnika iz kirurškog JIL-a KBC-a Zagreb, pratili smo promjene prevalencije uzročnika sepse koristeći se pri tome njihovim kliničkim i mikrobiološkim podacima. Cilj rada bio je odrediti smjernice za početnu antibiotsku terapiju teške sepse kod bolesnika u kirurškom JIL-u. Antimikrobna osjetljivost uzročnika izoliranih iz hemokulture određivana je metodom disk-difuzije prema CLSI (Clinical Laboratory Standard Institution). APACHE II score korišten je za procjenu težine i ishoda bolesti. Mann-Whitney i χ^2 test služili su za statističku obradu podataka, a kao granica statističke značajnosti uzet je $p<0.05$. Polimikrobna sepsa je bila posebno težak problem, kako za određivanje definitivne antibiotske terapije, tako i za određivanje empirijske antibiotske terapije. Izolirano je deset različitih uzročnika sepse, a najčešći su: meticilin-rezistentni *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa* i *Acinetobacter baumannii*. Njihova prevalencija se mijenjala kroz te tri godine, tako da je MRSA bila vodeći uzročnik sepse u 2003. godini, *P. aeruginosa* u 2004. a *A. baumannii* u 2005. Kod naših bolesnika, MRSA je pokazala dobru osjetljivost na vankomicin i linezolid, *P. aeruginosa na* ceftazidim i karbapeneme, a *A. baumannii* na ampicilin+sulbaktam i karbapeneme.