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Clostridium difficile infection in the intensive care unit

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Abstract

Background: *Clostridium difficile* (CD) infection is widespread throughout the world, showing an increased incidence over the recent years and may cause severe forms of disease. This infection most commonly affects patients whom were administered antibiotics. An increased resistance to commonly used antibiotics is associated with *Clostridium difficile infection* (CDI). CD has a generally recognized infectious potential on a clinical ground. CDI is unpleasant and may sometimes cause serious bowel disorders that are usually treated with another course of antibiotics. The evolution of CD infection depends on the individual characteristics of the patient along with risk factors, associated diseases as well as the particularities of the recommended treatment. However, even under the conditions of a correct and complete treatment the risk of the disease relapse is estimated to occur depending on risk factors. Many clinical instruments that are designated for the purposes to treat non-infectious diseases can be useful in estimating the severity of an infection. This review is important for understanding the abusive and irrational prescription of various groups of antibiotics, often unjustified, including the ones used in the treatment of an infection with SARS-CoV-2.

Conclusions: These infections mostly occur in people aged 65 and older that receive medical care, including antibiotics administration, people with a long-term hospital stay, people with a weakened immune system or with a previous CD infection. The following measures, in order to reduce the risk of CDI in patients, should be considered: hand hygiene, avoidance of unnecessary administration of antibiotics – the antibiotic treatment is recommended only if it is prescribed by an experienced specialist, avoidance of unnecessary administration of drugs that reduce gastric acidity, because it favors the invasion of the gastrointestinal tract with CD.

Key words: *clostridium difficile*, risk factors, treatment options.

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Introduction

Clostridium difficile (CD) is a gram positive, anaerobic and spore-forming bacillus [1]. CD causes a toxin-mediated colitis by expressing the toxin A and toxin B [2, 3] that are encoded by the tcdA and tcdB genes. These toxins lead to intercellular gap cytoskeleton destruction that results in cell death via apoptosis and necrosis [3] and in turn to pseudomembranous colitis [4, 5]. Sometimes a binary *Clostridium difficile* toxin (CDT) is expressed in hypervirulent CD species [2, 5]. The A+B+CDT-genotype was identified in 87.13% of cases in a brief study made in Shanghai (China) [6]. This microorganism may be transmitted within a community, causing a community-acquired *Clostridium difficile* infection (CDI), or within the hospitals, leading to a healthcare-associated CDI [7-10]. A study conducted in Spain revealed that 16% of the CDI were acquired before Intensive Care Unit (ICU) admission or before hospital admission and are commonly more severe [11]. The incidence of CDI is decreasing over the last 10 years in Spain [11]. A study showed that less than 1% of patients developed healthcare-associated CDI, but a high risk of recurrence and complications was associated with a long ICU stay [12].

On the other hand, the incidence and severity of *Clostridium difficile*-associated diarrhea (CDAD) have increased in the United States of America (USA) [13]. Up to 50% of newborns have a CDI in the first 10 days of life, and up to 70% in the first 30 days of life [9]. Other sources inform that up to 35% of infants had CDI within the ICU [10]. It is reported that CD causes 12-12.1% [14, 15] or 21-22.4%, according to another source, [16] of all healthcare-associated infections. The incidence of CDAD in hospitalized patients ranges between 3-29% [17, 18]. The prevalence for CDI in India was 5.6-15.4% [19], in Kuwait – 6.42% [20].

There is a seasonal incidence for CDI, being higher in March-June then in October-December in the Northern Hemisphere and Asia [21]. Approximately 1/3 of the patients who develop antibiotic-associated diarrhea will become infected with CD [22]. Almost one-third of hospital-associated CD infections referred to asymptomatic adult

carriers [9] in which the mortality incidence ranges between 3.4-15.1% [23].

Bacterial antibiotic resistance is a growing global concern [24], this fact being also observed for the CD occurence [25]. ICU patients have a higher risk to develop CDI [26]. Antibiotic-associated diarrhea (AAD) is present in 25-30% of the patients who take antibiotics, which is defined as 3 or more loose stools over 24 h [27].

The purpose of this study is to identify the most important risk factors and treatment options that are currently available for a CDI. The PubMed database was used in order to identify the relevant scientific articles. The following keywords were used: "*Clostridium difficile* in the intensive care unit", March 7, 2020. The study was carried out by analyzing the 100 scientific articles that were identified using the PubMed search engine, after excluding the scientific articles that were published before 2015 and were irrelevant (42 articles), finally 58 scientific articles remained. 13 sources were identified in a non-systematic manner after using the keywords "*Clostridium difficile* diagnostic". The study was performed on the prevalence, incidence and regional specificity of CD management including the risk factors, treatment options and the prevention methods within the ICU.

Results and discussion

Risk factors

The present study identified the following risk factors that were mentioned in one or more sources that were associated with the ICU:

1. Proton pump inhibitors [1, 3, 27-33]. One of the literature sources proves it wrong [14].
2. The use of some antibiotics is proven to be the leading cause of CDI [1, 14, 33-37] as well as administration of antimicrobial drugs [38] or long-term and multiple use of antimicrobials [13, 39, 40]. Clindamycin, cephalosporins, penicillins and fluoroquinolones are the antibiotics that commonly increase the risk of a CDI [3].
3. Advanced age (>65 years) [1, 3, 27, 39] and a long hospital stay [1, 3, 27, 39, 41].
4. Healthy adults, peripartum women and young children that are admitted to hospitals are the most incident carriers of CD [42].
5. Chemotherapy [3, 27] and H_2 receptor blockers [3].
6. Several comorbidities or comorbidity-related conditions, such as an increased serum creatinine level (an indicator of renal dysfunction) at the time of ICU admission [13, 14], admission to a neurological ICU [14], immunocompromising conditions, inflammatory bowel disease (IBD) [13], diabetes mellitus [18, 27], malignant neoplasms [13, 38], cirrhosis, hypoalbuminemia [36], fever, metabolic disorders [40].
7. Surgical intervention is a known risk factor for CDI, at the same time a known treatment option for patients with severe CDI [44], preoperative acute renal failure and postoperative acute hyperglycemia are regarded as isolated risk factors [45].
8. Chronic obstructive pulmonary disease (COPD) was positively associated with CDI in trauma/surgery patients compared with medical patients [41].
9. Positive toxin test, because it may not always indicate a CDI [43].

In addition, were identified unexpected neutral factors:

1. Trauma doesn't increase the CDI incidence [46, 47].
2. Metronidazole was not associated with a high CDI risk [48].

Prevention, diagnosis and treatment methods

The prevention methods involve hand hygiene and reduction of enviormental contamination [33, 49, 50]. Most sources attest that Chlorhexidine has no effect on the incidence of CDI [51], [52], while another source states that it is unclear [39] and only one source has reported a decreasing incidence, with 7% [53]. The probiotics usage is not a widely used preventive measure [33].

The diagnostic methods include the cell cytotoxicity test (CCT), which is the measurement of toxins in the feces or the cytotoxigenic culture (CC) study [54]. RT-PCR is a useful method in order to identify the CD toxins in the stool, though a very expensive one compared to other methods [5]. Nucleic acid amplification test is used in order to identify the CD strains [33, 54] with Glutamate dehydrogenase tests [54].

A strategy for identifying patients with a high risk for CDI is proven to be efficient for reducing the mortality rate in the ICU [55]. Therefore, the physiologic scores used for the assessment of the patients in the ICU may be quite useful – Acute physiology and chronic health evaluation II (APACHE II) [56-60], APACHE III [61], APACHE IV [34], Zar's score [23, 62, 63] and Charlson comorbidity index (CCI) [38, 64-66].

The treatment methods include basic antimicrobial programs and antimicrobial management, the usage of antibiotics (e.g. vancomycin) [67]. The first-line treatment is represented by metronidazole administration, while the second-line treatment is represented by administration of vancomycin or fidaxomycin [3, 33]. Mild or moderate CDI should be treated with oral vancomycin [3] or metronidazole [3, 40, 48, 68], other studies reported no effectiveness for metronidazole [33]. Severe cases were treated with intravenous/ileostoma-administered vancomycin [68]. Vancomycin is administered in 48.3% of cases, whereas metronidazole is administered in 34.5% of cases according to one study [69]. Other sources report that vancomycin usage should be revised [67]. Recent new treatment options involve fecal microbiota transplant [3] which was reported as an effective treatment option [70, 71]. Bezlotoxumab – antibody specific for *Clostridium difficile* is proven to be effective in the treatment of this infection [33].

Conclusions

1. Clostridium difficile remains an actual controversial issue according to the articles reviewed within this study. The present study concluded that the most reported risk factors were the following:

- Antibiotic usage (12 sources);
- Proton pump inhibitors (9 sources);
- Long duration of hospitalization (5 sources);
- Advanced age (4 sources).

2. No adequate or sufficiently proven preventive measures were found, the only exception accounts for the reduction of in-hospital circulation of different doctors and visitors.
3. The following useful tools, for the diagnostic act, were identified – APACHE scales, CCI and the Zar's score. The most efficient, though the most expensive, clinical test is RT-PCR.
4. The most efficient and wide-spread treatment options were as follows:
   - Oral vancomycin and metronidazole given in mild cases, as well as administered through the intravenous/ileostoma route in severe cases;
   - Fecal microbiota transplant.

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GP conceptualized the project and designed the research; VV revised the manuscript and designed the research; VP revised the manuscript critically; LC interpreted the data; VC performed the laboratory work; LP drafted the manuscript; DC drafted the manuscript and designed the research. All the authors revised and approved the final version of the manuscript.

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Ethics approval and consent to participate
No approval was required for this study.

Conflict of Interests
No competing interests were disclosed.