

# METHICILLIN SENSITIVE AND RESISTANT STAPHYLOCOCCUS AUREUS IN BLOODSTREAM INFECTIONS: FREQUENCY, OUTCOME AND COST OF TREATMENT IN THE SOUTHERN PART OF BOSNIA AND HERZEGOVINA

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received: 17.04.2023;

revised: 23.10.2023;

accepted: 18.12.2023

## SUMMARY

**Background:** Bloodstream infections (BSI) encountered in hospitals are one of the most complex infections that pose a great challenge. Methicillin-sensitive and Methicillin-resistant *Staphylococcus aureus* are common causes of severe bloodstream infections that are associated with organ failure and septic shock. Hence, better knowledge of the incidence of BSI caused by MRSA and MSSA and adequate antibiotic treatment are important to reduce length of hospital stay and improve treatment outcomes.

**Subjects and methods:** The aim of this study was to analyze the frequency of BSI with MSSA and MRSA in adult patients who were hospitalized at the same time and same departments of the University Hospital Centre Mostar in the course of six years.

**Results:** The incidence of BSI with MSSA and MRSA was shown to be 33,21% and 17,99%, respectively. Average age of patients infected with MRSA was 61.5 years and with MSSA was 67.5 years. MSSA and MRSA BSI were more common in men with average of 69,79% and 80,77%, respectively. In both groups of patients, one third had no associated diseases. Patients that had associated chronic disease with mild or moderately severe activity limitations constructed 41,67% with MSSA and 46,15% with MRSA. Cardiovascular diseases were most common chronic disease in both groups, 33.33% for MSSA and 40.38% for MRSA. Treatment of the of subjects with MSSA BSI averaged 15 days and lasted significantly shorter when compared to MRSA BSI treatment that averaged 36 days. Patients with MRSA BSI were more treated in middle and/or high-risk departments and with inadequate antibiotic therapy. MRSA BSI patients were more often mechanically ventilated (69,23%), which contributes to a higher cost of treatment (average of 8032.5€ in total) and higher drug consumption when compared to the MSSA BSI patients. The death rate was higher in patients treated for MRSA BSI and averaged 67.31%.

**Conclusions:** The results of this study are promising since they can be used in practice by clinicians as a guideline for choosing adequate antibiotics, and improve course of treatment, length, outcome and cost.

**Keywords:** Bloodstream infections, MSSA, MRSA, antimicrobial treatment

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## INTRODUCTION

Bloodstream infections (BSI) encountered in hospitals are one of the most complex infections, and due to various unknowns in diagnosis and therapy, they represent a great challenge. BSIs represent a significant problem of modern medicine due to their negative impact on the morbidity and mortality of hospitalized persons, and thus cause a significant increase in the total cost of treatment (Curic et al. 2006). Methicillin-resistant *Staphylococcus aureus* (MRSA) was described in 1961, and MRSA epidemics were reported in

the early 1960s (Barber 1961, Benner & Kayser 1968). Since then, MRSA infection has spread all over the world, and the prevalence of MRSA has increased in health and community. Prevalence of Methicillin resistance among *Staphylococcus aureus* isolates in US intensive care units was 60% (National Nosocomial Infections Surveillance System 2004), and more than 90,000 invasive infections due to MRSA were recorded in the United States in 2005 (Klevens et al. 2007). Methicillin-sensitive *Staphylococcus aureus* (MSSA) is a common cause of severe bloodstream infection (BSI) that leads to organ failure and septic shock (Barber 1961, Benner

& Kayser 1968). Incidence is estimated at 26/100 000 inhabitants per year, and 30-day cause of death is about 20%. Risk factors for MSSA BSI as well as factors associated with poor prognosis include older age, hemodialysis, diabetes mellitus and immunosuppression (Jacobsson et al. 2007). Time and choice of antibiotics are important because delay in treatment and inadequate selection of antibiotics are associated with a reduced survival rate. Patients with MRSA BSI have higher mortality, longer hospital treatment, and higher treatment costs than patients with MSSA BSI (Cosgrove et al. 2003, Antonanzas, Lozano & Torres 2015, Cosgrove et al. 2005, Reed et al. 2005, Abramson & Sexton 1999). Meta-analysis with data on approximately 4,000 patients showed that patients with MRSA BSI are 1.5 to 2.0 times more likely to die than those with BSI due to MSSA (Manzur et al. 2007). Patients with BSI MRSA have higher rates of acute renal failure, hemodynamic instability and longer need for mechanical ventilation when compared to patients with MSSA BSI (Antonanzas, Lozano & Torres 2015). The rate of MSSA and MRSA bloodstream infections, the cost of treatment and the outcome have not yet been investigated in Bosnia and Herzegovina. Therefore, the aim of this study is to investigate frequency of occurrence of MSSA and MRSA BSI, cost of treatment, mortality and patients features in individual Departments of the University Clinical Hospital Mostar.

## SUBJECTS AND METHODS

### Procedure and participants

This study is a cohort observational retrospective analysis of prospectively collected data of patients with BSI, in time period of six years, from January 1, 2010 to December 31, 2015. The collected data include gender, age, previous health condition, department in which the patient was treated, usage of antibiotics, hospitalization length, outcome and cost. Data was obtained from the information system of University Hospital Center Mostar with the approval of the local ethical committee board, approval number 1463/15. Sensitive and resistant agents in the blood cultures of patients were analyzed following the institution protocol and samples shown to be Methicillin-resistant *Staphylococcus aureus* (MRSA) and Methicillin-sensitive *S. aureus* (MSSA) were investigated in more depth in this study. The subjects were exclusively hospitalized adults (18-74 years old) treated for developed bloodstream infection (regardless of the age, gender and previous health condition) with positive MSSA and MRSA blood cultures during the period from January 1, 2010 to December 31, 2015. Control group were patients treated at the same time and the same departments but with no BSI. The study included all subjects with both primary and secondary infections. Primary infection occurs when peripheral blood causative agent is isolated without any signs

of infection of other localization in the body and secondary infection occurs when there is a previous infection of one or more organic systems with a subsequently isolated peripheral blood causative agent (Chan 1983). Patients included in the study were treated in three different risk departments. In risk departments patients have higher risk of acquiring and developing hospital infections. Three categories of risk departments are: High Risk Departments (Department of Anesthesia, Resuscitation and Intensive Care, Surgical and Interventional Surgery Units, Neonatology and Intensive Care Department, Surgery Clinic, Department of Otorhinolaryngology and Pediatrics Surgery, Internal Diseases Clinic), Mild-Risk Departments (Department of Gynecology and Obstetrics, Infectious Diseases Clinic, Department of Pulmonary Diseases and Tuberculosis, Neurology Clinic) and Low Risk Departments (Department of Cardiology, Gastroenterology, Endocrinology, Immunology with Rheumatology, Psychiatric Clinic, Department of Physical Medicine and Rehabilitation).

### Statistical analysis

In statistical data analysis, the symmetry of sociodemographic variables and clinical variables was tested by the Kolmogorov-Smirnov test. The obtained distribution of results significantly deviated from normal ( $p < 0.05$ ) therefore the mean values and the dispersion measures, median and interquartile scattering was used. In order to test differences in demographic and clinical parameters between groups of patients with BSI and control groups, non-parametric testing of differences between multiple independent groups was used. The differences as well as the correlation between the investigated variables were considered statistically significant when  $p$  values were greater than 0.05. Statistical analysis was done with SPSS software (version 15.1, SPSS, Chicago).

## RESULTS

During the six-year period of investigation, the number of patients with BSI caused by resistant and sensitive pathogens was 289 in total, out of which 96 patients had BSI caused by MSSA (33,21%) and 52 subjects had BSI caused by MRSA (17,99%). The remaining number of patients were diagnosed with BSI caused by other pathogens. As can be observed from Table 1, in both BSI infections, higher number of patients were male, 69,79% with MSSA BSI and 80,77% with MRSA BSI. Group of patients with MRSA BSI had an average age of 61.5 years versus the average age of MSSA BSI patients, which was 67.5 years. In both groups of patients, one third of the patients had no chronic comorbidity, and nearly half of them had associated chronic disease with mild to moderate severe restriction of activity. The most common chronic disease in both affected groups was

**Table 1.** Demographic and clinical features BSI with MSSA and MRSA

	Gram positive	bacteria	Test	p
	MSSA	MRSA		
Age				
Median	67,500	61,500	-1,371†	0,170
Interquartile scattering	52-74	44-73,500		
Gender				
Female	29 (30,21%)	10 (19,23%)	2,094‡	0,147
Male	67 (69,79%)	42 (80,77%)		
Previous health condition				
Healthy	29 (30,21%)	14 (26,92%)		
Chronic disease with mild limitation of activity	40 (41,67%)	24 (46,15%)		
Chronic disease with a medium to severe activity limitation	26 (27,08%)	13 (25%)	0,531‡	0,911
Chronic disease with a severe restriction of activity	1 (1,04%)	1 (1,92%)		
Comorbidities				
Infectious and parasitic diseases	6 (6,25%)	2 (3,85%)		
Neoplasms	14 (14,58%)	5 (9,62%)		
Blood and blood vessels and immune disorders	5 (5,21%)	0 (0%)		
Endocrine Disorders	7 (7,29%)	0 (0%)		
Mental Disorders and Behavioral Disorders	1 (1,04%)	0 (0%)		
Nervous system disorders	2 (2,08%)	2 (3,85%)		
Disease of the eye	0 (0%)	0 (0%)		
Disease of the ear	1 (1,04%)	0 (0%)		
Diseases of the cardiovascular system	32 (33,33%)	21 (40,38%)	-	-
Diseases of the respiratory system	7 (7,29%)	4 (7,69%)		
Gastrointestinal diseases	6 (6,25%)	8 (15,38%)		
Skin and subcutaneous tissue disorders	3 (3,13%)	0 (0%)		
Diseases of the musculoskeletal system and connective tissue	1 (1,04%)	0 (0%)		
Diseases of the genitourinary system	8 (8,33%)	3 (5,77%)		
Delivery	0 (0%)	0 (0%)		
Symptoms, signs and abnormal clinical and laboratory findings that are not classified elsewhere	1 (1,04%)	0 (0%)		

**Table 1.** Continuous

Injuries and effects of external factors	2 (2,08%)	7 (13,46%)		
Department				
Low risk	79 (82,29%)	14 (26,92%)		
Medium risk	8 (8,33%)	9 (17,31%)	47,096‡	0,000***
High risk	9 (9,38%)	29 (55,77%)		
Antibiotic treatment				
Adequate		71 (72,63%)	11 (21,15%)	35,901‡ 0,000***
Inadequate		25 (26,04%)	41 (78,85%)	38,064‡ 0,000***
Length of hospitalization				
Median	15	36	5,323†	0,000***
Interquartile scattering	11-25	21-58		
Mechanically ventilated				
Yes	9 (9,38%)	36 (69,23%)	57,108‡	0,000***
No	87 (90,63%)	16 (30,77%)		
Outcome				
Dead	31 (32,29%)	35 (67,31%)	16,738‡	0,000***
Alive	65 (67,71%)	17 (32,69%)		
Costs (€)				
Median	1729,500	8032,500	7,420†	0,000***
Interquartile scattering	1145-2727	3909-13430,50		
Costs per hospital day (€)				
Median	373	2040,500	5,440†	0,000***

† Mann-Whitney test; ‡  $\chi^2$ ; \*\*\*  $p < 0,001$

cardiovascular disease, 33.33% of patients with MSSA BSI and 40.38% of patients with MRSA BSI (Table 1). Significantly shorter time of treatment was noted in subjects with MSSA BSI, averaging 15 days of treatment mainly in low-risk departments. On the contrary, MRSA BSI patients were treated for an average of 36 days mainly in high-risk departments. Inadequate antibiotic therapy was applied to 41 subjects (78.85%) with MRSA BSI and to 25 patients (26,04%) with MSSA BSI. Patients with MRSA BSI

were more often mechanically ventilated (69,23%), when compared to MSSA BSI patients (9,38%). Consequently, mortality rate was higher in subjects treated for MRSA BSI and was shown to be 67.31%. All of the above reasons contributed to a higher cost of treatment of patients with MRSA BSI that was on average 8032.5 €, and enhanced drug use per day of hospitalization, which was 2040.5 €. As can be observed in Table 2, the most commonly used antibiotic in the therapy for MSSA patients was Cefazolin

**Table 2.** Adequate and inadequate antibiotic therapy BSI with MSSA and MRSA

Antibiotic	Gram positive bacteria	
	MSSA	MRSA
<b>ADEQUATE</b>		
Amikacin	1 (1,49%)	2 (18,18%)
Amox/Klav	16 (23,88%)	0 (0%)
Cefazolin	20 (29,85%)	0 (0%)
Ceftriaxone	16 (23,88%)	0 (0%)
Cefuroxime	1 (1,49%)	0 (0%)
Ciprofloxacin	4 (5,97%)	1 (9,09%)
Gentamicin	4 (5,97%)	0 (0%)
Clindamycin	1 (1,49%)	0 (0%)
Vancomycin	1 (1,49%)	7 (63,64%)
Amox/Klav+Gentamicin	0 (0%)	1 (9,09%)
Ceftriaxon+Clindamycin	1 (1,49%)	0 (0%)
Ceftriaxone+Kloksacilin	2 (2,99%)	0 (0%)
<b>INADEQUATE</b>		
Amox/Klav	0 (0%)	1 (2,44%)
Azithromycin	3 (18,75%)	1 (2,44%)
Cefazolin	0 (0%)	2 (4,88%)
Ceftazidime	1 (6,25%)	2 (4,88%)
Ceftriaxone	0 (0%)	6 (14,63%)
Cefuroxime	0 (0%)	1 (2,44%)
Ciprofloxacin	0 (0%)	3 (7,32%)
Colistin	0 (0%)	1 (2,44%)
Gentamicin	0 (0%)	1 (2,44%)
Meropenem	8 (50,00%)	8 (19,51%)
Metronidazole	4 (25,00%)	5 (12,20%)
Moxifloxacin	0 (0%)	1 (2,44%)
Cefazolin+Gentamicin	0 (0%)	1 (2,44%)
Ceftriaxon+Klindamicin	0 (0%)	1 (2,44%)
Ceftriaxon+Metronidazol	0 (0%)	3 (7,32%)
Ceftriaxon+Metronidazol	0 (0%)	1 (2,44%)
Gentamicin+Ceftriaxon	0 (0%)	1 (2,44%)
Meropenem+Gentamicin	0 (0%)	1 (2,44%)
Meropenem+Metronidazol	0 (0%)	1 (2,44%)

(29.85%), and in the case of MRSA BSI was Vancomycin in 7 patients (63.64%). Inappropriate antimicrobial therapy was the use of Meropenem in 50% patients treated with MSSA and in 19.51% patients with MRSA BSI.

## DISCUSSION

By comparing and analyzing demographic and

clinical indicators of BSI in patients hospitalized in the six-year period in University Hospital Centre Mostar, this study reveals some important features in incidence and clearly defines predictor values that affect the outcome of the disease and the cost of treatment. This study showed the incidence of BSI with MSSA pathogen to be 33,21% and the incidence of BSI with MRSA pathogen to be 17,99%. There have been no similar studies in the literature since other studies generally classified the

causative agents according to the affiliation of BSI according to gram positive cocci or gram-negative bacilli. In our research patients were more likely to be male, in contrast to Manzur, et al. (2007) that found higher incidence of BSI with MSSA and MRSA in females. An average age of patients, older than 60 years, corresponded with other studies. Most of the patients with MSSA BSI were treated in low-risk units as is expected in contrast to MRSA BSI patients that were treated in medium or high risk units similar to the results of research conducted by Wang, et al. (2016) (Manzur et al. 2007, Wang et al. 2016). In both groups of this study, longer treatment and higher mortality rate were recorded in patients with BSI associated with cardiovascular disease compared to those with other chronic diseases. This is not in accordance with previously published studies. Namely, Turkish research on the correlation between comorbidity and BSI found primarily association with chronic kidney failure and diabetes. Other studies point out malignant diseases and problems with gastrointestinal tract as most commonly associated with MSSA and MRSA BSI (Delle Rose et al. 2015, Süner et al. 2015). Adequate antimicrobial treatment was significantly more administrated in MSSA BSI patients (72,63%), while MRSA BSI was more treated with inadequate antimicrobial treatment (78,85%). The most common antibiotics for appropriate treatment in patients with MSSA BSI were Ceftriaxone and patients with MRSA BSI with Vancomycin, which affect the beneficial outcome of treatment. As far as inadequate antibiotic treatment is concerned, the most commonly used drug for both groups was Meropenem. This result is uncommon, but it can be explained with the fact that in the critically ill patient's Gram-negative bloodstream infections were expected. Inadequate antimicrobial therapy in heavily ill patients in ICU and a higher mortality rate were also reported by Zaragoza, et al. (2003). In cases of MSSA BSI that were investigated in this study have shown that the length of hospitalization, the increased number of hemocultures and the use of mechanical ventilation can significantly increase the costs of treatment and the consumption of drugs. Similarly, in cases of MRSA BSI, the age and length of hospitalization have proved to be significant predictor variables and important criteria of drug consumption per hospital day. Increasing the number of hospital days increases the consumption of drugs, especially in the younger group. Younger patients with MRSA BSI have higher costs of treatment and higher consumption drugs per hospital day. Similar research in the intensive care unit in Turkey has been conducted to determine the frequency and risk factors for BSI confirming that BSI increases mortality, length of stay in hospital and treatment costs (Süner et al. 2015). Longer hospitalization has been detected for patients with MRSA BSI with an average of 36 days, versus MSSA BSI patients treated for 15 days. Similarly, Laupland, et al. (2006) reported average of 15.5 days of ICU treatment of BSI, and 12 days of treatment outside

the ICU. In both groups (BSI with MRSA and MSSA) the duration of treatment did not depend on the type of BSI, but was in correlation with chronic heart disease. The cost of treating MRSA BSI was higher than the MSSA BSI, averaging 8032,5 EUR in total. The same was with the drug consumption per hospitalized day, averaging 2040,5 EUR for MRSA BSI patients. Similar results were reported by Rosenthal, et al. (2003) with total BSI costs between \$10000 and \$20000, and Brunelli, et al. (2016) with reports of \$129.000 in hospitalization costs.

## CONCLUSIONS

The length of treatment, use of mechanical ventilation, cost of treatment, consumption of drugs according to the hospitalized day and the greater mortality rate is higher in patients with chronic heart disease associated with MRSA BSI. Bloodstream infections with MSSA and MRSA are associated with a number of factors such as general health care, gender, age, comorbidity and the immune response of the host, which significantly affects the outcome and treatment costs. Results of this research could contribute to the development of clinical guidelines for the treatment of BSI and indicate the possibility of preventive action against BSI, improve control measures and control of hospital infections as an important indicator of quality in health care. The findings of this study can in practice give the clinician clear guidelines on the empirical choice of antibiotics for the treatment of BSI, thus influence the course of treatment, length, outcome and cost.

**Acknowledgements:** None.

**Conflict of interest:** None to declare.

## Contribution of individual authors:

Svjetlana Grgić: study design, literature search, data collection, statistical analyses, manuscript writing. Mladenka Vukojević, Emina Deumić, Sanja Jakovac: literature search, manuscript writing. Jelena Soldo: data collection. All the authors have approved the final version.

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