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Epidemiology, antimicrobial resistance, and incremental medical costs of hospital-acquired infections in the Intensive Care Unit: 2-year experience from Serbia

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Abstract

Background: Hospital-acquired infections are a major complication of hospital treatment. The growing presence of multidrug-resistant pathogens contributes to increased mortality and costs, particularly in intensive care units where patients are predisposed to numerous risk factors. Comprehensive data about hospital-acquired infections from Serbian intensive care units is scarce. The aim of this study was to determine the presence of hospital-acquired infections among intensive care unit patients and look into the patterns of antimicrobial resistance, risk factors, and incremental costs of diagnosis and antimicrobial treatment. Methods: This retrospective study included 355 patients over a two-year period. Etiology, antimicrobial resistance patterns, and incremental costs of diagnosis and antimicrobial treatment were examined. Risk factors for infection acquisition, as well as length of stay, were statistically analyzed using Pearson's chi-square tests and logistic regression analysis. Results: At least one hospital-acquired infection was identified in 32.7% of patients. A total of 204 infection episodes were documented, the most common type being urinary tract infections (36.3%). Clostridium difficile , Klebsiella spp. , and Acinetobacter baumanii were the most common isolates. Antimicrobial resistance rates < 20% were observed for linezolid (0%), colistin (9%), and tigecycline (14%). Resistance rates > 50% were seen in all other tested antibiotic agents. Mortality rates were not higher in patients who acquired only one hospital-acquired infection (p=0.09), but were significantly higher for patients in whom more than one episode occurred (p=0.038). Length of stay > 20 days carried a 7.5-fold increase in odds of acquiring an infection (CI 4.4-12.7, p<0.001), whereas length of stay > 30 days carried a 10-fold increase (CI 5.5-16.1, p<0.001). During the study period, over 37,000 EUR was incrementally spent on diagnosis and antimicrobial treatment for hospital-acquired infections. Conclusion: Our results suggest a high prevalence of hospital-acquired infections and very high antimicrobial resistance rates compared to most European countries. Together with the first published results regarding incremental costs from Serbia, our observations require large-scale prospective follow-up studies in order to obtain a deeper insight into the actual burden of hospital-acquired infections.

Background

According to the World Health Organization (WHO), "Healthcare-associated infections represent the most common adverse event among hospitalized patients" [1]. This is particularly true in the Intensive Care Units (ICUs) [2]. The latest research shows over 2.5 million hospital-acquired infection (HAI) episodes occur every year in Europe, with more than 90,000 deaths attributed to the six most common types: healthcare-associated pneumonia (HAP), healthcare-associated urinary tract infection (HA-UTI), surgical site infection (SSI), healthcare-associated *Clostridium difficile* (HA-CDI), healthcare-associated neonatal sepsis, and healthcare-associated bloodstream infection (HA-BSI) [3]. Acquisition of HAIs carries a substantial increase in mortality and cost of treatment [4], particularly if the isolates are multidrug- or extensively drug-resistant (MDR/XDR) [5, 6]. Incremental costs range from 6700 EUR to almost 30 000 EUR per episode and cause a significant loss of Disability-Adjusted Life Years (DALYs) [3, 5]. Some authors suggest that evidence-based strategies for surveillance and prevention could eliminate up to 70% of all HAIs [1, 7], which should serve as an incentive for optimizing healthcare policies. The European Centre for

Disease and Control (ECDC) has successfully implemented such efforts, leveraging advances in digital technology [8, 9].

In Serbia, isolated single-center reports from ICUs have been published and looked at the neonatal population [10], risk factors for acquisition in trauma patients [11], and antimicrobial resistance patterns of specific isolates [12]. However, virtually no studies have looked at the overall prevalence of HAIs in adult ICUs in our country.

The primary goal of our study was to investigate the rates of HAIs in the ICU over a two year period and assess the risk factors, etiologies and antimicrobial resistance patterns. The secondary goal was to calculate, for the first time in Serbia, incremental costs of diagnosis and treatment.

Methods

Study population

This 2-year retrospective study was conducted in the 15-bed ICU of the 150-bed University Teaching Hospital for Infectious and Tropical Diseases, Clinical Centre of Serbia, with a patient:nurse ratio of 4:1. From September 2016 to September 2018, healthcare records of all admitted and discharged patients were evaluated (n=495). Exclusion criteria were length of stay (LOS) < 48 hours (n=76) and incomplete patient record data (n=64).

Definitions

Each episode of HAI was defined using the criteria of the ECDC - occurring ≥ 48h after admission, with onset from day 3 onwards [8]. Each subtype of HAI was defined using the same ECDC criteria and abbreviations, and were classified as follows: bloodstream infection (BS), urinary tract infection (UTI), catheter-associated UTI (CAUTI), hospital-acquired *Clostridium difficile* infection (GI-CDI), pneumonia (PN), device-associated infection (DAI), hospital-acquired central nervous system infection (CNS-HAI), and skin infection (SST-SKIN) [8]. Infections of more than one site in the same patient were reported as independent events unless the same pathogen was isolated concurrently.
Two incremental direct medical costs were defined: (1) the costs of microbiological testing related to the diagnosis of HAI; and (2) the costs of antibiotics indicated for HAI treatment. To standardize the representation of costs, all expenses were converted from the national currency (Serbian dinar - RSD) to EUR using local conversion rates for each year [13], and

adjusted for annual inflation rates using standardized converters [14].

Data collection

Basic demographic (gender, age) and clinical characteristics (primary diagnosis, comorbidities, risk factors, antimicrobial use within 48h upon admission) were collected, LOS and clinical outcome. Each HAI was documented using the standardized ECDC criteria for HAI documentation [8], including the etiology, microbiological method of confirmation, date of onset, antimicrobial susceptibility testing, as well as the choice of treatment and duration. Antimicrobial susceptibility testing was conducted using the European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards [15], and all isolates identified as "intermediate" (I) were classified as "sensitive" (S). Multidrug-resistant pathogens were confirmed using the susceptibility criteria by Magiorakos et al. [16].

Statistical analysis

The Statistical Package for Social Sciences (SPSS) software version 23 (IBMCorp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) was used for analysis of patient data. Basic epidemiological indicators (incidence and mortality rates) were calculated. For normally distributed data mean and standard deviation were applied, whilst median and interquartile range (IQR) were used for data that did not exhibit normal distribution. Pearson`s chi-square test was appropriate to test the difference between categorical data, and Mann-Whitney U test was adequate for numerical data without normal distribution. A logistic regression analysis was performed to predict the probability of acquiring a HAI and derive odds ratios (ORs), followed by adjustment for potential confounding factors (age on admission, gender, number of comorbidities, and LOS).

The study was approved by the Ethics committee of the Clinical Centre of Serbia. All data that were included in the analysis were previously anonymized.

Results

A total of 355 patients were included in the study, of which 190 (53.5%) were male and 165 (46.5%) were female. The mean age was 63.14 years (SD=16.5). Main causes of admission included primary CNS infections and sepsis (63.5% and 16.9%, respectively). Comorbidities and risk factors are shown in Table 1.

CNS – central nervous system; WNV – West Nile infection; CVC – central venous catheter; AB – antibiotic; Penicillins – Amoxicillin, Ampicillin, Ampicillin-sulbactam; Cephalosporins – Cephalexine, Cefepime, Ceftazidime, Ceftriaxone, Cefuroxime; Aminoglycosides – Gentamycin, Amikacin; Quinolones – Ciprofloxacin, Moxifloxacin, Levofloxacin; Carbapenems – Meropenem, Carbapenemm Ertapenem;

In the study period, 116 patients were diagnosed with at least one HAI, an incidence rate of 32.7%, and a total of 204 HAI episodes were documented. Presence of an indwelling urinary catheter (p=0.001), nasogastric tube (p<0.001), and a CVC (p=0.001) were all associated with the development of HAI, as were

endotracheal intubation (p=0.001) and mechanical ventilation > 48 hours (p<0.001). HAI was common among patients with cardiovascular diseases and diabetes mellitus (p=0.01 in both cases), and among those who received penicillin in the 48h upon admission (p=0.008). Older age was also associated with an increased risk of acquiring HAI (66.63 vs. 61.42 years, p=0.003).

The principal HAIs were UTIs (74 episodes, 36.3%, of which 73 were CA-UTI), BSIs (40, 19.6%), GI-CDI (37, 18.1%), and PN (32, 15.7%). More than 1 HAI was identified in 53 patients (45.7%). A total of 249 isolates were identified, most common being *Clostridium difficile, Klebsiella spp., Acinetobacter baumanii,* and *Enterococcus spp.* (*T*able 2). Polymicrobial infections accounted for 20.1% of all HAIs.

Antimicrobial resistance profiles were investigated for all pathogens and stratified for the four most frequent isolates (Table 3). Resistance rates < 20% were only seen for linezolid (0%), colistin (9%), and tigecycline (14%), whereas overall resistance rates exceeded 50% in all other antimicrobials and antimicrobial groups. All but one isolate of *Acinetobacter baumanii* exhibited MDR patterns (32, 97%). Equally high MDR patterns were seen for *Klebsiella* (31, 91.2%) and *Pseudomonas aeruginosa* (24, 88.9%). 71.9% of *Enterococcus* isolates were MDR.

The median LOS was 20 days (IQR 21), and was significantly longer in patients with at least 1 HAI compared to patients who did not acquire a HAI (34.5 vs 16 days, p<0.001). Using logistic regression analysis (Table 4), each ICU day incrementally increased the odds of acquiring a HAI by 7.6%, even when adjusted for age, sex, and number of comorbidities. LOS > 20 days carried a 7.5-fold increase in odds of acquiring HAI (CI 4.4-12.7, p<0.001). Furthermore, LOS > 30 days carried a 10-fold increase in odds of acquiring a HAI (CI 5.5-16.1, p<0.001).

The overall mortality rate was 39.4% (140 patients), and was not significantly higher for patients who acquired a single HAI (p=0.09). A statistically significant increase in mortality, however, was observed in patients who acquired > 1 HAI (p=0.038).

During the study period, a total of 37,583 EUR was incrementally spent on the four most common types of infections, of which 5,804 EUR on microbial testing and 31,779 EUR on antimicrobial treatment (Table 5). Statistically significant differences in the costs for microbiological diagnosis and antimicrobial treatment for the two 12-month periods were not observed (p=0.764 and p=0.904 respectively).

Discussion

The primary aim of our study was to obtain a deeper insight into the epidemiology of HAIs and guide the next steps in terms of surveillance and hospital policies. As one of the rare studies looking at incidence rates and profiles of HAIs in adult ICU patients in Serbia, the incidence rate of 32.7% is in accordance with isolated European studies from Slovenia (35.7%) [17], and Poland (27.6%) [18], but still much higher than the overall rates of 19.4% in Europe [19].

The use of invasive devices and mechanical ventilation associated with the development of HAI in ours study is consistent with other reports that evaluated risk factors for HAI [20, 21]. Further prospective

analyses are, however, required to discern the relationship between the use of invasive devises and etiologies of HAIs.

Contrary to the findings in large European studies, where approximately 20% of all HAIs were UTIs [19, 21], this type of infection comprised more than a third of HAIs in our sample. These findings mandate a deeper assessment of current practices and patient protocols.

The antimicrobial resistance patterns and the percentage of MDR strains observed reiterates the concerning results from other Serbian studies [12, 22]. Overall resistance rates of 88% for cephalosporins, 85% and 75% for gentamycin and amikacin, 92% for ciprofloxacin, and 56% for carbapenems are higher compared to most European countries [19]. Such high resistance rates support the trend increasing prevalence MDR and XDR strains [23]. The emergence of colistin-resistant *Klebsiella spp.* is particularly troubling, as 1 in 4 of our isolates exhibited such characteristics. As effective therapeutic options narrow for HAIs, the use of colistin will increase, but may invariably lead to higher resistance rates [24]. For this reason, it is imperative to reserve colistin until antimicrobial susceptibility patterns mandate its use.

The retrospective nature of data collection, as well as numerous biases that arise when HAIs are associated prolonged LOS [25, 26], impeded us from determining the true relationship between LOS and HAIs. We have shown, however, that an extended LOS at our facility carries significantly higher odds of acquiring a HAI, regardless of patient age, gender, or accompanying comorbidity. Mortality rates were not higher if patients acquired a single HAI, contrary to other reports [27]. However, acquisition of > 1 HAI was associated with a higher mortality rate. Such findings necessitate a revision of existing healthcare policies and highlight the importance of HAI prevention.

This is the first study from Serbia which has described healthcare-economic data regarding HAIs. Incremental medical costs - microbiological testing and antimicrobial treatment, were obtained and revealed valuable insights into the burden of HAI in Serbia. Although we were not able to estimate an in-depth burden of HAIs by type and possibly by antimicrobial resistance patterns [4, 28], several small-scale studies such as ours were done in other countries and achieved to show a substantial burden of HAI [29-32]. Our intent is to use this data as the starting point to leverage large-scale prospective studies that would effectively show the actual costs of HAIs in our country.

Our study had several important limitations. First, a small patient sample gathered from a single center did not allow us to draw more generalized conclusions. The small sample also prevented us to perform appropriate patient matching, which is often the study of choice when comparing incremental costs of HAIs [33]. Second, the retrospective nature of the study was a limitation. Risk factors confirmed in other studies (such as prior room occupants) [34], as well as other variables necessary for an in-depth analysis of HAI occurrence were not available for analysis. The same limitation applies to the calculation of medical costs (both direct and indirect), which would be more comprehensive if a prospective study was conducted, possibly through use of automated systems for HAI surveillance [35, 36].

Conclusions

Our study showed a high prevalence of HAIs in our ICU. The antimicrobial resistance rates and the proportion of MDR strains are much higher compared to most European countries. First data regarding direct medical costs of HAIs in Serbia were documented. Large-scale multi-centric studies are necessary in order to investigate the true burden of HAIs and their cost.

Declarations

Abbreviations

AB: Antibiotic; BS: Bloodstream infection; CAUTI: Catheter-associated urinary tract infection; CNS: Central nervous system; CNS-HAI: Hospital-acquired central nervous system infection; CVC: Central venous catheter; DAI: Device-associated infection; DALYs: Disability-adjusted life years; ECDC: European Centre for Disease and Control; EUCAST: European Committee on Antimicrobial Susceptibility Testing; EUR: Euro; GI-CDI: Hospital-acquired Clostridium difficile; HA-BSI; Healthcare-associated bloodstream infection; HA-CDI: Healthcare-associated Clostridium difficile; HAI: Hospital acquired infection; HAP: Healthcare-associated pneumonia; HA-UTI: Healthcare-associated urinary tract infection; I: Intermediate resistance; ICU: Intensive care unit; IQR: Interquartile range; LOS: Length of stay; MDR: Multidrug-resistant; OR: Odds ratio; PN: Pneumonia; R: Resistant; RSD: Serbian Dinar; S: Sensitive; SD: Standard deviation; SPSS: Statistical Package for Social Sciences software; SSI: Surgical site infection; SST-SKIN: Skin infection; UTI: Urinary tract infection; WHO: World Health Organization; WNV: West Nile virus; XDR Extensive drug-resistant.

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Availability of data and material

The datasets that were obtained and used for this study are available from the corresponding author on request.

Authors' contributions

AD was involved in the conceptualization of the study, its design, and original draft preparation; BM was involved in the review and editing of the manuscript; IM was involved in analysis of data and review of the manuscript; SDJ was involved in acquisition and interpretation of microbiological and financial data ; AC was involved in interpretation of data and its analysis; GS was involved in conceptualization of the study, the original draft preparation, and rigorous revision of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was conducted after the approval of The Ethics Committee of The Clinical Centre of Serbia, in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Descriptive characteristics of patients admitted to the ICU (n=355)

Variable	Total	%	HAI (n=116)	No HAI (n=239)	P^*
Diagnosis					
CNS infection	225	63.5	72	153	0.40
Bacterial CNS infection	78	21.9	20	58	0.09
Viral CNS infection	84	23.9	39	45	**0.002**
WNV infection	70	19.9	32	38	**0.009**
Sepsis	60	16.9	20	40	0.51
Risk Factors					
Inserted Urinary catheter	318	89.6	112	206	**0.001**
Intubation	170	47.9	70	100	**0.001**
Mechanical Ventilation	128	36.1	57	71	**<0.001**
Presence of nasogastric tube	148	41.7	66	82	**<0.001**
Presence of CVC	17	4.8	12	5	**0.001**
AB use 48h upon admission	340	95.8	113	227	0.41
Penicillins	59	17.4	28	31	**0.008**
Cephalosporins	249	73.2	81	168	0.44
Aminoglycosides	14	4.1	7	7	0.14
Quinolones	15	4.4	7	8	0.19
Carbapenems	62	18.2	17	45	0.19
Metronidazole	52	15.3	17	35	0.55
Vancomycin	175	51.5	55	120	0.31
1 Antimicrobial used	109	32.1	36	73	0.54
2 Antimicrobials used	152	44.7	44	108	0.10
3 or more antimicrobials used	79	23.2	32	47	0.068
Comorbidities					
Immunosuppression	56	15.7	15	41	0.19
Cardiovascular disease	192	54.2	73	119	**0.01**
Diabetes mellitus	86	24.4	37	49	**0.01**
Urinary tract pathology	39	11.0	15	24	0.26
Respiratory disease	25	7.0	12	13	0.07

p- Chi-square test used at a level of 0.05*

Table 2 Etiology of HAIs

Isolate n = 249	n	(%)
Clostridium difficile	37	14.8
Klebsiella spp.	35	14.0
Acinetobacter baumanii	33	13.2
Enterococcus	32	12.8
Pseudomonas aeruginosa	27	10.8
Candida spp.	26	10.4
Proteus Mirabilis	12	4.8
Coagulase-negative staphylococci	11	4.4
Corynebacterium spp.	9	3.6
Achromobacter xylooxidans	5	2.0
Staphylococcus aureus	4	1.6
Providentia spp.	3	1.2
Stenotrophomonas maltophila	3	1.2
Staphylococcus haemolyticus	3	1.2
Escherichia coli	3	1.2
Enterobacter cloacae	2	0.8
Staphylococcus hominis	2	0.8
Staphylococcus epidermidis	2	0.8
Total	249	100

Table 3 Antimicrobial resistance patterns of isolated pathogens

Pathogen n of isolates	*A.Baumanii* 33		*Enterococcus* 32		*Klebsiella* 34		*P. Aeruginosa* 27		All isolates 177	
	R/tested	%	R/Tested	%	R/Tested	%	R/Tested	%	R/Tested	%
Penicillins										
Oxacillin/Methicillin	-	-	-	-	-		-	-	23/25	92
Ampicillin/Amoxicillin	-	-	18/32	56	14/14	100	-	-	54/73	74
Amoxicillin + clavulanic acid	-	-	13/27	48	12/15	80	-	-	40/63	63
Ampicillin+ sulbactam	1/9	11	8/14	57	15/15	100	-	-	27/41	66
Piperacillin/Tazobactam	9/9	100	7/13	54	16/17	94	18/27	67	57/78	73
Cephalosporins	10/10	100	-	-	32/34	94	20/23	87	89/101	88
Aminoglycosides										
Amikacin	17/17	100	14/15	93	10/20	50	20/26	77	85/114	75
Gentamycin	16/17	94.1	23/24	96	16/21	76	20/23	87	120/141	85
Fluoroquinolones										
Ciprofloxacin	17/17	100	27/28	96	18/22	82	26/27	96	129/140	92
Levofloxacin	24/29	82.7	26/26	100	20/32	63	25/26	96	133/161	83
Trimethoprim-Sulfamethoxazole	22/26	84.6			28/31	90	9/9	100	89/113	79
Carbapenems	33/33	100	6/18	33	12/33	36	21/26	81	79/141	56
Vancomycin	-		20/32	63	-	-	-	-	21/64	33
Linezolid	-	-	0/18	0	-	-	-	-	0/34	0
Tigecycline	3/10	30	0/12	0	3/15	20	-	-	7/49	14
Colistin	0/33	0			5/19	26	0/18	0	7/77	9

Cephalosporins - ceftriaxone, ceftazidime, and cefepime tested;
Carbapenems - Imipenem and meropenem tested.

Table 4 Regression analysis of LOS as a predictor of HAI occurrence

Variable	B	OR	95% CI	p
LOS*	0.077	1.080	1.060-1.101	<0.001
LOS > 20 days	2.016	7.51	4.4-12.7	<0.001
LOS > 30 days	2.273	9.71	5.5-16.1	<0.001

*adjusted for age, sex, and # of comorbidities

LOS – Length of Stay; B – regression coefficient; OR – odds ratio; CI – Confidence interval

Table 5 Incremental costs of HAI by site of infection

Type of HAI	N	Microbial testing (EUR) Median (IQR)	Microbial testing (EUR) Total	Antimicrobial treatment (EUR) Median (IQR)	Antimicrobial treatment (EUR) Total	Total costs by site (EUR) Total
01.09.16-01.09.17						
UTI	40	9(18)	€ 756.00	69 (194)	€ 6,031.00	€ 6,787.00
PN	18	26(31)	€ 570.00	277(459)	€ 7,026.00	€ 7,596.00
BSI	24	63(7)	€ 1,418.00	75(274)	€ 4,803.00	€ 6,221.00
GI-CDI	15	12 (1)	€ 165.00	8 (30)	€ 620.00	€ 785.00
			€ 2,909.00		**€ 18,480.00**	**€ 21,389.00**
01.09.17-01.09.18						
UTI	34	9(18)	€ 542.00	81 (153)	€ 5,342.00	€ 5,884.00
PN	14	34(36)	€ 572.00	189(204)	€ 3,465.00	€ 4,037.00
BSI	16	84(88)	€ 1,465.00	115(213)	€ 2,621.00	€ 4,086.00
GI-CDI	22	14 (0)	€ 316.00	10 (29)	€ 1,871.00	€ 2,187.00
			€ 2,895.00		**€ 13,299.00**	**€ 16,194.00**
01.09.16-01.09.18						
UTI	74	9 (18)	€ 1,298.00	*81 (164)*	€ 11,373.00	€ 12,671.00
PN	32	26(32)	€ 1,142.00	*220(169)*	€ 10,491.00	€ 11,633.00
BSI	40	63(29)	€ 2,883.00	*100(243)*	€ 7,424.00	€ 10,307.00
GI-CDI	37	14 (2)	€ 481.00	*9 (29)*	€ 2,491.00	€ 2,972.00
Total cost			**€ 5,804.00**		**€ 31,779.00**	**€ 37,583.00**

UTI – urinary tract infection; PN – pneumonia; BSI – bloodstream infection; GI-CDI – *Clostridium difficile* infection; IQR – interquartile range.