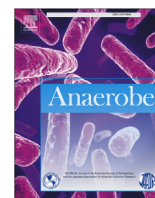




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*Clostridioides (Clostridium) difficile* (including epidemiology)

## COVID-19 and *Clostridioides difficile* infection (CDI): Possible implications for elderly patients

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### ABSTRACT

COVID-19 dramatically affects the elderly. Due to the large usage of antibiotics during the current pandemic and the gastrointestinal manifestations of COVID-19, the elderly population, hospitalized patients, residents in LTCFs and persons that survived the COVID-19 might be more prone to *Clostridioides difficile* infections (CDI). A renewed attention to CDI is necessary during the ongoing COVID-19 pandemic.

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The novel coronavirus disease (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), also known as the 2019 novel coronavirus (2019-nCoV), has emerged in Wuhan (China) in early December 2019 and it has rapidly spread worldwide causing a major pandemic [1].

Frail individuals with underlying diseases and chronic conditions are the most vulnerable to COVID-19 infections. In particular, the elderly are highly affected by COVID-19 compared to young and middle-aged people, both in terms of prevalence of the disease and mortality [2–4]. In China, where the elderly represent a small proportion of the total population, patients >60 years or older affected by COVID-19 were reported to be between 15% and 26%, with a mortality rate which was significantly higher compared to younger patients (5.3%, vs 1.4%) [5,6]. In Italy, one of the countries most severely affected by COVID-19, a mortality rate of 13.1% was reported, based on data up to April 23, 2020 [7]. Mortality increases with age, with a rate of 10.6% for 60–69 year-old patients, 25.7% for 70–79-year-old patients and 31.7% 80–89-year-old patients. Furthermore, 8.1% of cases were reported in older patients (>90 years) with a mortality rate of 28.5%. Mean age of Italian patients

died for SARS-CoV-2 infection was 79 years (median 81, range 0–100, IQR 73–87), 60.3% of them had three or more comorbidities and 12.6% experienced co-infections [8].

The impact of COVID-19 is particularly dramatic in LTCFs. In a recent report – including data from 19 countries worldwide – the rate of mortality associated with COVID-19 pandemic in these settings was reported ranging from 24% to 82% [9]. The European Centre for Disease Prevention and Control (ECDC) indicated that in Europe deaths occurred in LTCFs represent from 37% to 66% of all fatal cases linked to COVID-19 [10]. In the month of May, 49.5% (1061/2143) of the COVID-19 cases registered in Italy occurred in LTCFs [11]. The total rate of mortality in a survey on 3276 Italian LTCFs was reported of 8.2% (6773 deaths/80131 residents), with 40.2% (2724/6773) of deaths resulted positive to COVID-19 [12].

Although a low number of studies have been published so far, the rates of bacterial infection in COVID-19 patients are considerable and probably underestimated due to the complexity of bacterial infection diagnosis during the health emergency of the moment [13,14]. It has been estimated that about 72% of COVID-19 patients were treated with broad-spectrum antibiotics, mostly respiratory quinolones, to prevent bacterial co-infections and super-infections [15–19]. About 75% of LTCF residents receive at least one course of antibiotics during 6 or more months of

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permanence [20]. Due to the high prevalence of neurological conditions (dementia and neuropathic disorders), the elderly may have atypical COVID-19 clinical presentations [10] that can make it difficult to differentiate COVID-19 from bacterial infections, with potential further consumption of antibiotics in LTCFs.

The large use of broad-spectrum antibiotics during the actual COVID-19 pandemic raises serious concerns about a consequent possible increase of *Clostridioides difficile* infections (CDIs), particularly in the elderly population. *C. difficile* is a multi-resistant pathogen recognized as the leading cause of diarrhea in health-care settings and it is considered one of the most important public health threats, because it is associated with antibiotic treatments and high morbidity and mortality [21,22]. In the United States, *C. difficile* caused about half a million infections and 29,000 deaths [23], while in Europe it is estimated that about 152,905 CDI cases and 8382 CDI-associated deaths occurred every year [24]. Although CDI can affect individuals of all ages, the elderly are recognized at high-risk for this infection [25,26]. After the recent emergence of highly-virulent types, such as BI/NAP1/027, increased CDI incidence, severity of infection and associated mortality have been reported not only in hospitals but also in LTCFs, where residents are at high risk of CDI for advanced age, previous hospitalization and exposure to antibiotics [27–29]. A very recent retrospective study reported nine cases of co-infection with SARS-CoV-2 and *C. difficile* in elderly hospitalized patients, all which were treated with antibiotics [30]. Interestingly, Sandhu et al. also reported an increase of the rate of CDI from 3.32/10,000 patient-days to 3.60/10,000 patient-days during January–April 2020.

All these data indicate that antimicrobial stewardship programs for the appropriate and responsible use of antibiotics, in addition to local and national monitoring systems of CDI are crucial to prevent a possible increase of this infection in the frail elderly during the current COVID-19 pandemic. Now more than ever, some open questions concerning CDI need to be rapidly addressed. In fact, despite improvements in the epidemiological and microbiological aspects of CDI, some countries, as Italy, still lack an effective surveillance [31] and the real incidence of CDI is still unknown. CDI diagnosis and identification of highly-virulent/new types could be even more complicated during the current health emergency. CDI and COVID-19 may have similar manifestations, in fact about 19% of COVID-19 patients have diarrhea as the onset symptom because the angiotensin-converting enzyme 2 receptor (ACE2) and the cellular serine protease, transmembrane protease serine 2 (TMPRSS2), necessary for a successful entry of SARS-CoV-2 in human cells, are co-expressed not only in lung alveolar type 2 cells and esophageal upper epithelial but also in the ileum and colon [32–34]. Therefore, both COVID-19 and CDI should be considered in diarrheic patients.

The situation regarding LTCFs is extremely worrisome, as the burden of CDI is far from being determined in these settings, and data are still scarce in several countries. Transfer of elderly between hospitals and LTCFs increases during a pandemic, and it might facilitate acquisition and diffusion of CDI among this population. However, it is equally true that the increase of infection control measures due to COVID-19, such as contact precautions and strict isolation of patients affected by SARS-CoV-2, might help in reducing *C. difficile* transmission.

The role of *C. difficile* asymptomatic colonization in the progression to symptomatic CDI still remains a complex and challenging problem. This aspect could be extremely relevant for the high rates of *C. difficile* colonization reported among hospitalized patients and in LTCFs, where up to 51% of residents may be colonized [35]. Damage to the gut due to SARS-CoV-2 infection might facilitate occurrence of CDI, particularly in patients already colonized by *C. difficile*.

Finally, the long-term impact of COVID-19 on patients is still unknown. Although SARS-CoV-2 has high tropism for the upper

respiratory tissue, it can extensively attack all organs that express ACE2 and TMPRSS2 (gastro-intestinal tract, heart, kidney and vast distal vasculature) [36]. Therefore, it is possible that patients surviving a SARS-CoV-2 infection, particularly the elderly, might be more susceptible to diseases and new infections, with further risks to be exposed to antibiotics and to acquire CDI. In addition, several evidences supports that gut microbiota disequilibrium is necessary for *C. difficile* colonization [37,38]. Therefore, COVID-19 convalescents, particularly those that had gastrointestinal manifestations and had received antibiotic treatments, might have a microbiota with reduced colonization resistance against *C. difficile* and consequently they could be more prone to CDI. All these features highlight the importance of a renewed attention to CDI during the current pandemic, especially in the perspective of additional waves of COVID-19 that might have an even more devastating impact on elderly population, until a vaccine and/or a specific therapy for this infection will be developed.

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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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