EDITORIAL

Clostridioides difficile infection in the COVID-19 era: old and new problems

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that emerged in late 2019 in Wuhan, China, has rapidly spread worldwide and become a global pandemic of viral pneumonia, termed coronavirus disease 2019 (COVID-19).1 The emergency situation experienced by most hospitals during the pandemic, such as the need for strict isolation and management of patients with COVID-19, overcrowding, and a greater workload of the hospital staff, has given rise to concerns about an additional burden of transmitting healthcare-associated infections. Furthermore, although the incidence of bacterial superinfections in COVID-19 seems to be lower than in severe influenza, the overuse of broad-spectrum antibiotics has been reported during the current pandemic, resulting in a substantial proportion of patients with COVID-19 who have received empiric antibiotic treatment.2 These observations and the occurrence of Clostridioides difficile (C. difficile) infection (CDI) in patients with COVID-193 have raised concerns about a possible increase in the incidence of nosocomial CDI, particularly in frail patients.4 Clostridioides difficile is a multiresistant pathogen recognized as the leading cause of antibiotic-associated diarrhea in healthcare settings. Clostridioides difficile infection is considered one of the most significant nosocomial infections worldwide,5 with symptoms that range from mild diarrhea and abdominal discomfort to the most severe colitis, toxic megacolon, and death. The elderly and the immunocompromised patients represent the main target populations at risk of CDI.

In this issue of Polish Archives of Internal Medicine (Pol Arch Intern Med), Lewandowski et al6 reported the results of a retrospective study on CDI, performed in the Central Clinical Hospital of the Ministry of the Interior and Administration in Warsaw, Poland. In total, 441 patients with COVID-19 hospitalized between March and June 2020 and 2961 prepandemic patients hospitalized between January and December 2019 were included. The analysis indicated that the rate of CDI incidence significantly increased from 2.6% in the prepandemic period to 10.9% during the COVID-19 pandemic. Interestingly, this study is the first to report a significant increase in the number of CDI cases during the COVID-19 pandemic, in contrast to other studies reporting stable7 or even lower rates8 of CDI incidence.

The results obtained by Lewandowski et al6 indicated that age, length of hospitalization, some comorbidities (cardiovascular disease, chronic kidney disease, and nervous system disease), onset of abdominal symptoms during hospitalization, and antibiotic therapy were all risk factors for CDI, although weakly associated with CDI development in patients with COVID-19. Antibiotic treatment represented the most striking difference between patients from the prepandemic period and those with COVID-9. In fact, 87.5% of COVID-19 patients with CDI received antibiotic therapy compared with 67.5% of patients affected by CDI before the pandemic, which shows a significant increase in antibiotic consumption (57.2 vs 105, expressed as daily antibiotic intake per 100 person-days of hospitalization). In general, an increase in the use of azithromycin has been reported during the COVID-19 pandemic, although without any robust evidence of the efficacy of this macrolide against SARS-CoV-2.2 Interestingly, Lewandowski et al6 observed that azithromycin did not have any effect on CDI development in patients with COVID-19 compared with other antibiotics (considered all together), probably due to a lower risk of CDI associated with this antibiotic.9 Unfortunately, Lewandowski et al6 did not evaluate the contribution of the various classes to the general increase in antibiotic consumption observed in their study. A qualitative analysis of antibiotic use would be of value, since some classes, such as cephalosporins and fluoroquinolones, have been more potently associated with CDI, and differences in the associated risk can also be found within

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Received: January 26, 2021.
Accepted: January 30, 2021.
Published online: February 26, 2021.
Pol Arch Intern Med. 2021;131(2):118-120
doi:10.20452/pamw.15838
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a single class of antibiotics. Since the CDI risk depends not only on the type of the antibiotic used but also on the length of treatment, further studies would be useful to evaluate whether various antibiotic prescribing choices could lead to differences in the CDI risk in patients with COVID-19.

The current treatment of COVID-19 involves antiviral medications, anti-inflammatory drugs, anticoagulants, and immune system modulators. Lewandowski et al found that chloroquine and lopinavir/ritonavir did not have a significant effect on the development of CDI in patients with COVID-19. Apart from these results, there are no other data available on the impact of the drugs (or combinations of drugs) used for COVID-19 on CDI, an issue that would deserve to be further investigated.

In their study, Lewandowski et al speculated about other possible factors influencing CDI incidence to account for the different incidence rates reported during the pandemic. Strict infection prevention and control (IPC) measures adopted to prevent healthcare-associated transmission of COVID-19 could have a potential positive effect also on the transmission of other healthcare-associated infections, partially explaining the general decrease in CDI incidence observed in some hospitals. In fact, the extraordinary reinforcement of all IPC measures and the implementation of more stringent visitor restrictions may limit not only the circulation of C. difficile inside hospitals but also the introduction of C. difficile from the community into hospitals. The rates of toxigenic, asymptomatic C. difficile colonization range from 4% to 15% among healthy adults, and 3% to 21% among patients on admission.

The burden of carriers in introducing and maintaining C. difficile transmission in healthcare settings still represents one of the main open issues regarding CDI. Nevertheless, other studies have indicated that the improvement of infection control measures due to the COVID-19 pandemic seems not to have a significant impact on CDI, and Lewandowski et al reported an increased CDI incidence despite stricter IPC measures adopted in their hospital.

Lewandowski et al also highlighted a reduction in the rates of requests for C. difficile testing during the current pandemic in some settings. Since a considerable proportion of patients with COVID-19 experienced gastrointestinal symptoms in the course of infection, Lewandowski et al speculated that the misleading interpretation of gastrointestinal symptoms in these patients could result in underreporting of C. difficile infection. The underdiagnosis of CDI has been recognized as an alarming issue even in the prepandemic period.

In fact, a recent European multicenter study (EU-CLID) demonstrated how the absence of clinical suspicion and suboptimal diagnostic laboratory methods lead to about 40,000 inpatients with CDI potentially undiagnosed in European hospitals every year. These data highlight the necessity of establishing a differential diagnosis of CDI in patients with COVID-19 to avoid further underascertainment of this infection.

Intestinal damage and microbiota alterations caused by SARS-CoV-2 were hypothesized by Lewandowski et al to facilitate CDI development in patients with COVID-19. This hypothesis seems to be supported by recent studies that have demonstrated significantly reduced bacterial diversity in the fecal microbiome of patients with COVID-19, with an enrichment of opportunistic pathogens and depletion of beneficial commensal. Furthermore, first investigations indicated a dysregulated immune response in COVID-19 patients with an exacerbated systemic inflammatory response. These alterations in the immune response could have an effect on the onset of CDI in patients with COVID-19, although further studies will be necessary to clarify possible interactions between COVID-19 and CDI.

Finally, the biological characteristics and pathogenicity of C. difficile strains should not be disregarded. In fact, several highly virulent and multiresistant to antibiotics C. difficile types (ribotypes, when the PCR-ribotyping method is used) have been identified. These types are associated with increased morbidity and mortality. Besides the well-known ribotype 027, which caused the majority of hospital-acquired CDIs in the last decades worldwide, other ribotypes characterized by high virulence have recently emerged and presented international or regional diffusion. These ribotypes are commonly isolated not only in hospitals but also in the community, in which CDI cases are on the rise. Therefore, an effective CDI surveillance and a constant monitoring of emergence and spread of highly virulent strains become even more crucial during the COVID-19 pandemic.

In conclusion, first studies have provided a complex and, in many ways, alarming picture of CDI in the era of COVID-19. Some old issues related to CDI, such as underdiagnosis and inappropriate use of antibiotics, are still unsolved and even exacerbated by the COVID-19 pandemic. Furthermore, the consequences of the direct action of SARS-CoV-2 on the host (such as intestinal damage, alteration of the intestinal microbiota, and derangement of immune response) could impact the short- and long-term development of CDI in patients with COVID-19, raising new concerns. These findings highlight the need to attract renewed attention to CDI during the current COVID-19 pandemic and call for a stronger commitment of all people dealing with CDI to find answers to old and emerging issues.

ARTICLE INFORMATION

DISCLAIMER The opinions expressed by the author(s) are not necessarily those of the journal editors, Polish Society of Internal Medicine, or publisher.

CONFLICT OF INTEREST None declared.
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HOW TO CITE Spigaglia P. Clostridioides difficile infection in the COVID-19 era: old and new problems. Pol Arch Intern Med. 2021; 131: 118-120. doi:10.20452/pamw.15838

REFERENCES
1. Hu B, Guo H, Zhou P, et al. Characteristics of SARS-CoV-2 and COVID-19. Nat Rev Microbiol. 2020 Oct 6. [Epub ahead of print].
2. Huttner BD, Catho G, Pano-Pando JR, et al. COVID-19: don’t neglect antimicrobial stewardship principles! Clin Microbiol Infect. 2020; 26: 808-810.
3. Sandhu A, Tillotson G, Polistico J, et al. Clostridioides difficile in COVID-19 patients, Detroit, Michigan, USA, March-April 2020. Emerg Infect Dis. 2020; 26: 2272-2274.
4. Spigaglia P. COVID-19 and Clostridioides difficile infection (CDI): possible implications for elderly patients. Anaerobe. 2020; 64: 102233.
5. Czepiel J, Dróżdż M, Pituch H, et al. Clostridium difficile infection: review. Eur J Clin Microbiol Infect Dis. 2019; 38: 1211-1221.
6. Lewandowski K, Rosołowski M, Kaniewska M, et al. Clostridioides difficile infection in coronavirus disease 2019 (COVID-19): an underestimated problem? Pol Arch Intern Med. 2020; 131: 121-127.
7. Luo Y, Grinspan JT, Fu Y, et al. Hospital-onset Clostridioides difficile infections during the COVID-19 pandemic. Infect Control Hosp Epidemiol. 2020; 23: 1-2.
8. Ponce-Alonso M, Sáez de la Fuente J, Rincón-Carlavilla A, et al. Impact of the coronavirus disease 2019 (COVID-19) pandemic on nosocomial Clostridioides difficile infection. Infect Control Hosp Epidemiol. 2020; 8: 1-5.
9. Brown KA, Langford B, Schwartz KL, et al. Antibiotic prescribing choices and their comparative C. difficile infection risks: a longitudinal case-cohort study. Clin Infect Dis. 2020 Feb 18. [Epub ahead of print].
10. Crobach MJT, Vernon JJ, Luo VG, et al. Understanding Clostridium difficile colonization. Clin Microbiol Rev. 2018; 31: e00021-17.
11. Luo S, Zhang X, Xu H. Don’t overlook digestive symptoms in patients with 2019 novel coronavirus disease (COVID-19). Clin Gastroenterol Hepatol. 2020; 18: 1636-1637.
12. Davies KG, Longshaw CM, Davis GL, et al. Underdiagnosis of Clostridium difficile across Europe: the European, multicentre, prospective, bimannual, point-prevalence study of Clostridium difficile infection in hospitalized patients with diarrhea (EUCLID). Lancet Infect Dis. 2014; 14: 1208-1219.
13. Gu S, Chen Y, Wu Z, et al. Alterations of the gut microbiota in patients with COVID-19 or H1N1 Influenza. Clin Infect Dis. 2020; 4: ciaa709.
14. Blanco-Melo D, Nilsson-Payant BE, Liu WC, et al. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell. 2020; 181: 1036-1045.
15. Couturier J, Davies K, Gateau C, Barbut F. Ribotypes and new virulent strains across Europe. Adv Exp Med Biol. 2018; 1050: 45-58.