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UNIVERSITY OF MEDICINE AND PHARMACY

”CAROL DAVILA”, BUCHAREST

DOCTORAL SCHOOL

MEDICINE

CLOSTRIDIOIDES DIFFICILE INFECTION: EPIDEMIOLOGICAL AND CLINICAL ASPECTS

SUMMARY OF THE DOCTORAL THESIS

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I. General part

Since 1978, *Clostridioides difficile* (known as *Clostridium difficile* until 2016) has been identified as the cause for the majority of cases of antibiotic-associated colitis. The severity of the damage caused by *C.difficile* varies from asymptomatic colonization to fulminant forms of colitis, which sometimes can lead to colectomy or even death. The increase in the incidence of community-acquired infection has been observed since the period of 2011-2017 when cases of unusually severe community-acquired *C.difficile* infections (CDI) were reported in patients from populations previously considered to have a low risk for CDI, such as women during the peripartum period and healthy individuals without a history of antibiotic use, recent hospitalization, or other classical risk factors for CDI. Therefore, CDI should be considered and investigated even in the absence of a history of antibiotic exposure or recent hospitalization [1].

Widely recognized risk factors for CDI include antibiotic therapy, advanced age, hospitalization or recent history of hospitalization, and severe comorbidities. Other risk factors are represented by nasogastric tube feeding, recent gastrointestinal surgery, obesity, ongoing chemotherapy for oncological conditions, hematopoietic stem cell transplantation, inflammatory bowel diseases, cirrhosis, and gastric acid suppression [1, 2]. A review published in 2021 listed the following as associated with a higher risk of CDI: female sex, residing in chronic care institutions, and treatment with corticosteroids. Among comorbidities, diabetes mellitus and cardiac comorbidities were significantly associated with a higher risk [3].

All patients with typical manifestations of CDI (acute diarrhea defined as ≥3 watery stools in 24 hours, without another evident cause) and a positive laboratory test for *C.difficile* should receive specific treatment. Furthermore, empirical treatment is justified in cases with a very high clinical suspicion of CDI (especially in patients with symptoms of severe or fulminant colitis) while waiting for diagnostic test results. Treatment is not indicated for patients with a positive laboratory test but without diarrhea or other manifestations of CDI, considering the possibility of asymptomatic carriage [4].

The main recommendations from the leading international guidelines regarding the treatment of the initial episode of CDI, severe forms of CDI, and CDI recurrences are summarized in *Figure 1*, reproduced from the European Society guideline [5].

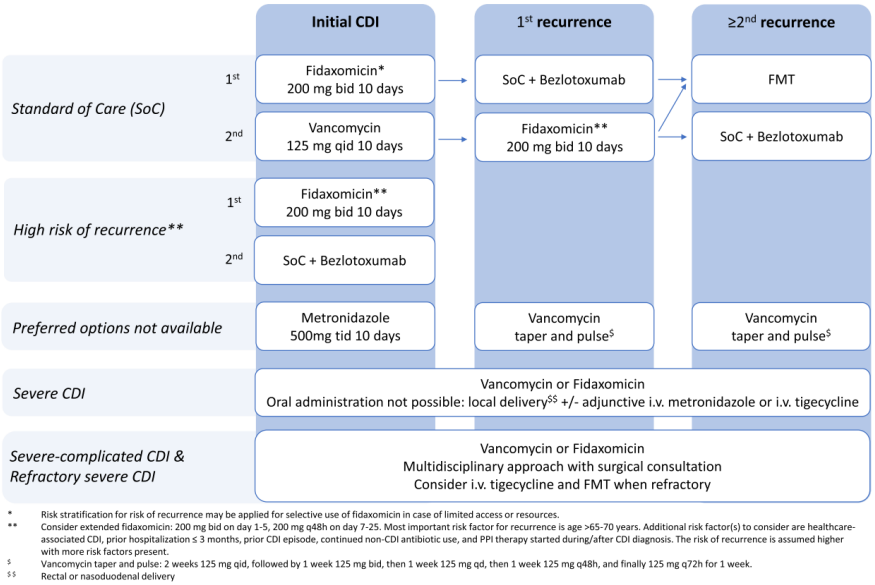


Fig 1. CDI treatment algorithm (according to ESCMID guideline recommendations)

II. Personal contributions

Aim and objectives

Through this paper, I aimed to study the epidemiological and clinical aspects of patients diagnosed and treated for CDI at the National Institute of Infectious Diseases "Prof. Dr. Matei Balș", with the purpose of improving the management of this infection. To achieve this goal, I formulated six objectives (four main objectives and two secondary objectives), based on which I conducted three studies, detailed in *Figure 2*.

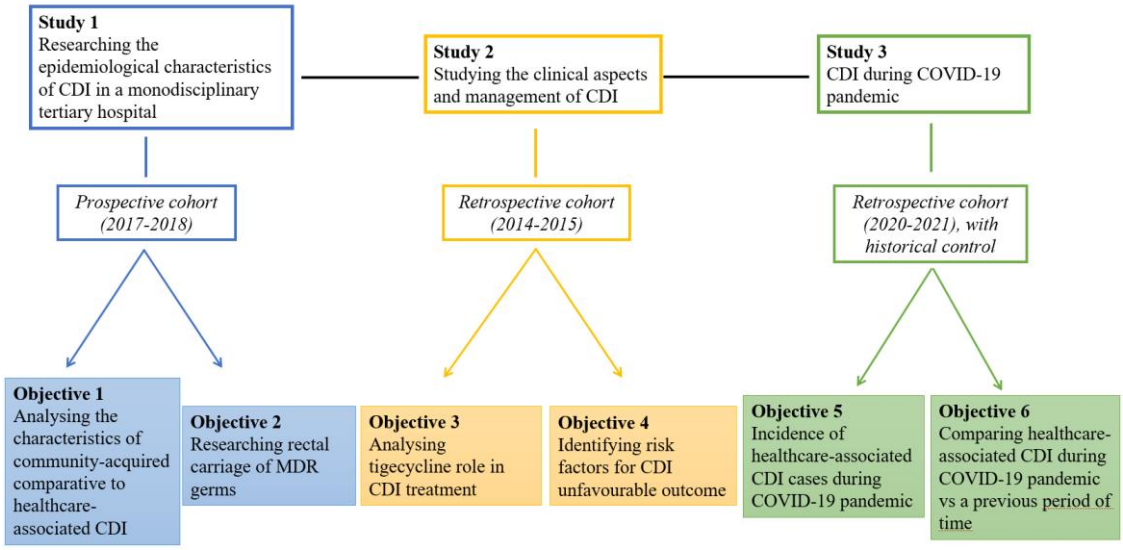


Fig 2. The plan for doctoral research studies

Researching the epidemiological characteristics of *Clostridioides difficile* infection in a tertiary monodisciplinary hospital

Objective 1: Comparative analysis of the characteristics of hospitalized cases of *Clostridioides difficile* infection, according to the origin of *Clostridioides difficile* infection (healthcare-associated infections versus community-acquired infections).

Introduction

Differentiating between the acquisition modes of CDI, community-acquired versus healthcare-associated, is crucial as it contributes to understanding the epidemiological trends of this infection and improving efforts for CDI prevention. Currently, prevention measures are mainly focused on controlling transmission within healthcare facilities. CDI can also affect populations previously considered low-risk or without risk, such as young patients and those without exposure to antibiotic treatment within the 12-week period before the CDI diagnosis. This suggests the existence of other additional risk factors that could play a role in acquiring CDI in the community [6, 7].

Methods

I conducted a prospective study that included all adult patients hospitalized for CDI between March 2017 and February 2018. I classified the CDI cases based on case definitions as healthcare-associated, community-acquired, and cases with undetermined origin.

Results

During the study period, I identified 553 cases of CDI, recorded in 502 patients. Among these, 447 (80.8%) were healthcare-associated CDI cases, 75 (13.6%) were community-acquired CDI cases, and 31 (5.6%) were CDI cases with undetermined origin. Among the patients with healthcare-associated CDI, 221 (49.4%) were male, compared to 31 (41.3%) in the community-acquired CDI group (p=0.1). In the healthcare-associated CDI group compared to the community-acquired CDI group, the median age was 71 years (IQR: 60-81) versus 55 years (IQR: 40-74) (p <0.001), the median Charlson comorbidity score was 5 (IQR: 3-6) versus 3 (IQR: 0-4) (p <0.001), the median Atlas score was 3 (IQR: 2-5) versus 1 (IQR: 0.5-3) (p <0.001), and the median SOFA score was 1 (IQR: 0-2) versus 0 (IQR: 0-1) (p=0.001).

Ribotype 027 was identified in 271 (82.6%) patients with healthcare-associated CDI versus 30 (53.5%) patients with community-acquired CDI, p<0.001. I identified four cases of toxic megacolon in the healthcare-associated CDI group and none in the community-

acquired CDI group. Additionally, patients with healthcare-associated CDI required a longer hospitalization duration compared to patients with community-acquired CDI (median of 12 days versus 8 days, p=0.001). Moreover, in the healthcare-associated CDI group, more patients died, with a total of 41 deaths, out of which 21 deaths were directly attributed to CDI, while in the community-acquired CDI group, only one patient died (death due to CDI).

Discussions

A study from 2010 in the USA, which identified a total of 10,342 cases of CDI, of which 3,269 (32%) were community-acquired cases, presents similar results regarding the characteristics of patients with community-acquired CDI [8]. Similarly, a study published in 2019 by Turner et al. identified that patients with healthcare-associated CDI were older and had a higher proportion of males compared to those with community-acquired CDI [6].

Conclusion

The majority of hospitalized CDI cases during the 12-month study period were healthcare-associated CDI cases. Ribotype 027 was more frequently detected in healthcare-associated CDI cases. In contrast to healthcare-associated CDI cases, community-acquired CDI cases were more commonly found in women, younger patients, with fewer comorbidities, and resulted in fewer severe forms of CDI.

Objective 2: Describing the characteristics of patients hospitalized for *Clostridioides difficile* infection with concomitant rectal carriage of vancomycin-resistant enterococci and/or *Enterobacteriaceae* with antibiotic resistance issues.

Introduction

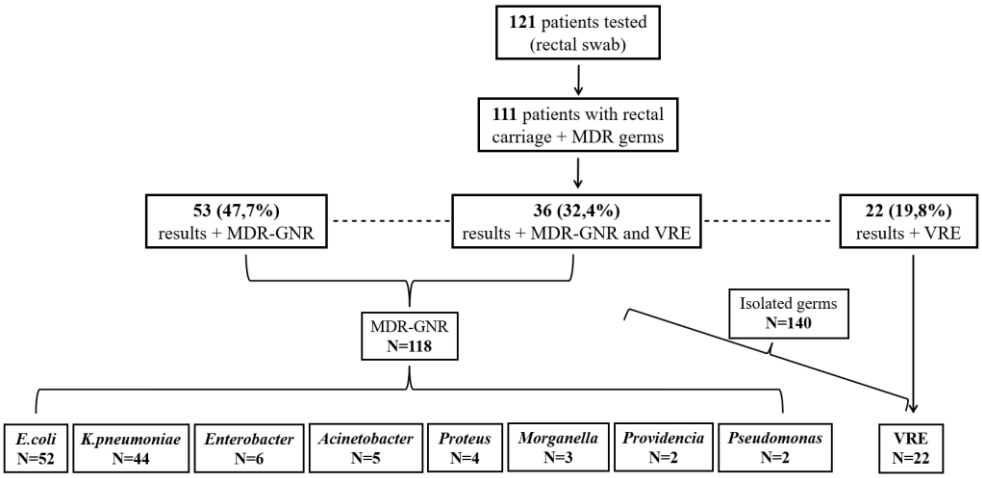
The risk factors for the colonization of patients with resistant bacteria are similar to those for CDI [9]. Patients colonized with vancomycin-resistant enterococci and concurrent CDI have an increased risk of skin contamination and environmental dissemination of resistant enterococci. The administration of vancomycin may be a risk factor for colonization with multidrug-resistant *Enterobacteriaceae* strains [10].

Methods

Rectal swabs were collected from patients admitted to the Intensive Care Units or transferred from other hospitals. We conducted a prospective study that included adult patients hospitalized for CDI between March 2017 and February 2018, in whom rectal swabs were taken.

Results

I included 121 cases of CDI out of a total of 553 reviewed CDI episodes. In 111 (91.7%) patients, rectal swabs were positive for multidrug-resistant (MDR) bacteria. The identified bacteria are represented in *Figure 3*.



*MDR = multidrug resistance; GNR = Gram negative rods; VRE = vancomycin resistant enterococci

Fig 3. The distribution of rectal swab samples collected, according to positive results and the types of MDR germs identified in the rectal carriage

Men were more frequently rectally colonized with vancomycin-resistant enterococci (77.3% versus 47.2% of those colonized with MDR Gram-negative bacilli, p=0.05), while rectal colonization with MDR Gram-negative bacilli was more frequent among patients with a history of prior CDI (71.7% versus 68.2% of those colonized with vancomycin-resistant enterococci, p=0.05). Additionally, patients rectally colonized with MDR Gram-negative bacilli had a greater severity of CDI, assessed by the ATLAS score (median 4 versus 3 points in patients colonized with vancomycin-resistant enterococci, p=0.005), and patients colonized with both MDR Gram-negative bacilli and vancomycin-resistant enterococci more frequently had an unfavourable outcome (25% versus 4.5% for those with vancomycin-resistant enterococci only versus 9.4% for those with MDR Gram-negative bacilli only, p=0.04).

Discussions

In the literature, vancomycin-resistant enterococci have been most frequently identified concurrently with CDI. In a study published in 2018, patients colonized with vancomycin-resistant enterococci were more frequently positive for *C.difficile*, although the difference between those colonized and those without colonization was not statistically

significant (15% versus 10%, p=0.11) [11]. In another study published in 2017, vancomycin-resistant enterococci were isolated in 17% of samples positive for *C.difficile*, compared to 5.7% of samples negative for *C.difficile* ($p < 0.05$) [12].

We did not find any data in the literature regarding a potential association between CDI and concurrent gastrointestinal colonization with MDR *Enterobacteriaceae*. However, according to data from the European report in 2020, 19.7% of *Escherichia coli* strains and 67.9% of *Klebsiella pneumoniae* strains isolated from patients in Romania were ESBL type, and the high prevalence of these types of bacteria could explain the high rate of rectal colonization with MDR Gram-negative bacilli in patients with CDI [13].

Conclusion

A higher rate of colonization with vancomycin-resistant enterococci, multidrug-resistant *Enterobacteriaceae*, or both was found in patients with CDI. Contrary to expectations, in the majority of cases in this study, the bacteria identified in rectal swabs belonged to the category of *Enterobacteriaceae*, with one-third of patients actually being colonized concurrently with both multidrug-resistant *Enterobacteriaceae* and vancomycin-resistant enterococci.

Studying the clinical aspects of *Clostridioides difficile* infection

Objective 3: Comparative analysis of the outcomes of patients with *Clostridioides difficile* infection treated with tigecycline in combination with vancomycin versus those treated with vancomycin alone.

Introduction

Therapeutic options for CDI are limited, with oral vancomycin and metronidazole being the most commonly used antibiotics for CDI treatment and recommended by current guidelines [5, 14]. Tigecycline is an antibiotic with in vitro activity against *C.difficile* [15]. This antibiotic is mentioned in the ESCMID guideline for CDI treatment as a therapeutic option only for severe forms of CDI when oral therapy is not possible [5, 16]. A retrospective study that compared the outcomes of patients with severe CDI who received tigecycline monotherapy versus those who received vancomycin in combination with metronidazole suggests a better prognosis in terms of clinical cure among patients treated with tigecycline [17].

Methods

I conducted a retrospective cohort study that included all adult patients hospitalized for their first episode of CDI between September 2014 and August 2015. My goal was to analyse the rate of favourable outcomes. For patients who received tigecycline, I built a logistic regression model and applied the propensity score.

Results

I included 266 patients with a first episode of CDI: 62 patients who received combination treatment with vancomycin and tigecycline, and 204 patients who received vancomycin monotherapy. The patients in both groups were similar in terms of demographic characteristics and comorbidities, but the patients in the treatment group that included tigecycline had more severe forms of CDI and more frequently had another concurrent infection with CDI.

Favourable outcome was identified in 50 out of 62 (81%) cases in the tigecycline group versus 193 out of 204 (95%) cases in the vancomycin monotherapy group. I grouped the patients according to the propensity score and obtained 86 patients (43 pairs). The relative risk for favourable outcome for those who received tigecycline in addition to treatment was 0.92 (95% CI: 0.60-1.44; p=0.74) for the patient groups obtained using the propensity score. The recurrence rate for CDI was 8 out of 62 (13%) cases in the tigecycline group versus 39 out of 204 (19%) cases in the vancomycin monotherapy group (p=0.2).

Discussions

In general, tigecycline is used in the treatment of severe CDI, in cases of oral intolerance, or for patients non-responsive to standard therapy. However, upon comparative analysis of the two groups, we did not identify an association between the use of tigecycline in combination with oral vancomycin for CDI treatment and a better outcome for patients, compared to those who received treatment with oral vancomycin alone, even after balancing the compared groups using the propensity score.

In a review published in 2015, 11 articles were identified, totalling 47 patients, who received tigecycline treatment for CDI, with a clinical cure rate of 74% [18]. In comparison, our study included a larger patient cohort, identifying a higher rate of favourable outcomes (84%), but without achieving an improvement in prognosis by adding tigecycline, regardless of the type of statistical analysis used (univariate, multivariate, and propensity score integration). In contrast to our results, another retrospective study that analysed the outcomes of patients with severe CDI treated with tigecycline compared to those treated with oral vancomycin in combination with intravenous metronidazole identified a healing rate of

75.6% for the tigecycline treatment group, significantly higher compared to the rate for patients in the vancomycin and metronidazole treatment group (53.3%) [17]. However, the multivariate analysis in this study showed a very wide 95% confidence interval, making the results from that analysis difficult to interpret.

Conclusion

Adding tigecycline to the standard therapy for CDI did not increase the rate of clinical cure, nor did it reduce the rate of CDI recurrence.

Objective 4: Studying severe *Clostridioides difficile* infection

Introduction

Publications on risk factors and clinical parameters that could allow the prediction of unfavourable outcomes in CDI are extremely heterogeneous, and there is still no consensus. The first systematic review, which analysed all publications aimed at developing or validating clinical prediction scores for CDI recurrence, complications, and mortality, was published in 2012. It identified three types of variables that were consistent in the analysed studies: leucocytosis, hypoalbuminemia, and advanced age [19]. Another recent review also found leucocyte count, albumin, and age frequently associated with severity in the analysed studies, along with comorbidities, serum creatinine levels, and the need for Intensive Care Unit admission [20].

Methods

I conducted a retrospective cohort study that included all adult patients hospitalized for CDI between September 2014 and August 2015. I excluded patients for whom the ATLAS severity score could not be calculated. To define severe forms of CDI, we used the ATLAS score (which includes age, temperature, leucocytosis, albumin, and systemic antibiotic therapy), with a score of at least 5 points, and also the severity criteria according to the SHEA-IDSA guidelines (leucocytosis ≥ 15x10^9/L, or a serum creatinine value ≥ 1.5 times the pre-morbid value).

Results

A total of 660 episodes of CDI were identified, out of which 409 cases were included in the analysis, with 266 (65%) of them being incident episodes of CDI. The median age was 70 years (IQR: 59-80 years), and the median Charlson comorbidity index was 4 (IQR: 3-5). According to the ATLAS score, 194 (47.4%) severe cases were identified, and according to the SHEA-IDSA severity criteria, 151 (36.9%) severe cases. Comparing the group of patients with severe forms of CDI to those with non-severe forms (identified according to the ATLAS

score), I found the following: the analysed episode of CDI constituted a first episode of CDI for 134 (69.1%) severe patients versus 132 (61.4%) non-severe patients, p=0.1 (OR: 0.7, 95%CI: 0.4-1); the median age was 76 years (IQR: 64-82 years) for severe cases versus 66 years (IQR: 51-77 years) for non-severe cases, p<0.001; the mean Charlson score was 4.2 among severe patients versus 3.5 among non-severe patients, p<0.001; 175 (90.2%) severe patients versus 206 (95.8%) non-severe patients, p=0.02 (OR: 0.4, 95%CI: 0.1-0.9) had a favourable outcome. On the other hand, comparing the group of severe patients to the non-severe patients defined according to the SHEA-IDSA severity criteria, I found: a first episode of CDI for 112 (74.2%) severe patients versus 154 (59.7%) non-severe patients, p=0.003 (OR: 0.5, 95%CI: 0.3-0.8); the median age was 73 years (IQR: 64-82 years) for severe cases versus 68 years (IQR: 57-78 years) for non-severe cases, p<0.001; the mean Charlson score was 4 for severe patients versus 3.7 for non-severe patients, p=0.1; 135 (89.4%) severe patients versus 246 (95.3%) non-severe patients, p=0.02 (OR: 0.4, 95%CI: 0.1-0.8) had a favourable outcome.

Using ROC curves, I obtained the following threshold values for the variables subsequently analysed in association with mortality: for age, the threshold was 75 years; for the Charlson comorbidity index, the threshold value was 5 points; for serum creatinine, the threshold value was 1.7 mg/dL; for the ATLAS score, the threshold value was 5 points; and for the SOFA score, the threshold value was 3 points. Following the multivariate analysis using logistic regression, mortality was associated with the following factors: age over 75 years (p=0.009), HIV infection (p=0.008), concomitant treatment with linezolid for CDI (p=0.004), serum albumin level (p=0.009), ATLAS score with a value of at least 5 points (p=0.03), and meeting the criteria for severe complicated CDI according to the SHEA-IDSA guidelines (p<0.001).

Discussions

The observed mortality rate in this study (6.8%) is comparable to the data from the literature, according to a review that included 15 studies, where CDI-associated mortality ranged between 5.7% and 6.9% [21]. In a systematic review published in 2014, 30-day mortality was associated with comorbidities, age, hypoalbuminemia, leucocytosis, elevated serum creatinine and/or urea levels, and ribotype 027 [22]. Another study, published in 2016, also found that the presence of concurrent comorbidities was an independent predictor of CDI-associated mortality in multivariate analysis [23].

Conclusion

Approximately one-third of the included cases were severe forms of CDI. Both methods of severity classification predicted the mortality of the CDI cases included in this study similarly. Mortality was associated with age, the presence of comorbidities, hypoalbuminemia, acute renal failure, and elevated values of the ATLAS and SOFA scores.

Analysis of *Clostridioides difficile* infection cases during the COVID-19 pandemic

Introduction

Until now, there is no clear data regarding the actual impact of CDI among patients with COVID-19. In this context, I aimed to analyse whether the prevention and control measures for SARS-CoV-2 infection, implemented in our institution, have had a favourable impact on the spread of healthcare-associated CDI cases. Thus, my objective was to evaluate the incidence of healthcare-associated CDI in our institution during the COVID-19 pandemic period and compare the characteristics of patients with co-infection of SARS-CoV-2 and CDI to cases of healthcare-associated CDI from the pre-COVID-19 pandemic period.

Methods

I conducted a retrospective study at a tertiary hospital in Romania, which was transformed into a first-line healthcare facility for COVID-19 patients, starting from March 2020. In this study, I included patients diagnosed with healthcare-associated CDI during their hospitalization for COVID-19, in the period from March 2020 to February 2021. This cohort of COVID-19 patients was compared to another cohort of adult patients diagnosed with healthcare-associated CDI during their hospitalization at the same institution but in the period from March 2017 to February 2018.

Results

I identified 51 cases of CDI during the period 2020-2021 (COVID-19 group), with an incidence of 5.6/1000 discharged adult patients, and 99 cases of CDI during the period 2017-2018 (pre-COVID-19 group), with an incidence of 6.1/1000 discharged adult patients ($p=0.6$). The patients in the COVID-19 group were older compared to those in the pre-COVID-19 group (median age of 66 versus 62 years), with similar rates of comorbidities. The use of proton pump inhibitors was more frequent among patients in the COVID-19 group compared to those in the pre-COVID-19 group (94.1% vs. 32.3%), and the length of

hospitalization was longer for patients in the COVID-19 group (median of 19 versus 14 days).

The consumption of antibiotics prior to the diagnosis of CDI was identified in 85 (85.9%) patients in the pre-COVID-19 group and 44 (86.3%) patients in the COVID-19 group – mainly cephalosporins (34.1%), fluoroquinolones (22.3%), and glycopeptides (21.1%) in the pre-COVID-19 group, and for the COVID-19 group: cephalosporins and macrolides (63.6% for each of the two classes of antibiotics).

Discussions

Unlike our results, a recently published retrospective study identified a lower incidence of healthcare-associated CDI during the pandemic (between March and June 2020) compared to the same period in 2017 (OR=2.98; p=0.002), 2018 (OR=2.27; p=0.02), and 2019 (OR=2.07; p=0.04). However, the same study highlighted a higher incidence of healthcare-associated CDI in departments dedicated to COVID-19 patients compared to non-COVID-19 departments, suggesting that SARS-CoV-2 infection could be a possible risk factor for acquiring CDI [24].

Additionally, in our study, we observed an overuse of antibiotics, as data showed that 86.3% of COVID-19 patients received antibiotic therapy before being diagnosed with CDI. This excessive antibiotic prescription may explain the unchanged incidence rates of healthcare-associated CDI during the COVID-19 pandemic compared to the pre-pandemic period.

Conclusion

The incidence of healthcare-associated CDI during the COVID-19 period remained unchanged compared to the same time period between 2017 and 2018. The administration of antibiotic therapy was the most significant factor associated with healthcare-associated CDI. We identified a high level of prescription of broad-spectrum antibiotic therapy, even though there are no recommendations in the literature or current guidelines in favour of empirical antibiotic administration in SARS-CoV-2 infection.

Bibliography

1. Lamont JT, Bakken JS, Kelly CP. *Clostridioides difficile* infection in adults: Epidemiology, microbiology, and pathophysiology. UpToDate. Last updated 17.01.2023. https://www.uptodate.com/contents/clostridioides-difficile-infection-in-adults-epidemiology-microbiology-and pathophysiology?search=clostridioides%20difficile%20epidemiology&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Link accessed in 29.01.2023.
2. Yingchao C. Risk factors for *Clostridioides difficile* infection and colonization among patients admitted to an intensive care unit in Shanghai, China. BMC Infect Dis; 19(1): 961; 2019.
3. Finn E, Andersson FL, Madin-Warbuton M. Burden of *Clostridioides difficile* infection (CDI) – a systematic review of epidemiology of primary and recurrent CDI. BMC Infect Dis; 21(1): 456; 2021.
4. Kelly CP, Lamont JT, Bakken JS. *Clostridioides difficile* infection in adults: Treatment and prevention. UpToDate. Last updated: 11.01.2023. https://www.uptodate.com/contents/clostridioides-difficile-infection-in-adults-treatment-and-prevention?search=clostridioides%20formerly%20clostridium%20difficile%20infection%20in%20adults%20treatment%20and%20prevention&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H35. Link accessed in 23.03.2023.
5. Van Prehn J, Reigadas E, Vogelzang EH, Bouza E, Hristea A, Guery B, et al. European Society of Clinical Microbiology and Infectious Diseases: 2021 update on the treatment guidance document for *Clostridioides difficile* infection in adults. Clin Microbiol Infect; 27(2): 1-21; 2021.
6. Turner NA, Grambow SC, Woods CW, Fowler Jr VG, Moehring RW, Anderson DJ, et al. Epidemiologic Trends in *Clostridioides difficile* Infections in a Regional Community Hospital Network. JAMA Netw Open; 2(10): e1914149; 2019.
7. Al Assaad R, Dakessian A, Bachir R, Bizri AR, El Sayed M. Signifcance of *Clostridium difcile* in community-acquired diarrhea in a tertiary care center in Lebanon. Scientific Reports; 10(1): 5678; 2020.

8. Lessa FC. Community-associated *Clostridium difficile* infection: How real is it? Anaerobe; 24: 121-3; 2013.
9. Sidler JA, Battegay M, Tschudin-Sutter S, Widmer AF, Weisser M. Enterococci, *Clostridium difficile* and ESBL-producing bacteria: epidemiology, clinical impact and prevention in ICU patients. Swiss Med Wkly; 144:w14009; 2014.
10. Harris AD, McGregor JC, Johnson JA, Strauss SM, Moore AC, Standiford HC, et al. Risk factors for colonization with Extended-Spectrum β-Lactamase– producing bacteria and Intensive Care Unit admission. Emerg Infect Dis; 13(8): 1144-9; 2007.
11. Axelrad JE, Lebwohl B, Cuaresma E, Cadwell K, Green PHR, Freedberg DE. Gut colonization with vancomycin resistant Enterococcus and risk for subsequent enteric infection. Gut Pathog; 10(28); 2018.
12. Özsoy S, Ilki A. Detection of vancomycin-resistant enterococci (VRE) in stool specimens submitted for *Clostridium difficile* toxin testing. Brazilian Journal of Microbiology; 48(3): 489-92; 2017.
13. European Centre for Disease Prevention and Control. Antimicrobial resistance in the EU/EEA (EARS-Net) – Annual Epidemiological Report 2020. Stockholm: ECDC; 2022.
14. McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, et al. Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis; 66(7): 987-94; 2018.
15. Britt NS, Steed ME, Potter EM, Clough LA. Tigecycline for the Treatment of Severe and Severe Complicated *Clostridium difficile* Infection. Infect Dis Ther; 3(2): 321–31; 2014.
16. Crobach MJT, Planche T, Eckert C, Barbut F, Terveer EM, Dekkers OM, et al. European Society of Clinical Microbiology and Infectious Diseases: update of the diagnostic guidance document for *Clostridium difficile* infection. Clin Microbiol Infect; 22(4): 63-81; 2016.
17. Gergely SB, Kadar B, Lenart KS, Dezsenyi B, Kunovszki P, Fried K, et al. Use of intravenous tigecycline in patients with severe *Clostridium difficile* infection: a retrospective observational cohort study. Clin Microbiol Infect; 22(12): 990-5; 2016.
18. Di Bella, Nisii C, Petrosillo N. Is tigecycline a suitable option for *Clostridium difficile* infection? Int J Antimicrob Agents; 46(1): 8–12; 2015.

19. Abou Chakra CN, Pepin J, Valiquette L. Prediction Tools for Unfavourable Outcomes in *Clostridium difficile* Infection: A Systematic Review. PLoS ONE; 7(1): e30258; 2012.
20. Zhang VRY, Woo ASJ, Scaduto C, Cruz MTK, Tan YY, Du H, et al. Systematic review on the definition and predictors of severe *Clostridiodes difficile* infection. J Gastroenterol Hepatol; 36(1): 89–104; 2020.
21. Khan A, Elashery A, Kapadia S, Chandra S. Performance of severity of illness classification for *Clostridium difficile* infection to predict need-for-colectomy or inpatient death. J Community Hosp Intern Med Perspect; 4(3): 24711; 2014.
22. Abou Chakra CN, Pepin J, Sirard S, Valiquette L. Risk Factors for Recurrence, Complications and Mortality in *Clostridium difficile* Infection: A Systematic Review. PLoS ONE; 9(6): e98400; 2014.
23. Kassam Z, Fabersunne CC, Smith MB, Alm EJ, Kaplan GG, Nguyen GC, et al. *Clostridium difficile* associated risk of death score (CARDS): a novel severity score to predict mortality among hospitalised patients with *C. difficile* infection. Aliment Pharmacol Ther; 43(6): 725–33; 2016.
24. Bentivegna E, Alessio G, Spuntarelli V, Luciani M, Santino I, Simmaco M, et al. Impact of COVID-19 prevention measures on risk of health care-associated *Clostridium difficile* infection. Am J Infect Control; 49(5): 640-2; 2021.

The list of published scientific papers

Published papers in extenso

1. **Manea E**, Sojo-Dorado J, Jipa RE, Benea S, Rodríguez-Baño J, Hristea A. The role of Tigecycline in the management of *Clostridium difficile* infection: a retrospective cohort study. Clin Microbiol Infect; 24(2): 180-4; 2018.
   ISI indexed journal (Print ISSN 1198-743X; Online ISSN 1469-0691), impact factor 14.2 – 2022 Journal Citation Reports (Clarivate Analytics, 2023); in 2018: impact factor 5.292. Cited in Web of Science: 18 times.
   Paper awarded UEFSCDI, List 6 – Published papers in 2018 (updated 07.12.2018)
   Link to access the paper: *The role of tigecycline in the management of Clostridium difficile infection: a retrospective cohort study - Clinical Microbiology and Infec https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(17)30324-5/fulltexttion*
   (Chapter 6, subchapter 6.1, pages 71-86 from PhD thesis)

2. **Manea E**, Jipa R, Milea A, Roman A, Neagu G, Hristea A. Healthcare-associated *Clostridioides difficile* infection during the COVID-19 pandemic in a tertiary care hospital in Romania. Rom J Intern Med; 59(4): 409-15; 2021.
   ISI indexed journal (eISSN 2501-062X), impact factor 1.91 – Scopus Data 2023 (5 year impact factor 1.7). Cited in Web of Science: 6 times.
   Link to access the paper: *https://sciendo.com/article/10.2478/rjim-2021-0020*
   (Chapter 7, pages 111-127 from PhD thesis)

Abstracts published and presented at national conferences

1. **Manea E**, Bacruban R, Pițigoi D, Jipa R, Dumitrescu A, Ianosik E, Azamfire D, Ilie F, Hristea A. Current status of *Clostridium difficile* infection in a tertiary care hospital in Bucharest. 13th Edition of the Scientific Days of the National Institute for Infectious Diseases „Prof Dr Matei Balș" – Abstract volume; p 39-40; 2017. Abstract accepted as oral presentation. Bucharest, 8-10 November 2017.
   Indexed journal ISSN 2457-8525
   (Chapter 5, subchapter 1, pages 38-55 from PhD thesis)

2. **Manea E**, Jipa R, Niculae C, Hristea A. Assessment of severity of Clostridium difficile infection. 13th Edition of the Scientific Days of the National Institute for Infectious Diseases „Prof Dr Matei Balș" – Abstract volume; p 31-32; 2017. Abstract accepted as oral presentation. Bucharest, 8-10 November 2017.
   Indexed journal ISSN 2457-8525
   (Chapter 6, subchapter 2, pages 86-109 from PhD thesis)
3. **Manea E**, Jipa R, Scoicaru A, Ciont C, Hristea A. Factors associated with in hospital mortality in *Clostridium difficile* infection. The journal of Critical Care Medicine 2 (Supplement 1); p 39; 2018. Abstract accepted as oral presentation in the National Conference Management of Critical Patient in Infectious Diseases, Târgu Mureș, 25-27 April, 2018.
   Indexed journal ISSN 2393-1809
   (Chapter 6, subchapter 2, pages 86-109 from PhD thesis)
4. **Manea E**, Trică L, Jipa R, Bacruban R, Pițigoi D, Florea D, Hristea A. Healthcare-associated *Clostridium difficile* infection in a tertiary care hospital in Bucharest. Maedica A Journal of Clinical Medicine; 13 (Supplement); p 56; 2018. Abstract accepted as poster in the Congress of University of Medicine and Pharmacy "Carol Davila", Bucharest, 7-9 June 2018.
   Indexed journal ISSN 2501-6903
   Link to access the abstract: *https://www.congresumf.ro/editia-2018/#!fancybox/75cd2638*
   (Chapter 5, subchapter 1, pages 38-55 from PhD thesis)
5. **Manea E**, Anghel AMJ, Voicu AE, Jipa RE, Nedelcu I, Hristea A. Characterization of cases of *Clostridium difficile* infection: healthcare-associated infections versus community-associated infections. Abstracts volume; p 47-48; 2019. Abstract accepted as oral presentation in the National Conference of Infectious Diseases, Craiova, 28-30 March, 2019.
   Indexed journal ISBN 978-973-106-304-1
   (Chapter 5, subchapter 1, pages 38-55 from PhD thesis)
6. **Manea E**, Voicu AE, Anghel AMJ, Ștefănache C, Damalan A, Hristea A. Fecal carriage of vancomycin-resistant enterococci and ESBL-producing bacteria in patients with *Clostridium difficile* infection. Abstracts volume; p 49-50; 2019. Abstract accepted as oral presentation in the National Conference of Infectious Diseases, Craiova, 28-30 March, 2019.

Indexed journal ISBN 978-973-106-304-1

(Chapter 5, subchapter 2, pages 55-70 from PhD thesis)