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Review Article

Clostridioides difficile infection (CDI) during the COVID-19 pandemic

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A B S T R A C T

The ongoing coronavirus disease (COVID-19) pandemic has dramatically tested healthcare systems around the world, with serious repercussions on the measures of prevention and control of hospital-acquired infections (HAIs). Among HAIs, *Clostridioides difficile* infection (CDI) represents one of the most important global public health threats. Although the full impact of the COVID-19 pandemic on CDI remains undetermined, depending on the development of the pandemic in the coming months, in this review literature studies of the last three years have been considered in order to depict the current situation, and make some considerations about possible future developments. If on the one hand, a general reduction in CDI incidence has been reported in several settings, mainly due to the extraordinary reinforcement of infection prevention measures, on the other hand, the critical circumstances experienced in many hospitals have limited the effectiveness of these measures, particularly in the intensive care units (ICUs), increasing the possibility of the occurrence of hospital-acquired CDI (HA-CDI). New concerns have arisen from the decrease in *C. difficile* testing and the increased use of broad-spectrum antibiotics reported during the pandemic. In particular, overuse of antibiotics and disinfectants may lead to a selection of resistant *C. difficile* strains not only in hospitals but also in the community. Furthermore, patients infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and patients that have survived COVID-19 may represent a new group of frail patients potentially at a higher risk of CDI, a group that could potentially increase in size due to SARS-CoV-2 evolution. In the dramatic COVID-19 era, the multifactorial nature of CDI has emerged more clearly than before, highlighting the necessity of a strong refocus on efforts to improve prevention strategies and to integrate CDI surveillance in a One Health prospective in order to curtail the public health threat posed by this infection in the next future.

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1. *Clostridioides difficile* infection (CDI) in the pre-COVID-19 pandemic period

In the last decades, *Clostridioides* (*Clostridium*) *difficile* has emerged as the main cause of healthcare-associated infective diarrhea, rapidly becoming an urgent global public health threat [1–3]. In the United States (US), *C. difficile* causes about half a million infections and 29,000 deaths in a year [4], while in Europe about 152,905 *C. difficile* infection (CDI) cases and 8382 CDI-associated deaths occur every year [5]. The target population for CDI is represented by the elderly, the immune-depressed, and hospitalized patients, or those under antimicrobial treatment, which is the main risk factor for this infection [6,7]. In this respect, *C. difficile* is a multidrug-resistant (MDR) pathogen that is ranked by the US Centers for Disease Control and Prevention (CDC) as an urgent antimicrobial resistance (AMR) threat [8]. CDI symptoms range from mild diarrhea and abdominal discomfort to the most severe colitis, toxic megacolon, and pseudomembranous colitis [9]. Recurrences after an initial episode of CDI are common, with a rate of around 15–35% of all CDI cases, [10].

The incidence of CDI, infection severity, recurrences, and mortality rates has increased in the last years. These epidemiological changes have largely been attributed to the emergence of new highly virulent *C. difficile* strains, in particular belonging to the PCR ribotype (RT) 027 [11,12], although other highly virulent epidemic types have recently emerged [13,14]. Among these types, RT 078 has increasingly been recognized as a cause of infection acquired in the community (CA-CDI) [15,16] and genomic analysis supports a possible zoonotic transfer of RT 078 strains between humans and pigs [17,18]. Notably, CA-CDI often lacks the traditional risk factors, such as previous hospitalization/contact with health-care settings and antibiotic treatment [19].

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The emergence of strains with characteristics of high virulence and the increasingly aging population in many high-income countries have led to a renewed attention to this important hospital-associated infection (HAI).

2. CDI and the COVID-19 pandemic

The novel coronavirus disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has emerged in Wuhan (China) in December 2019 [20] and it has rapidly spread worldwide causing a major pandemic that is still ongoing [21] and that has dramatically impacted healthcare systems around the world.

In the early stages of the COVID-19 pandemic, hundreds of millions of people were infected with an immediate and dramatic impact on hospitals, in particular acute-care hospitals, which faced a high number of hospitalizations [22]. COVID-19 can affect all age groups but frail individuals, in particular the elderly, with underlying diseases and chronic conditions, have been reported to be the most vulnerable to COVID-19 infection [23,24].

The burden of response to the COVID-19 pandemic have determined alterations in routine patient care practices, in compliance with antibiotic stewardship programs (ASPs) and in the use of personal protective equipment (PPE) [25,26] that have impacted on HAIs, including CDI. If on the one hand, redirection of the usual efforts to monitor and prevent HAIs to the COVID-19 response may have reduced the focus on routine HAIs prevention [27,28] (Table 1), on the other hand, enhanced infection prevention and control practices, emphasis on hand hygiene and the use of PPE have positively impacted the HAIs rates [29–31].

In general, data available from January 2019 to September 2021 indicate that hospital-acquired CDI (HA-CDI) incidence decreased during the COVID-19 pandemic [32–35] (Table 1). Barrier precautions, increased focus on hygiene, environmental cleaning, patient isolation and the increased use of PPE, have certainly played an important role in preventing *C. difficile* transmission, despite the increased/inappropriate use of broad-spectrum antibiotics, with about 70% of patients with COVID-19 subjected to antibiotic therapy mainly for the suspected acquisition of secondary bacterial infections [36,37]. However, it has to be considered that some antibiotics, such as azithromycin, are more extensively used compared with others for treatment of COVID-19 patients [38–40]. Although treatment with any antibiotic may precede the development of CDI, certain antibiotic classes have higher rates of association and, in addition, the associated CDI risk can be different within the same class [41]. Interestingly, azithromycin has been demonstrated to not have any effect on CDI development in patients with COVID-19 compared with other antibiotics, probably due to a lower risk of CDI associated with this antibiotic [41,42]. Although antibiotic treatment remains one of the main CDI risks also among COVID-19 patients [42–44] (Table 1), the contribution of the different antibiotic classes to the general increase in antibiotics consumption during the pandemic, as well as the length of treatment and the combination of drugs, may have a different impact on the occurrence of CDI in these patients.

In the evaluation of the general decrease of the CDI incidence rates recently observed, it is important to consider that the COVID-19 pandemic may complicate CDI diagnosis. In fact, SARS-CoV-2 frequently causes gastrointestinal symptoms including nausea, vomiting, and diarrhea [45], with a possible lack of clinical suspicion for CDI in patients with COVID-19 [46,47] (Table 1). In addition, stool tests may have been discouraged during the pandemic to limit nursing contact with feces during collection, due to concerns on the presence of SARS-CoV-2 [48], contributing to CDI underreporting. In this regard, delays in CDI diagnosis during the course of hospitalization of COVID-19 patients have been observed [49,50] (Table 1). A recent study conducted in nine hospitals in Massachusetts reports that about 40% of patients with COVID-19 have experienced diarrhea after admission and that two of these patients, critically ill, died prior to receiving a correct therapy for CDI [50] (Table 1). Some single-center studies have reported a trend toward decreased *C. difficile* testing and a stable or decreased CDI incidence [51,52] (Table 1). These results could be partially explained with a potential over- or inappropriate testing in the pre-COVID-19 period or more thoughtful testing during the current pandemic. Besides the problems related to CDI diagnosis, also the drastic reduction in outpatient hospital admissions, probably in response to the fear of contagion and in consequence of lockdown measures [53], may have contributed to the reduction in CDI incidence.

Despite improvement of prevention and control strategies, some single-center studies have observed an increase in HA-CDI cases during the COVID-19 pandemic [42,54,55] (Table 1). In the study of Sandhu et al., conducted in a hospital of Michigan, USA, the rate of CDI increased from 3.32/10,000 patient-days during January–February 2020 to 3.6/10,000 patient-days during March–April 2020. Lewandowski et al. have observed an increase in the CDI rates in a hospital of Warsaw from 2.6% in the pre-pandemic period to 10.9% during the COVID-19 pandemic, while Boccolini et al. have reported that CDI increased from 0.0% to 3.2%, between March–April 2019 and March–April 2020 in an intensive care unit (ICU) of an Italian hospital. Another study, including eight different Italian acute-care hospitals admitting COVID-19 patients, has reported differences in CDI incidence (from 0.7 to 12.3 per 10,000 patient days) among the participating hospitals, with the occurrence of *C. difficile* outbreaks in two of these settings associated with a higher CDI incidence [43]. These data highlight one more importance of local factors in HA-CDI occurrence. In fact, particularly during the first wave of the pandemic, many hospitals experienced extraordinary circumstances (increased patient caseload, staffing challenges, physical space limitations, constrained availability of personnel, shortages in personal protective equipment) that may have limited the effectiveness of standard infection prevention and control practices, particularly in the ICUs [56].

3. What about CDI in the next future?

Published data indicate that the pandemic may have important effects on CDI, suggesting some considerations for the next future. The first consideration is that the extraordinary reinforcement of infection prevention and control measures due to the COVID-19 pandemic has contributed to the reduction in HA-CDI incidence [32,33,47,50] (Table 1) and, therefore, it is necessary that the focus on a continuous improvement of these measures does not wane after the COVID-19 emergency. In particular, improvement of hand washing, donning and doffing protocols, environmental cleaning and the more stringent restrictions for visitors may have limited not only the circulation of *C. difficile* in the hospitals, but also the introduction of *C. difficile* from the community. In fact, carriers represent a potential vehicle of transmission considering that asymptomatic *C. difficile* colonization ranges between 4% and 15% among healthy individuals and between 3% and 21% among patients on admission [57]. Nevertheless, some factors may contribute to the exposure of COVID-19 patients to a higher risk of CDI, as highlighted in a recent study conducted in an Italian hospital, in which, although the total CDI incidence was not significantly changed compared with the pre-pandemic period, a higher CDI incidence was observed in COVID-19 wards compared with that observed in COVID-19 free wards [35]. In this regard, it is notable that COVID-19 seems to have adversely affected some HAIs and, in

Table 1
Relevant publications reported in this review.

CDI and Covid-19 patients	CDI and HAIs	CDI and diagnostic testing	CDI incidence reported as		
			Increased	Decreased	Stable
McMullen KM et al. Impact of SARS-CoV-2 on hospital acquired infection rates in the United States: Predictions and early results. Am J Infect Control. 2020 Nov; 48(11):1409–1411.	McMullen KM et al. Impact of SARS-CoV-2 on hospital acquired infection rates in the United States: Predictions and early results. Am J Infect Control. 2020 Nov; 48(11):1409–1411.	Luo Y et al. Hospital-onset *Clostridioides difficile* infections during the COVID-19 pandemic. Infect Control Hosp Epidemiol 2021; 42:1165–1166.	Lewandowski K et al. *Clostridioides difficile* infection in coronavirus disease 2019 (COVID-19): an underestimated problem? Pol Arch Intern Med 2021; 131:121–127.	McMullen KM et al. Impact of SARS-CoV-2 on hospital acquired infection rates in the United States: Predictions and early results. Am J Infect Control. 2020 Nov; 48(11):1409–1411.	Wee LEI et al. Unintended consequences of infection prevention and control measures during COVID-19 pandemic. Am J Infect Control 2021; 49:469–477.
Weiner-Lastinger LM et al. The impact of coronavirus disease 2019 (COVID-19) on healthcare-associated infections in 2020: A summary of data reported to the National Healthcare Safety Network. Infect Control Hosp Epidemiol. 2021 Sep 3:1–14.	Fakih MG, Bufalino A, Sturm L, Huang RH, Ottenbacher A, Saake K, Winegar A, Fogel R, Cacchione J. Coronavirus disease 2019 (COVID-19) pandemic, central-line-associated bloodstream infection (CLABSI), and catheter-associated urinary tract infection (CAUTI): The urgent need to refocus on hardwiring prevention efforts. Infect Control Hosp Epidemiol 2021; 19:1–6.	Laszkowska M et al. Prevalence of *Clostridioides difficile* and other gastrointestinal pathogens in patients with COVID-19. Dig Dis Sci 2021; 22:1–8.	Sandhu A et al. *Clostridioides difficile* in COVID-19 Patients, Detroit, Michigan, USA, March–April 2020.	Weiner-Lastinger LM et al. The impact of coronavirus disease 2019 (COVID-19) on healthcare-associated infections in 2020: A summary of data reported to the National Healthcare Safety Network. Infect Control Hosp Epidemiol. 2021 Sep 3:1–14.	Luo Y et al. Hospital-onset *Clostridioides difficile* infections during the COVID-19 pandemic. Infect Control Hosp Epidemiol 2021; 42:1165–1166.
Lewandowski K et al. *Clostridioides difficile* infection in coronavirus disease 2019 (COVID-19): an underestimated problem? Pol Arch Intern Med 2021; 131:121–127.	Wee LEI et al. Unintended consequences of infection prevention and control measures during COVID-19 pandemic. Am J Infect Control 2021; 49:469–477.	Allegretti JR et al. Prevalence and impact of *Clostridioides difficile* infection among hospitalized patients with coranavirus disease 2019. JGH Open 2021; 5:622–625.	Baccolini V et al. The impact of the COVID-19 pandemic on healthcare-associated infections in intensive care unit patients: a retrospective cohort study. Antimicrob Resist Infect Control 2021; 10:87.	Baker MA et al. The Impact of COVID-19 on Healthcare-Associated Infections. Clin Infect Dis 2021; 9:ciab688.	Hawes AM et al. Did *Clostridioides difficile* testing and infection rates change during the COVID-19 pandemic? Anaerobe 2021; 70:102384.
Granata G, Bartoloni A, Codeluppi M, Contadini I, Cristini F, Fantoni M, Ferraresi A, Fornabaio C, Grasselli S, Lagi F, Masucci L, Puoti M, Raimondi A, Taddei E, Trapani FF, Viale P, Johnson S, Petrosillo N, On Behalf Of The CloVid Study Group. The burden of Clostridioides difficile infection during the COVID-19 pandemic: a retrospective case-control study in Italian hospitals (CloVid). J Clin Med 2020; 9:3855.	Weiner-Lastinger LM et al. The impact of coronavirus disease 2019 (COVID-19) on healthcare-associated infections in 2020: A summary of data reported to the National Healthcare Safety Network. Infect Control Hosp Epidemiol. 2021 Sep 3:1–14.	Hawes AM et al. Did *Clostridioides difficile* testing and infection rates change during the COVID-19 pandemic? Anaerobe 2021; 70:102384.		Ochoa-Hein E et al. Substantial reduction of healthcare facility-onset *Clostridioides difficile* infection (HO-CDI) rates after conversion of a hospital for exclusive treatment of COVID-19 patients. Am J Infect Control 202; 49:966–968.	
Páramo-Zunzunegui J et al. Severe *Clostridium difficile* colitis as potential late complication associated with COVID-19. Ann R Coll Surg Engl 2020; 102:e176-e179.	Baker MA et al. The Impact of COVID-19 on Healthcare-Associated Infections. Clin Infect Dis 2021; 9:ciab688.	Ponce-Alonso M et al. J. Impact of the coronavirus disease 2019 (COVID-19) pandemic on nosocomial *Clostridioides difficile* infection. Infect Control Hosp Epidemiol 2021; 42:406–410.		Bentivegna E et al. Impact of COVID-19 prevention measures on risk of health care-associated *Clostridium difficile* infection. Am J Infect Control. 2021 May; 49(5):640–642.	
Tariq R et al. Prevalence and mortality of COVID-19 patients with gastrointestinal symptoms: a systematic review and meta-analysis. Mayo Clin Proc 2020; 95:1632–1648.	Baccolini V, Migliara G, Isonne C, Dorelli B, Barone LC, Giannini D, Marotta D, Marte M, Mazzalai E, Alessandri F, Pugliese F, Ceccarelli G, De Vito C, Marzuillo C, De Giusti M, Villari P. The impact of the COVID-19 pandemic on healthcare-associated infections in intensive care unit patients: a retrospective cohort study. Antimicrob Resist Infect Control 2021; 10:87.			Allegretti JR et al. Prevalence and impact of *Clostridioides difficile* infection among hospitalized patients with coranavirus disease 2019. JGH Open 2021; 5:622–625.	

(*continued on next page*)

Table 1 (*continued*)

CDI and Covid-19 patients	CDI and HAIs	CDI and diagnostic testing	CDI incidence reported as		
			Increased	Decreased	Stable
Khanna S, Kraft CS. The interplay of SARS-CoV-2 and *Clostridioides difficile* infection. Future Microbiol. 2021 Apr; 16:439–443.	Grasselli G, Scaravilli V, Mangioni D, Scudeller L, Alagna L, Bartoletti M, Bellani G, Biagioni E, Bonfanti P, Bottino N, Coloretti I, Cutuli SL, De Pascale G, Ferlicca D, Fior G, Forastieri A, Franzetti M, Greco M, Guzzardella A, Linguadoca S, Meschiari M, Messina A, Monti G, Morelli P, Muscatello A, Redaelli S, Stefanini F, Tonetti T, Antonelli M, Cecconi M, Foti G, Fumagalli R, Girardis M, Ranieri M, Viale P, Raviglione M, Pesenti A, Gori A, Bandera A. Hospital-Acquired Infections in Critically Ill Patients With COVID-19. Chest 2021; 160:454–465.			Ponce-Alonso M et al. J. Impact of the coronavirus disease 2019 (COVID-19) pandemic on nosocomial *Clostridioides difficile* infection. Infect Control Hosp Epidemiol 2021; 42:406–410.	
Laszkowska M et al. Prevalence of *Clostridioides difficile* and other gastrointestinal pathogens in patients with COVID-19. Dig Dis Sci 2021; 22:1–8.					

particular, increased incidence rates for device-related HAIs have been reported in COVID-19 patients [28,33,55,58,59] (Table 1). The growing burden of HAIs different from CDI, may indirectly favor CDI occurrence due to worsening of the patient's condition, prolongation of hospitalization and possible repeated antibiotics treatments. Furthermore, it is notable that COVID-19 itself may represent a risk for CDI. In fact, COVID-19 can be considered as an evolving systemic pathology, which may affect many organs and tissues other than the lungs. In particular, recent studies have reported an exacerbated systemic inflammatory response [60,61] and alterations in the gastrointestinal microflora similar to antibiotic exposure in patients infected by SARS-CoV-2 [62–65], conditions that could favor CDI occurrence in these patients. Furthermore, COVID-19 damages seem to seriously affect long-term health of the discharged patients [66]. Therefore, there is the possibility that the pandemic may result in a large number of survivors with residual post-COVID-19 damages, such as chronic lung disease or neurologic/cardiological/intestinal complaints, which might warrant frequent hospital admissions and/or antibiotics treatments, with a consequently higher risk of CDI. In addition, this cohort of frail patients may increase in the future due to the ongoing evolution of SARS-CoV-2. Several genetic variants of SARS-COV-2 have been identified and associated with higher transmissibility, higher risk of hospitalization/mortality and increased immune escape in comparison with the wild-type lineage. In fact, very recent studies have reported an increased risk of 28-day mortality and critical care unit admission for the recently emerged SARS-CoV-2 delta variant (B.1.617.2) [67–69]. More importantly, this variant seems to infect prevalently younger people, while older adults are more frequently infected by SARS-CoV-2 alpha (B.1.1.7) earlier in the pandemic [68,70].

In the COVID-19 era, a correct diagnosis of CDI has returned to the limelight as a cardinal point to avoid under-ascertainment of this infection. The underdiagnosis of CDI has already been recognized as an alarming issue in the pre-pandemic period, with about 40 000 inpatients with this infection potentially undiagnosed in European hospitals every year due to the absence of clinical suspicion and/or suboptimal diagnostic laboratories in the pre-pandemic period [71]. Recent studies have reported a trend toward decreased *C. difficile* testing in several hospitals [47,49,51,52] (Table 1), suggesting that the COVID-19 pandemic may lead to a further underreporting of CDI and highlighting the importance of a differential diagnosis of CDI in patients with COVID-19.

A final consideration is with regards to the heavy burden of the current pandemic on antimicrobial stewardship activities. The overused of antibiotics reported in the recent past [38,39,72] has raised several concerns about the consequent selection and increase in the AMR in pathogenic bacteria. In particular, *C. difficile*, as a possible component of the intestinal microflora of patients, may be subjected to "bystander selection", a selective pressure for resistance due to antibiotic exposure for a condition caused by other species [73], with a consequent selection of resistant *C. difficile* strains. Furthermore, the increased emission of antibiotics and disinfectants in the environments (including wastewater, surface waters, soils and sediment) during the current pandemic [37,74–77] could promote and accelerate bacterial evolution toward AMR outside the hospitals [78]. The ecology of *C. difficile* enhances its potential to acquire and develop AMR in the environment [79], favoring the selection of resistant *C. difficile* strains with a higher capability to diffuse and to cause infection in both animals and humans in the community. About 60% of the clinical *C. difficile* strains have been reported as MDR in European hospitals [80], but AMR strains have frequently been also detected outside the hospitals, in animals, food and the environment [81–85]. Animals represent an important reservoir of this pathogen, however, the frequent detection of epidemic *C. difficile* RTs in soil, water, sediment, vegetables, meat, etc, also suggests additional sources of human infection and the possibility of a more extensive transmission of this pathogen [86].

In conclusion, the COVID-19 pandemic has dramatically highlighted the complex interactions between bacterial and viral infections. Although the full impact of the COVID-19 pandemic on CDI remains to be determined, first data strongly suggest that a general reinforcement of prevention and control practices, a correct diagnosis, and a constant implementation of ASPs will be critical issues for the next future. In the challenging era of COVID-19, the multifactorial nature of CDI has become even more evident, urgently requiring the inclusion of CDI global and local surveillance programs in a One Health integrated approach, with a stronger interconnection among public health authorities, veterinary medicine, and agriculture in order to improve prevention strategies and curtail public health threat posed by this infection.

4. Search for relevant literature

Papers published between January 2019 and September 2021, reporting data on CDI and COVID-19, were searched using medical databases: PubMed, Medline, Scopus, Web of Science. Combinations of the following keywords were used: [(COVID-19) OR (SARS-CoV-2) OR (coronavirus)] AND [(Clostridioides difficile) OR (clostridium difficile) OR (CDI)]; [(COVID-19) OR (SARS-CoV-2) OR (coronavirus)] AND [(HAI) OR (hospital-acquired infections) OR (bacterial infections)]; [(COVID-19) OR (SARS-CoV-2) OR (coronavirus disease 2019)] AND [(antibiotics) OR (AMR) OR (antibiotic resistance)]. Publications written in languages other than English and studies published only in abstract form were not included.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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