THE INCIDENCE OF NOSOCOMIAL INFECTIONS IN PATIENTS WITH ISOLATED SEVERE TRAUMATIC BRAIN INJURY

Valencic Lara,¹ Sotosek Tokmadzic Vlatka,² Kuharic Janja,² Sustic Alan²

¹ Medical Faculty, University of Rijeka, Rijeka, Croatia
² Department of Anesthesiology, Reanimatology and Intensive Care, Medical Faculty, University of Rijeka, Rijeka, Croatia

Abstract: Introduction: Traumatic brain injury is the leading cause of death in children and adults in developed countries. Severe traumatic brain injury is classified with Glasgow Coma Scale score 8 and less. About 50% of patients with severe traumatic brain injury develops at least one infection as a complication of primary condition during hospitalization in the Intensive Care Unit, resulting with fatal outcome in 28% of patients. Ventilator — associated pneumonia is the leading infection that affects patients with severe traumatic brain injury, with an incidence between 41% and 74%. Following are sepsis and urinary tract infections.

The aim: To analyze the number of patients with nosocomial infection and isolated severe traumatic brain injury hospitalized in the Intensive Care Unit of the Clinical Hospital Centre Rijeka, Croatia, from 31st January 2013 to 31st December 2014.

Patients and methods: A two — year retrospective study included 46 patients with isolated severe traumatic brain injury hospitalized in the Intensive Care Unit of the Clinical Hospital Centre Rijeka, Croatia, in the period from 31st January 2013 to 31st December 2014. All medical data was collected from the Division of Intensive Care Unit, Clinical Hospital Centre Rijeka, Croatia.

Results: From 67 patients with isolated severe traumatic brain injury, 46 (68,65%) of them developed nosocomial infection. There was statistically significant more male patients than female (p < 0.05). The average age of infected patients was 57,8 years. The leading were the infections of the respiratory system. Gram — negative bacteria Proteus mirabilis and Pseudomonas aerugionsa were the leading pathogens. The average duration of the infection was 5,77 day. Duration of mechanical ventilation accounted for the majority of the patients more than 10 days. The average duration of treatment for all 46 patients was 10,475 days, and for 16 (34,78%) of them, the treatment outcome was lethal.

Conclusion: Nosocomial infections are becoming a major public health problem. The emphasis must be set on the prevention which includes maintaining the hygiene and the antiseptic rules among the medical personnel of the Intensive Care Unit. Already developed infections must be adequately treated so the negative treatment outcomes can be reduced.

Key words: isolated severe traumatic brain injury, Glasgow Coma Scale, Intensive Care Unit, nosocomial infections, gram – negative bacteria.

INTRODUCTION

Traumatic brain injury (TBI) presents traumatically induced structural damage of brain as a result of external force. It is usually followed by temporary or permanent cognitive brain dysfunction. Some of the early onset clinical signs that can indicate TBI are quantitative loss of consciousness, immediate memory loss before or after the injury, alteration in mental state, neurological sequelae and presence of intracranial lesions (1).

In developed countries, TBI is the leading cause of death in children and adults (2). In European countries, every year is hospitalized about 1,6 milion people with TBI. That forms a brain injury rate of 235/100 000 per year (3). Epidemiological data from Center for disease control and prevention, shows that in the United States TBI makes 30% of all injury deaths (4). The most vulnerable groups are children aged 0 to 4, older adolescents between the ages of 15 and 19, and people older than 75 years. Incidence is highest between the ages of 15 and 30, with the greatest risk between the ages of 15 and 24. Men have 1,4 times greater risk compared to
female (5). The most common cause of TBI are traffic accidents, accounting for 50%. Falls are the second leading cause with 20% to 30%. Incidence of TBI caused by falls is increasing as the population ages. On that way contusions of brain, that are more frequent in older patients, are becoming the most common biomechanical mechanism of TBI. Violence is the third leading cause, accounting for 7% to 10%. The incidence of injuries due to firearms rises on the fourth place (6).

Using the most widely applied system for observation and assessment of the level of consciousness called Glasgow Coma Scale (GCS), TBI is divided into the three levels. Scoring the opening of the eyes, verbal and motor response, the total sum from 13 to 15 places the patient into the group with the mild TBI. Total score from 9 do 12 places the patient into the group with moderate TBI. Severe TBI is classified with total score 8 and less (7). Studies indicate that the severity of the injury is proportional to the treatment outcomes; the more difficult injury is related with greater chance of complications and death. Patients with severe TBI are 37 times more likely to die of neurological sequels such as seizures, 12 times more often from sepsis, 4 times more often from pneumonia, and 3 times more often from other respiratory (except pneumonia) and digestive difficulties than healthy population (8). Using the combination of clinical examination and radiological diagnosis, that includes native computed tomography of the brain, it can be achieved prompt diagnosis, and therefore adequate therapy. The aim is to prevent secondary brain injury, primarily hypotension and hypoxia, in order to prevent the patients deterioration and complications like nosocomial infections and potential death (6).

Patients with severe TBI have a high risk for development of nosocomial infections. Nosocomial infections are defined as infections occurred in the hospital environment at least 48 hours from receiving patient for treatment. Approximately 9% to 37% of patients admitted to an Intensive Care Unit (ICU), will acquire one or more infections. Risk factors are invasive intensive monitoring, intravenous therapy, mechanical ventilation, and according to some studies, the release of catecholamines after stimulation of the sympathetic nervous system during brain injury that results with induction of systemic immunosuppression (9, 10). The incidence of people with severe TBI is only 10%, but is associated with the highest mortality rate which ranges between 30% and 54% (11). About 50% od patients with severe TBI develops at least one infection as a complication of primary condition during hospitalization in ICU, resulting with fatal outcome in 28% of patients (9, 12, 13).

Nosocomial, ventilator – associated pneumonia (VAP) is the most common infection that affects patients with severe TBI. The incidence ranges between 41% to 74%. The main risk factors for this type of infection are endotracheal intubation and mechanical ventilation. During the first week of hospitalization the risk for developing VAP is 15%, and in the second week rises on 20% and more. VAP is dived into the two groups. First one is early – onset VAP that occurs in the first 48 to 72 hours from the beginning of intubation and ventilation. It is the result of microaspiration of colonized oropharyngeal secretions and it is caused by pathogens that are sensitive to antimicrobial therapy (13). The second one is late – onset VAP that develops after 72 hours from the beginning of intubation and ventilation. This type of infection is a result of long lasting intubation and ventilation, as well as prophylactic application of broad – spectrum antibiotics. Pathogens are highly virulent and multiresistant. The most common pathogen is gram – negative bacteria Pseudomonas aeruginosa, whose incidence reaches up to 47% (14, 15). Therapy includes de – escalating antibiotic therapy (13).

Patients with severe TBI present one of the most vulnerable group of patients for development of the second most common nosocomial infection called sepsis, whose incidence ranges between 10% and 41%. The leading cause is bacteremia, while something less frequent causes are fungemia, viremia, and parasitemia (9, 16). Early diagnostic is essential for prompt prevention and treatment of this type of infection. Diagnostic criteria for sepsis are documented or suspected infection that is associated with some of the following variables like general, inflammatory, hemodynamic, organ dysfunction and tissue perfusion variables (17, 18). Treatment includes adequate intravenous antimicrobial therapy, drainage of abscesses, debridement of necrotic tissue or removal of infected foreign body. The most common is combination of a penicillin/β – lactamases inhibitors or third – generation cephalosporins with an aminoglycosides. It is essential to maintain adequate perfusion with intravenous fluids and inotropic and vasopressor agents (18).

The third most common nosocomial infections are urinary tract infections (UTIs) that are catheter – associated, with an incidence about 15%. Studies show that bacteriuria occurs in patients who require a bladder catheter for longer than 48 hours (19). The leading pathogens are gram – negative bacteria such as Escherichia coli, Enterobacter species, Proteus species, Klebsiella species, non – lactose – fermenting bacteria such as Pseudomonas aeruginosa, and some other organisms such as staphylococcal species and Enterococcus. Bacteriuria can lead to bacteremia, and subsequently in sepsis in about 5% of the time. Therapy also includes combination of a penicillin/β – lactamases inhibitors or third – generation cephalosporins with an aminoglycosides.
Prevention of ICU-acquired UTIs is important because UTIs are associated with increased mortality (13).

The aim of this two-year retrospective study was to analyze the number of patients with isolated severe TBI hospitalized in the Intensive Care Unit of the Clinical Hospital Centre Rijeka, Croatia from 1st January 2013 to 31st December 2014, who developed infection during their hospitalization. The aim was also to analyze the type of infection and leading pathogens, as well as the duration of infection and treatment outcomes.

PATIENTS AND METHODS

This retrospective study was undertaken at Department of Anesthesiology, Reanimatology and Intensive Care, Division for Intensive Care Unit, Clinical Hospital Centre Rijeka, Croatia. It was included 67 patients with isolated severe TBI who were hospitalized in the period from 1st January 2013 to 31st December 2013, and between 1st January 2014 and 31st December 2014. General informations which included the name, surname, gender and age of every patient were considered. From 67 patients with severe TBI, 46 of them developed nosocomial infection. We analyzed GCS score at admission to the ICU, types of nosocomial infections, and the leading pathogens for every hospitalized infected patient with severe TBI during analysis of the study. We analyzed most commonly used antimicrobial drugs in treatment of infected patients, as well as the duration of infection, mechanical ventilation and treatment during the hospitalization in the ICU, as well as the treatment outcomes. Privacy rights of all patients were maintained with respect to all ethical and moral standards in accordance with the Declaration of Helsinki.

We collected medical data of all patients from database of Department of Anesthesiology, Reanimatology and Intensive Care, Division for Intensive Care Unit, Clinical Hospital Centre Rijeka, Croatia. All medical records were analyzed using Microsoft Excel. Statistical analysis was performed using STATISTICA 12 (StatSoft, Tulsa, USA). For calculation of statistical significance we used Mann – Whitney non-parametric test for small independent samples, and a chi-squared test for the test of independence of two variables. P < 0.05 was considered statistically significant.

RESULTS

During the period of time from 1st January 2013 to 31st December 2013, at Department of Anesthesiology, Reanimatology and Intensive Care, Division for Intensive Care Unit, Clinical Hospital Centre Rijeka, Croatia, there was 36 hospitalized patients with severe TBI, out of whom 25 (69.44%) developed nosocomial infection. From 1st January 2014 to 31st December 2014, the total number of patients with severe TBI was 31, and 21 (67.74%) of them developed nosocomial infection during the hospitalization (Figure 1).

Of the 25 patients with severe TBI and nosocomial infection that were hospitalized in the ICU during the 2013, 19 (76%) of them were male gender, and the remaining 6 (24%) were members of the female gender. Out of total number of 21 patient with severe TBI and nosocomial infection during 2014, 16 (76.19%) of them were male gender, and 5 (23.80%) of them were female gender. Overall, during 2013 and 2014, there was 35 (76.08%) members of male gender, and 11 (23.91%) members of female gender with severe TBI and nosocomial infection. There was statistically significant more male gender participant than female (Figure 2).

Of all patients with isolated severe TBI and nosocomial infection in 2013, the largest number of patients was between ages 80 and 89, and the second were patients between ages 50 and 59. The average age of patients in 2013 amounted 58.08 years, while the median was 57 years. Analyzing the year 2014, the highest number of patients was also between ages 80 and 89. Second largest group was between ages 60 and 69. The
The average age for 2014 was 57.52 years, while the median was 67 years. Overall, the largest number of patients was between 80 and 89 years old. The average age was 57.8 years, while the median was 62 years (Figure 3).

During the admission of patients with severe TBI who subsequently developed nosocomial infection in 2013, GCS for the highest number of patients accounted for 3. Also, the same GCS score accounted for the highest number of patients in 2014. Overall, for 2013 and 2014, the highest number of patients were scored GCS 3 (Figure 4).

Respiratory tract infections are proved to be the most common. Lead nosocomial infection for the year 2013 and 2014 was ordinary and mucopurulent bronchitis (41.30%). Second most common infection was VAP (30.43%). The following are UTIs, which accounted for 21.73%, and sepsis, which accounted for 6.52% (Table 1.). In the year 2013, the leading cause of respiratory tract infections were bacteria Proteus mirabilis and Pseudomonas aeruginosa. Sepsis was caused by Candida albicans and Proteus mirabilis, while Escherichia coli was the leading cause of the UTIs (Table 2.). Analyzing the year 2014, Pseudomonas aeruginosa was proved to be the major cause of respiratory tract infections and sepsis. Bacteria Enterococcus faecalis and Staphylococcus aureus were the leading pathogens in the years 2013 and 2014 (Table 2.).

**Table 1.** The leading types of nosocomial infections in patients with severe TBI that were hospitalized in the ICU during year 2013 and 2014

<table>
<thead>
<tr>
<th>Type of the infection</th>
<th>2013 (n = 25)</th>
<th>2014 (n = 21)</th>
<th>OVERALL (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator-associated pneumonia (VAP)</td>
<td>6</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Urinary tract infection (UTI)</td>
<td>7</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Other infections - ordinary and mucopurulent bronchitis</td>
<td>10</td>
<td>9</td>
<td>19</td>
</tr>
</tbody>
</table>

**Table 2.** Overview of the leading pathogens considering the type of infection in patients with severe TBI hospitalized in the ICU in the period between 1st January and 31st December 2013.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Ventilator - associated pneumonia (VAP)</th>
<th>Sepsis</th>
<th>Urinary tract infections (UTI)</th>
<th>Other infections (ordinary and mucopurulent bronchitis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escherichia coli</td>
<td>1</td>
<td>0</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Proteus vulgaris</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>OVERALL</td>
<td>6</td>
<td>2</td>
<td>7</td>
<td>10</td>
</tr>
</tbody>
</table>
Enterococcus faecalis is determined as leading cause of UTIs (Table 3).

The most commonly used antimicrobial medications to treat infected patients in the ICU during 2013 and 2014, were the beta – lactam antibiotics involving meropenem, cloxacillin, and a combination of piperacillin and tazobactam. In the second place were cephalosporins such as cefazolin, cefepime, ceftriaxone. Less frequently used group of antimicrobial medications were non – beta lactam antibiotics including teicoplanin and vankomycin. Other used medications where aminoglycosides, quinolones, medications against anaerobic bacteria and fungal infection (Figure 5).

Table 3. Overview of the leading pathogens considering the type of infection in patients with severe TBI hospitalized in the ICU in the period between 1st January and 31st December 2014.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Ventilator - associated pneumonia (VAP)</th>
<th>Sepsis</th>
<th>Urinary tract infections (UTI)</th>
<th>Other infections (ordinary and mucopurulent bronchitis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escherichia coli</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Proteus vulgaris</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>OVERALL</td>
<td>8</td>
<td>1</td>
<td>3</td>
<td>9</td>
</tr>
</tbody>
</table>

Duration of infection in days, overall in the 2013 and 2014, was for the majority of patients longer than 7 days with an average of 5,77 days (Figure 6).

Overall in 2013 and 2014, duration of mechanical ventilation for patients with infection was for most of them more than 10 days (Figure 7).
The average duration of treatment of patients in the ICU, was in 2013 and 2014 overall 10,475 days (Figure 8).

From 46 patients with isolated severe TBI and nosocomial infection, 29 (63.04%) was dismissed to the Department of Neurosurgery. For 16 (34.78%) patients treatment outcome was lethal, and 1 (2.17%) patient was dismissed to the Department of Pulmonology (Figure 9).

**DISCUSSION**

Based on the results of analysis that was undertaken at the Department of Anesthesiology, Reanimatology and Intensive Care, Division of Intensive Care Unit, Clinical Hospital Centre Rijeka in a period of time between 1\textsuperscript{st} January 2013 and 31\textsuperscript{st} December 2013, the incidence of nosocomial infections in patients with severe TBI was 69.44%. During the period between 1\textsuperscript{st} January 2014 and 31\textsuperscript{st} December 2014, incidence was 67.74%. These results show a higher incidence of nosocomial infections in patients with severe TBI compared to global studies, where the percentage of infections in patients with severe TBI is about 50% (9, 12, 13). The results can be explained by the presence of multiresistant pathogens that are found in the ICU, and are transmitted primarily through medical personnel, despite their efforts to maintain hygiene and antiseptic rules. Medical personnel must be familiar with the standards of control of hospital infections.

According to gender of infected patients with severe TBI, during 2013 and 2014, overall was hospitalized 76.08% members of male gender, and the remaining 23.92% were female members. There was statistically significantly more male gender members than female (p < 0.05). Results are confirmed by the fact that members of male gender have 1.4 times higher risk for the development of severe TBI, and consequently of nosocomial infections (5).

Analyzing the age distribution of patients with nosocomial infection and severe TBI, it was observed that the incidence of nosocomial infections was highest at the oldest patients between ages 80 and 89. On the second place was working population aged between 50 and 59 years old, and in third young people aged between 18 and 29 years old. The average age of all infected patients with severe TBI was 57.8 years, and median was 62 years. Comparing the results with the global literature, we confirm that the most vulnerable group of patients is the one aged 75 and more, as well as the population aged between 15 and 30 years old (5). An average age of 57.8 years is associated with the fact that it is the active working population, increasing on that way the risk of accidents and consequent injury.

Out of 46 patients with nosocomial infection and severe TBI, 20 (43.47%) of them had on the admission to the ICU, GCS score 3. Severe TBI is defined as GCS score 8 and less. The lower GCS score is proportional with higher risk for development of complications, including nosocomial infections, thus increasing the risk of lethal outcome (8).

From all 46 patients with nosocomial infection and severe TBI, 14 (30.43%) had been diagnosed with VAP, 3 (6.52%) of them with sepsis, and UTI had 10 (21.73%) patients. The leading infection was ordinary and mucopurulent bronchitis which occurred in a total of 19 (41.30%) patients. As is confirmed by other studies, including our own, the most common are respiratory tract infections which predispose endotracheal intubation and mechanical ventilation. Ordinary and mucopurulent bronchitis consequently leads to VAP. Following infections are sepsis and UTI, and that corresponds to the incidence recorded in the world literature (9, 12, 13, 20, 21). The leading pathogens were *Proteus mirabilis* in a year 2013, and *Pseudomonas aeruginosa* for the year 2014. These bacteria belong to the group of gram-negative multiresistance pathogens that are the leading etiological causes of nosocomial infections (12, 13).
Most commonly used antimicrobial drugs were beta-lactamic group of antibiotics, and cephalosporins, which is in accordance with the world literature (13).

The average duration of infection, overall in 2013 and 2014, was 5.77 days. Overall, duration of mechanical ventilation was more than 10 days, and average length of patients treatment in days was 10,475 days. It is essential to start with adequate treatment and to set early tracheostomy so the hospitalization can be shorter, and consequently the risk of negative treatment outcomes can be reduced (12).

Treatment outcome was for 29 (63.04%) of 46 patients dismiss to the Department of Neurosurgery, for 16 (34.78%) patients outcome was lethal, and 1 (2.17%) patient was dismissed to the Department of Pulmonary Medicine. According to global literature, mortality from severe TBI is between 31% and 54%, and if it is complicated with nosocomial infection it rises to 70% (11,13). Comparing this records with results of our analysis, we conclude that lethal outcome in patients with nosocomial infection and severe TBI is at the lower limit, which indicates on early and adequate therapy and positive treatment outcomes.

**CONCLUSION**

Based on our retrospective study, we can conclude that the incidence of nosocomial infections in patients with severe TBI can be equated with an incidence that is recorded in the global literature. The leading cause of this posttraumatic complications is presence of multiresistant pathogens in the ICU. Severe TBI complicated by nosocomial infections leads to prolonged hospitalization, thus raising the cost of treatment. On that way, nosocomial infections in patients with severe TBI are becoming one of the major global health problems. The emphasis must be set on prevention of nosocomial infections, where the key role has medical personnel of the ICU. Maintenance of hygiene and antiseptic rules is one way how the nosocomial infections can be prevented among this difficult group of patients. Medical personnel must be familiar with the standards of control of hospital infections. Also, proper care of the patient such as placing the patient in the appropriate position, and use of a mobile bed, may help prevent the development of nosocomial infections. Already developed nosocomial infection should be recognized and adequately treated in order to improve patients treatment course, and to reduce the number of potential negative treatment outcomes.

**DECLARATION OF INTEREST.** None.

**ACKNOWLEDGMENTS.** This work was supported by the grand of University of Rijeka, Rijeka, Croatia (grant no. 13.06.1.1.12)

**ABBREVIATIONS**

GCS — Glasgow Coma Scale

ICU — Intensive Care Unit

TBI — Traumatic Brain Injury

UTI — Urinary Tract Infection

VAP — Ventilator – Associated Pneumonia

Zaključak: Bolničke infekcije postaju veliki obzidan problem javnog zdravlja. Akcenat mora biti na prevenciji koja uključuje održavanje higijene i poštovanje pravila antisepte među medicinskim osobljem Jedinice intenzivnog lečenja. Već razvijene infekcije moraju biti adekvatno lečene kako bi se redukovali negativni ishodi lečenja.

Ključne reči: izolovana traumatska povreda mozga, Glasgow koma skala, Jedinica intenzivnog lečenja, bolničke infekcije, gram – negativne bakterije.

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Correspondence to/Autor za korespondenciju
Vlatka Sotošek Tokmadžić
Department of Anesthesiology, Reanimatology and Intensive Care, Medical Faculty, University of Rijeka, Tome Strižića 3, 51 000 Rijeka, Croatia
Telephone number: +38551407400
Fax number: +38551218400
E-mail: vlatkast@medri.uniri.hr