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ARTICLE

Healthcare associated *Clostridioides difficile* infection in adult surgical and medical patients hospitalized in tertiary hospital in Belgrade, Serbia: a seven years prospective cohort study

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ABSTRACT

Introduction: *Clostridioides difficile* (*C. difficile*) infection (CDI) is one of the most common healthcare-associated (HA) infections in contemporary medicine. The risk factors (RFs) for HA CDI in medical and surgical patients are poorly investigated in countries with a limited resource healthcare system. Therefore, the aim of the study was to investigate differences in patients' characteristics, factors related to healthcare and outcomes associated with HA CDI in surgical and medical patients in tertiary healthcare centre in Serbia.

Materials and Methods: A prospective cohort study was conducted including adult patients diagnosed with initial episode of HA CDI, first recurrence of disease, readmission to hospital, while deaths within 30 days of CDI diagnosis and in-hospital mortality were also recorded. Patients hospitalized for any non-surgical illness, who developed initial HA CDI were assigned to medical group, whereas those who developed initial HA CDI after surgical procedures were in surgical group. The data on patients' characteristics and factors related to healthcare were collected, too.

Results: During 7-year period, from 553 patients undergoing in-hospital treatment and diagnosed with CDI, 268 (48.5%) and 285 (51.5%) were surgical and medical patients, respectively. Age ≥ 65 years, use of proton pump inhibitors, chemotherapy and fluoroquinolones were positively associated with being in medical group, whereas admission to intensive care unit and use of second- and third-generation cephalosporins were positively associated with being in surgical group.

Conclusions: Based on obtained results, including significant differences in 30-day mortality and in-hospital mortality, it can be concluded that medical patient were more endangered with HA CDI than surgical ones.

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1. Introduction

Clostridioides difficile (*C. difficile*) infection (CDI) became one of the most common healthcare-associated (HA) infections in modern medicine. It is associated with the increased morbidity, in-hospital mortality, prolonged hospitalization, and increased costs [1]. The reported incidence of HA CDI varies according to the country, the size of institution and ward location, the type of population studied [2–4]. Several studies conducted in industrialized countries of North America, Europe, and Western Pacific region, synthesized in different systematic review, provide valuable insights into the role of different risk factors (RFs) for CDI. Meta–analytic evidence of association has been reported for factors such as antibiotics, gastric acid suppressants, non–selective steroid anti-inflammatory drugs (NSAIDs), and some co–morbidities [5,6]. Systematic review of existing literature describing the epidemiology and management of CDI in developing countries showed that the rate of community-associated (CA) and HA CDI appears to be lower in developing countries than in developed countries, yet RFs appear to be broadly similar between these two populations. Accordingly, the future epidemiological studies in developing countries describing basic epidemiology of CDI, RFs for development of CDI, patient morbidity and mortality, as well as financial burden of infection are urgently needed [7].

The differences in RFs for HA CDI between medical and surgical patients are also poorly investigated in countries with socioeconomic transition with a limited resource healthcare system. Some studies from well-developed healthcare systems provided evidence that although surgical patients tend to suffer more severe CDIs than medical patients, overall they still do better than medical ones [8]. Southern et al. showed that in comparison with medical patients with CDI, surgical patients with CDI were significantly less likely to have had a prior hospitalization, less likely to have received

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a proton-pump inhibitors (PPIs) and more likely to have received antibiotics [9].

The aim of this study was to investigate differences in patients' characteristics, factors related to healthcare and outcomes in surgical and medical patients with HA CDI in tertiary healthcare centre in Serbia.

2. Materials and methods

2.1. Study design, patients and definitions

A prospective cohort study was conducted including adult patients (≥ 18 years) diagnosed with initial episode of HA CDI from 1 January 2011 to 31 December 2017 at the Military Medical Academy (MMA), Belgrade (Serbia), a 1200-bed teaching hospital of the University of Defence. The hospital is divided into 27 departments. In our tertiary healthcare centre positive testing for CDI is immediately reported to infectious diseases specialist and healthcare epidemiologist. Infectious diseases specialist evaluates best treatment options (metronidazole or vancomycin or combination of both antibiotics). Healthcare epidemiologist evaluates origin, patients' characteristics, factors related to healthcare and outcomes of infection. Infection control nurse recommends CDI control measures. CDI control measures: includes contact isolation, personal safety equipment at patient contact, extensive handwashing with soap and water, and daily disinfection of a patient room with sporicidal agent.

We gathered data on the following variables: intrinsic factors (existing at admission) sex, age, *Diabetes mellitus*, malignancy, and factors related to healthcare, including previous hospitalization in other hospitals, previous infections, intensive care unit (ICU) admission, duration of treatment in ICU, mechanical ventilation (MV), nasogastric tubes (NT), use of histamine-2-receptor antagonists (H2RAs), PPIs, chemotherapy and antibiotics (number, type, and duration of antibiotic usage). Data about the length of stay (LOS) in hospital, first recurrence of CDI, readmission to MMA, deaths within 30 days of CDI diagnosis and in-hospital mortality were also recorded.

HA CDI case was defined as any hospitalized patient with laboratory confirmation of a positive toxin assay of *C. difficile* associated with diarrhoea (≥ 3 daily in a 24-hour period with no other recognized cause) or visualization of pseudomembranes on sigmoidoscopy, colonoscopy, or histopathologic analysis on day three or later, following admission to an MMA on day one [10–12]. We also included all patients readmitted to MMA. Readmission to MMA was defined as readmitted patients who did not have a CDI during their index admission to hospital, but had onset of symptoms within four weeks of discharge from MMA [13]. Microbiological testing was performed at the Institute of Medical Microbiology at the MMA. Enzyme immunoassay kits for *C. difficile* toxins A and B were used (*BIOMERIEUX- VIDAS C. difficile toxins A&B CDAB*).

First CDI recurrence was defined as return of symptoms associated with repeated positive test within 15–56 days after the initial diagnosis was established [10]. Patients with CA CDI and HA CDI acquired in another hospital were excluded from study.

Patients hospitalized for any non-surgical illness, who developed initial HA CDI were assigned to medical group, whereas those who developed initial HA CDI after surgical procedures were assigned to a surgical group. The Ethics Committee of the MMA approved the research protocol (MF VMA 02/17-19).

2.2. Statistical analysis

Data analyses were performed with SPSS, version 21.0 (SPSS, Chicago, IL). Results were expressed as the mean ± SD or as the proportion of the total number of patients. The χ^2 test or Fischer exact test were used for categorical variables and relative risk, and their corresponding 95% confidence intervals (CI) were calculated. For parametric continuous variables, mean values were compared using the Student *t* test. For nonparametric continuous variables the Mann-Whitney *U* test was used. RF independently associated with CDI were identified by stepwise logistic regression analysis of variables selected by univariable logistic regression analysis (ULRA), with a limit for entering and removing categorical variables from the model at 0.05. The in-hospital mortality rate was defined as the number of deaths per 100 patients with HA CDI. The 30-day mortality was defined as death within 30 days after the diagnosis of HA CDI per 100 patients with HA CDI.

3. Results

During 7 years we registered 836 patients with laboratory proven CDI. Among them, 183 patients acquired infection in community or in another hospital, and were not included in study. There were 553 patients undergoing in-hospital treatment at MMA who developed initial HA CDI and were included in the study. No major CDI outbreaks were observed during the study period.

More detailed characteristics of patients and factors related to healthcare are shown in Table 1. Of these, 268 (48.5%) and 285 (51.5%) were surgical and medical patients, respectively.

There were 251 female patients, 123 (45.9%) surgical and 128 (44.9%) medical, without significant differences between cohorts according to gender. Medical patients were significantly older than surgical (68.59 ± 15.46 *vs*. 64.91 ± 14.86, respectively; $p = 0.005$). We observed that both, medical and

Table 1. Comparison of patients' characteristics and factors related to healthcare in surgical and medical patients with HA CDI.

	Surgical patients *N* = 268	Medical patients *N* = 285	Crude RR*	ULRA* P	MLRA* RR (95%CI)	MLRA p
Patients characteristic						
Female sex, *n* (%)	123 (45.9)	128 (44.9)		0.883		
Age, X ± SD	64.91 ± 14.86	68.59 ± 15.46		0.005		
Age ≥ 65 years, *n* (%)	154 (57.5)	190 (66.7)	1.481	0.026	2.015 (1.347–3.014)	0.001
Diabetes mellitus, *n* (%)	37 (13.8)	51 (17.9)		0.231		
Malignancy, *n* (%)	63 (23.5)	66 (23.2)		1.000		
Previous infection, *n* (%)	97 (36.2)	128 (44.9)	1.437	0.037		
Factors related to healthcare						
Season of CDI infection			0.524			
Spring	78 (29.1)	95 (33.3)				
Summer	59 (22.0)	66 (23.2)				
Autumn	65 (24.3)	56 (19.6)				
Winter	66 (24.6)	68 (23.9)				
Previous hospital admission	103 (38.4)	149 (52.3)	1.755	0.001		
ICU*admission, *n* (%)	95 (35.4)	31 (10.9)	4.499	<0.001	4.730 (2.877–7.775)	<0.001
Length of stay in ICU, (days), X ± SD	7.16 ± 12.09	25.23 ± 33.97		<0.001		
Nasogastric tube, *n* (%)	28 (10.4)	32 (11.2)		0.874		
Mechanical ventilation, *n* (%)	39 (14.6)	44 (15.4)		0.863		
Days of hospitalization prior CDI, X± SD	21.22 ± 18.68	17.79 ± 17.48		0.004		
Proton-pump inhibitors, *n* (%)	51 (19.0)	111 (38.9)	2.714	<0.001	3.431 (2.188–5.379)	<0.001
H2 receptor antagonist, *n* (%)	109 (40.7)	111 (38.9)		0.744		
Chemotherapy, *n* (%)	5 (1.9)	36 (12.6)	7.605	<0.001	4.708 (1.718–12.906)	0.003
Antibiotic exposure, n (%)	263 (98.1)	262 (91.9)	4.618	<0.001		
Number of received antibiotics				0.269		
One	118 (44.9)	102 (38.9)				
Two	66 (25.1)	79 (30.2)				
Three	41 (15.6)	50 (19.1)				
Four	38 (14.4)	31 (11.8)				
Days of usage an antibiotic (X± SD)	6.59 ± 4.79	8.63 ± 5.60		<0.001		
Days of usage two antibiotics (X± SD)	7.50 ± 5.06	7.83 ± 5.46		0.519		
Days of usage three antibiotics (X± SD)	7.62 ± 5.89	7.43 ± 4.23		0.656		
Days of usage four antibiotics (X± SD)	8.45 ± 4.05	8.58 ± 4.79		0.995		
Cephalosporins 1st gen, n (%)	24 (9.1)	17 (6.5)		0.335		
Cephalosporins 2nd gen, n (%)	79 (30.0)	46 (17.6)	2.016	0.001	1.924 (1.177–3.145)	0.009
Cephalosporins 3rd gen, n (%)	170 (64.6)	139 (53.1)	1.618	0.007	2.173 (1.421–3.322)	<0.001
Cephalosporins 4th gen, n (%)	1 (0.4)	4 (1.5)		0.216		
Aminoglycosides, n (%)	45 (17.1)	44 (16.8)		1.000		
Fluoroquinolones, n (%)	26 (9.9)	75 (28.6)	3.656	<0.001	3.025 (1.751–5.226)	<0.001
Sulfonamides, n (%)	19 (7.2)	24 (9.2)		0.516		
Carbapenems, n (%)	53 (20.2)	63 (24.0)		0.332		
Macrolides, n (%)	5 (1.9)	14 (5.3)		0.060		
Clindamycin, n (%)	7 (2.7)	2 (0.8)		0.176		
Tigecyclin, n (%)	1 (0.4)	1 (0.4)		1.000		
Fosfomycin, n (%)	0 (0)	2 (0.8)		0.249		
Colistin, n (%)	4 (1.5)	2 (0.8)		0.686		

*ICU, intensive care unit; *ULRA, univariable logistic regression analysis; *MLRA, multivariable logistic regression analysis; *RR, relative risk

surgical patients, had similar distribution of *Diabetes mellitus* (17.9% *vs* 13.8%, respectively, $p = 0.231$) and malignancy (23.2% *vs*. 23.5%, respectively, $p = 1.000$) without significant differences between them. Previous infection and previous hospital admission were significantly more frequent in medical than in surgical patients (44.9% *vs*. 36.2%; $p = 0.037$ and 52.3% *vs*. 38.4%; $p = 0.001$, respectively). There were no differences according to the season of HA CDI between cohorts ($p = 0.524$).

ICU stay was registered significantly more frequently in surgical patients (35.4% *vs*. 10.9%, $p < 0.001$), while the LOS in ICU was significantly longer in medical patients (25.23 ± 33.97 *vs*. 7.16 ± 12.09, $p < 0.001$). There were no differences in frequency of use of NT and MV between surgical and medical patients (10.4% *vs*. 11.2%, $p = 0.874$ and 14.6% *vs*. 15.4%, $p = 0.863$, respectively). There were no differences in frequency of H2RAs use (40.7% *vs*. 38.9%, $p = 0.744$), but medical patients were treated significantly more frequently with PPIs than surgical patients (38.9% *vs*. 19.0%, respectively, $p < 0.001$). Chemotherapy was also significantly more frequently administered to medical than to surgical patients (12.6% *vs*. 1.9%, respectively, $p < 0.001$).

Antibiotic exposure was registered more frequently in surgical than in medical patients (98.1% *vs*. 91.9%, respectively, $p < 0.001$), but duration of antibiotic treatment, in days, was significantly longer in medical patients than in surgical ones (8.63 ± 5.60 *vs*. 6.59 ± 4.79, respectively, $p < 0.001$). In comparison with medical patients, surgical patients were significantly more often administered second-generation cephalosporins (17.6% *vs*. 30.0%, respectively, $p = 0.001$) and third-generation cephalosporins (53.1% *vs*. 64.6% respectively, $p = 0.007$), while medical patients received more often fluoroquinolones in comparison to surgical patients (28.6% *vs*. 9.9%, respectively, $p < 0.001$). More detailed characteristics of patients, factors related to healthcare itself, and results of ULRA and multivariate logistic regression analysis (MLRA) are shown in Table 1.

Table 2. Outcomes in surgical and medical patients with *Clostridioides difficile* Infections (CDI).

	Surgical patients $N = 268$	Medical patients $N = 285$	p
Length of stay in hospital, (days), X ± SD	39.93 ± 30.64	36.49 ± 28.80	0.262
In hospital mortality, *n* (%)	53 (19.8)	80 (28.1)	0.029
30-day mortality, $p <$ (%)	42 (15.7)	73 (25.6)	0.006
Recurrent CDI, $p <$ (%)	22 (8.2)	17 (6.0)	0.388
Readmission to MMA*	14 (5.2)	13 (4.6)	0.718

*MMA, Military Medical Academy

MLRA was used to control for confounding variables. Age ≥ 65 years, use of PPIs, chemotherapy and fluoroquinolones were positively associated with being in medical group, whereas admission to ICU and use of second- and third-generation cephalosporins were positively associated with being in surgical group.

When we analysed outcomes of HA CDI (Table 2), there were no significant differences between surgical and medical patients taking into account the LOS in hospital (39.93 ± 30.64 *vs*. 36.49 ± 28.80, respectively, $p = 0.262$), frequency of recurrent HA CDI (8.2% *vs*. 6.0%, respectively, $p = 0.388$), and readmission to MMA (5.2% *vs*. 4.6%, respectively, $p = 0.718$).

There were significant differences between them in 30-day mortality (15.7% *vs*. 25.6%, $p = 0.006$) and in-hospital mortality (19.8% *vs*. 28.1%, $p = 0.029$) (Table 2).

4. Discussion

We found a number of studies conducted in health care systems of developed countries regarding epidemiology, clinical features, and outcomes of HA CDI in the available literature [2,3,8,9]. The present one provides important data on patient characteristics, factors related to health care as well as outcomes in patients with HA CDI in large cohort of patients admitted to tertiary care centre in Southeast Europe. Study also provides further information about epidemiological differences between HA CDI in medical and surgical patients in health care system of Serbia as developing country.

4.1. Medical patients

We found that age ≥ 65 years, use of PPIs, chemotherapy and fluoroquinolones were positively associated with medical group and could be significant predictors of CDI in medical patients compared with surgical patients.

Advance age is frequently cited as one of the primary RF for CDI. Olsen et al. demonstrated that age did not improve CDI risk prediction after controlling for a wide variety of infections, other acute conditions, frailty indicators, and prior healthcare utilization [14]. Silva-Velazco et al. showed that surgical patients were significantly older than medical patients with HA CDI (60.4 ± 18.2 *vs*. 57.2 ± 20.4, respectively) [8]. On the contrary, our medical patients were significantly older than surgical ones (68.59 ± 15.46 *vs*. 64.91 ± 14.86; respectively, $p = 0.005$). MLRA in our study also showed that age ≥ 65 years were more frequent among medical than surgical patients with HA CDI (RR: 2.015; 95% CI: 1.-347–3.014; $p = 0.001$).

Since their release in the late 1980s, PPIs have become some of the most widely prescribed agents both in outpatient and inpatient settings throughout the world [15]. Craig et al. conducted large prospective observational study and concluded that the majority of intravenous PPI prescriptions within hospital practice were inappropriate [16]. With a wide range of prescription practices, the undesirable effects of these drugs have also been reported. Meta-analysis which included the largest number of observational studies published to date found that the risk of CDI was almost two-times higher in PPIs users than in nonusers [6]. In our study MLRA determined that the use of PPI was positively associated with CDI in the medical patients compared with the surgical cohort (RR: 3.431; 95% CI: 2.188–5.379; $p < 0.001$). This result is not surprising and is similar to that reported by Southern and colleagues [9]. Yet, in the last update of recommendations of the clinical practice guidelines for CDI in adults and children by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) there is the state that 'Although there is an epidemiologic association between PPI use and CDI, and unnecessary PPIs should always be discontinued, there is insufficient evidence for discontinuation of PPIs as a measure for preventing CDI' [12].

An association between the chemotherapy use and CDI has already been reported in previous studies [17,18]. On the contrary, Fuereder et al. demonstrated that chemotherapy *per se* is not a RF for CDI in hemato-oncological patients. They concluded that antimicrobial therapy was a major RF observed independently from chemotherapy in the examined cohort [19]. Oncology patients are at a high risk of CDI, in keeping with the frequency of known RF in that population: chemotherapy, antibiotic use, prior and prolonged hospitalizations, use of feeding tubes, use of PPIs, etc. In our study the chemotherapy was significantly more frequently administered to medical than surgical patients (12.6% *vs* 1.9%, respectively, $p < 0.001$) and this significance did retain in MLRA.

According to patients' risk of developing CDI, cephalosporins, carbapenems, fluoroquinolones and clindamycin were in the group of high-risk antibiotics [20]. Our results showed that previous infection was more frequent in medical patients than in surgical patients

(44.9% vs. 36.2%, respectively, $p = 0.037$). That could explain why the use of fluoroquinolones was significantly higher in medical group of patients than in surgical group (28.6% vs 9.9%, respectively, $p < 0.001$). CDI and in particular infections caused by the virulent strain referred to as the North Pulsed Field type 1 (NAP1) and PCR ribotype 027 (NAP-1/027) strain were known complications of fluoroquinolones treatment [21]. In the early 2000s, a previously uncommon *C. difficile* strain NAP1/027 acquired increased resistance to fluoroquinolone antibiotics and caused large outbreaks in North America and Northern Europe [11,22]. Kurti et al. reported an epidemic of CDI with incidence of 12.6% in a tertiary academic centre in Eastern Europe between 2010 and 2013. One of the RF for CDI was antibiotic therapy, including third-generation cephalosporins or fluoroquinolones ($p < 0.001$) [23]. In tertiary care hospital in Portugal CDI incidence achieved a peak in 2009/2010 coinciding with the increase in quinolone and carbapenem prescriptions as well as introduction of alcohol-based hand products [24]. Although many countries continued to have high rates of CDI, England achieved to decrease CDI with fluoroquinolone restriction [25].

A recent systematic review followed by a meta-analysis regarding HA CDI exhibited increased risks for this infection after use of several antimicrobial classes [26]. Among them, fluoroquinolones imposed lower risk than other classes of antibiotics: third-generation cephalosporins, clindamycin, second-generation cephalosporins, fourth-generation cephalosporins, carbapenems and trimethoprim/sulphonamides [26]. In the study concerning antibiotic consumption and HA infections conducted in our hospital from 2011 to 2016, we did not find a correlation between fluoroquinolones consumption and incidence density of CDI, but consumption of fluoroquinolones was very low and varied from 1.7% to 5.4% of total consumption of antibiotics in that period [27]. However, more rational prescribing process of fluoroquinolones is not only important due to HA CDI, but also due to disabling and potentially permanent side effects which already lead to their suspensions or restrictions by European Medicines Agency safety committee (PRAC) in 2018 [28].

4.2. Surgical patients

We found that ICU stay and use of second- and third-generation cephalosporins were positively associated with surgical group and could be significant predictors of CDI in surgical patients compared with medical ones.

Diarrhoea is one of the most common symptoms in ICU patients. Many factors may cause diarrhoea in critically ill, including non-infectious (drugs, enteral feeding, etc.) and infectious (*C. difficile* and other bacteria, viruses etc.). According to data from Europe and North America, reported incidence of HA CDI in ICU was in the range from 8.7 in Spain [29] to 53.9 cases per 10 000 patient days in US [30]. Our previous data demonstrated that ICU stay were significantly associated with HA CDI in surgical patients [4]. We also observed the differences in incidence density of HA CDI in medical and surgical patients [27]. In the current study, there were significant differences in ICU admission and LOS in ICU between medical and surgical patients ($p < 0.001$ concerning both variables). Surgical patients were treated more often than medical in ICU, but medical patients were longer treated there (25.23 ± 33.97 *vs.* 7.16 ± 12.09, $p < 0.001$). Since only the categorical variables that were statistically significant in ULRA were also included in our MLRA, ICU admission was positively associated with CDI in surgical patients compared with medical patients (RR: 4.730; 95% CI: 2.877–7.775; $p < 0.001$). Similarly, Watkinson et al. reported that longer ICU stay was positively associated with CDI in trauma/surgery patients compared with medical patients [31].

MV is one of the most common interventions implemented in ICU. Study from Taiwan's National Intensive Care Unit Data base conducted in the large cohort of intubated patients showed that prolonged MV (> 21 days) and prolonged carbapenems therapy (> 15 days) were independent predictors of HA CDI [32]. In our study there were no differences in frequency of MV use between surgical and medical patients (14.6% *vs.* 15.4%, respectively, $p = 0.863$). Second-generation cephalosporins were used more frequently in our surgical than in medical patients (30.0% vs 17.6%, respectively, $p = 0.001$) and this significance was verified in MLRA (RR: 1.924; 95% CI: 1.177–3.145; $p = 0.009$). Similar data were registered in the use of third-generation cephalosporins (64.6% vs 53.1%; RR: 2.173; 95% CI: 1.421–3.322, $p < 0.001$).

Slimings and Riley found that third-generation cephalosporins (e.g. cefotaxime) showed increased risk for HA CDI (OR: 3.20, 95% CI: 1.80–5.71) and that the second-generation cephalosporins had lower risk than the third-generation (OR: 2.23, 95% CI: 1.47–3.37) [26]. The consumption of the third-generation cephalosporins (ceftriaxone and ceftazidime) was 66.8% of all cephalosporins used in our hospital from 2011 to 2016 and surgical antimicrobial prophylaxis was one of the reasons for these findings [27]. Southern et al. also found that risk for developing post-surgical CDI was increased with exposure to pre-operative antibiotics, especially the third-generation cephalosporins and concluded that unnecessary use of antibiotics before surgery should be avoided [9]. Since, according to our National Guidelines of Good Clinical Practice for Rational Usage of Antibiotics [33], only first and second generation of cephalosporins should be used for surgical antimicrobial prophylaxis, our

multidisciplinary hospital healthcare team will continue to make further efforts in the implementation of the antibiotic stewardship program as a whole in order to decrease unnecessary exposures of patients to antimicrobial agents [27].

4.3. Outcomes

Study of CDI burden following digestive tract surgery in Japan showed that increased LOS is both a RF for CDI and its outcomes [34]. Authors Honda et al. reported a median LOS among 126 CDI cases of 41.5 days (17.5 days before and 18 days post-CDI diagnosis) [35]. In the USA, patients with HA CDI, compared with controls, had significantly longer total LOS (mean ± SD: 14.4 ± 18.3; median (IQ range) 10 (5–17) *vs*. mean ± SD: 8.7 ± 15.6, median (IQ range) 6 (3–10)) [36].

In our study, there were no differences between surgical and medical patients in total LOS (39.93 ± 30.64 *vs*. 36.49 ± 28.80, $p = 0.262$), but surgical patients had statistically longer hospitalization prior CDI (21.22 ± 18.68 *vs* 17.79 ± 17.48, $p = 0.004$). Silva-Velazco et al. also reported statistically longer hospitalization prior CDI in surgical patients [8]. National statistics from Serbia shows that mean LOS for all eligible patients decreased from 8.3 in 2013 to 7.3 in 2017 in tertiary healthcare centres [37]. Based on all of the above, it could be concluded that CDI in our hospital was HA infection in long-standing patients, whether they were medical or surgical.

Hungarian study reported 30-day mortality rate of 21.9% in CDI patients treated in an academic centre in Eastern Europe [23]. In our experience, the prognosis of CDI was poorer in medical than in surgical patients, what was substantiated by the higher 30-day mortality rate observed in medical patients (25.6% *vs*. 15.7%, respectively, $p = 0.006$). It is higher than it was reported in Cleveland Clinic in Ohio concerning both categories of patients (9.9% in medical *vs*. 6.9% in surgical patients, $p = 0.003$) [8]. This difference is explained by the different levels of healthcare and treatment of patients in hospitals in Serbia and the USA. Similar differences were found regarding in-hospital mortality between medical and surgical cohorts (28.1% vs 19.8%, respectively, $p = 0.029$) in our survey. The research of Watkins and colleagues is in accordance with our results since the overall survival rate was significantly higher in the trauma/surgery group than in the medical group (100% *vs*. 81%, respectively, $p = 0.003$) [31]. The study of Oake et al. showed that HA CDI was independently associated with an increased risk of in-hospital death and that across all baseline risk strata, for every 10 patients acquiring the infection, one person died [38].

Disease recurrence is observed in 15–35% of patients after an initial episode of CDI, with the rate rising to 35–65% after the first recurrence [39]. National retrospective cohort study of the burden of CDI among adult veterans in the USA conducted during 11- year period, documented increases in CDI initial and recurrent episodes [40]. Overall 5011 patients or 17% of the total CDI cohort experienced first recurrence over the study period. In our survey, first CD recurrence was detected in 8.2% of surgical patients and 6.0% of medical patients, without significant differences between groups ($p = 0.388$). On the contrary, Silva-Velazco et al. registered statistically higher rate of first recurrence in medical than in surgical patients (8.1% *vs*. 6.3%, $p = 0.07$) [8].

5. Limitations and strengths of study

First, it is single centre study and our data may not be generalized to other healthcare centres. Second one is connected with the fact that although patients from all MMA departments were included for the surveillance of HA CDI, we had no surveillance of patients after discharge from the hospital. Therefore, the frequency and impact of postdischarge CDI, initial and recurrent, could be widely underestimated. Important limitation of this study was the fact that CDI testing was based on toxin A/B enzyme immunoassay (EIA) as the only diagnostic procedure in laboratory (no EIA detecting glutamate dehydrogenase, no isolation of *C. difficile* and detection of toxigenic isolates, no nucleic acid amplification tests). This procedure has shown poor sensitivity of less than 50% in studies of Shin [41] and Swindells [42]. In addition, the meta-analysis of Crobach et al. showed that no single test can be used as a stand-alone test for diagnosed CDI as a result of inadequate positive predictive values at low CDI prevalence [43]. Another major limitation was the lack of culture and molecular typing data.

However, the strengths of our study include its prospective cohort design, 7 years of duration, as well as ULRA and MLRA strengthened evidence.

6. Conclusions

From our 7-year long cohort study it can be concluded that age ≥ 65 years, use of PPIs, chemotherapy and fluoroquinolones were positively associated with medical group and could be significant predictors of CDI in medical patients compared with surgical patients. Conversely, ICU stay and use of second- and third-generation cephalosporins, were positively associated with surgical group and could be significant predictors of CDI in surgical patients compared with medical ones.

Based on all obtained results, including significant differences in 30-day mortality and in-hospital

mortality and all limitations of the study, it can be concluded that medical patients were more endangered with HA CDI than surgical ones. We believe that our findings could be useful not only for clinicians, but also for the management of the hospitals in countries in socioeconomic transition and with a limited resource healthcare system.

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