

Clostridium difficile infection a public health problem

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Abstract

Clostridium difficile is a Gram-positive rod that produces spores that are commonly found in animals, humans and the environment. Asymptomatic carriage of Clostridium difficile occurs in 3-15% of healthy adult population and increases up to 20-30% in hospitalized patients [1,2]. The number of nosocomial and non-hospital infections caused by the Clostridium difficile is increasing. The number of relapses is also increasing. In older patients with multi-organism, the serious course of the disease is more and more often observed. Multi-organism and the associated necessity to apply therapeutic activities disturb the homeostasis of the intestinal microbiome. Important factors disturbing the balance, favoring the occurrence of diarrhea symptoms and Clostridium difficile infection are: pharmacotherapy (mainly antibiotics, steroids, proton pump inhibitors) and past inflammations and procedures of the gastrointestinal tract. Fast identification of a pathogen in a stool sample taken from a patient with diarrhea is of therapeutic and, above all, epidemiological significance. Awareness of the existing threat, the use of effective prevention and isolation of infected patients and effective decontamination of the hospital environment gives hope for reducing the incidence of CDI.

Streszczenie

Bakteria *Clostridium difficile* jest Gram-dodatnią laseczką wytwarzającą spory obecnie powszechnie w organizmach zwierząt, ludzi oraz w środowisku. Bezobjawowe nosicielstwo *Clostridium difficile* występuje u 3-15% populacji zdrowych dorosłych i wzrasta do 20-30% u pacjentów hospitalizowanych [1,2]. Wzrasta liczba zakażeń szpitalnych jak i pozaszpitalnych wywołanych przez laseczkę *Clostridium difficile*. Wzrasta też liczba nawrotów choroby. U pacjentów starszych z wielochorobowością coraz częściej obserwuje się ciężki przebieg choroby. Wielochorobowość i związana z nią konieczność stosowania działań leczniczych zaburza homeostazę mikrobiotu jelit. Istotne czynniki zaburzające równowagę, sprzyjające wystąpieniu objawów biegunki i zakażeniu *Clostridium difficile* to: farmakoterapia (głównie antybiotyki, sterydy, inhibitory pompy protonowej) oraz przebyte stany zapalne i procedury zabiegowe w obrębie przewodu pokarmowego.

Szybka identyfikacja patogenu w próbce stolca pobranej od pacjenta z biegunką ma znaczenie terapeutyczne i przede wszystkim epidemiologiczne. Świadomość istniejącego zagrożenia, zastosowanie skutecznej profilaktyki oraz izolowanie pacjentów zakażonych i skuteczna dekontaminacja środowiska szpitalnego daje nadzieję na zmniejszenie zapadalności na CDI.

Introduction

Clostridium difficile is a Gram-positive bacterium that produces spores that are commonly found in animals, humans and the environment. Asymptomatic carriage of *Clostridium difficile* occurs in 3-15% of healthy adult population and increases up to 20-30% in hospitalized patients [1, 2]. *Clostridium difficile* is responsible for 10-25% of the cases of antibiotic diarrhea, for 50-75% of antibiotic colic inflammation and for 90-100% of cases of antibiotic pseudomembranous colitis [3]. Bacteria are usually spread by fecal or oral route. Thanks to spores, it has a large infectious potential. Spores are resistant to high temperatures, acids and antibiotics. They survive in the acidic environment of the stomach, in the small intestine they transform into vegetative forms capable of producing toxins, the main factor of virulence [4]. Their pathogenic effect is mainly due to the production of protein toxins with cytotoxic and enteropathogenic effects [5,6]. The amount and type of toxins produced varies depending on the strain, which results in a different degree of severity of clinical symptoms. The incidence of post-antibiotic infections caused by *Clostridium difficile* (CDI - *Clostridium difficile* infection) The incidence of post-antibiotic infections caused by *Clostridium difficile* depends largely on: age and clinical status of the patient, the number and type of comorbidities and the level of virulence of the *Clostridium difficile* strain.

Epidemiology

For several years, there has been an increase in the occurrence of diarrhea associated with healthcare. In Canada, between 1991 and 2003, the incidence increased from 36 to 156/100,000 [7]. The incidence of HAI (Healthcare Associated Infection) increased by 11.7% over 7 years, mainly due to the increase in CDI-induced infection [8]. In the United States, the number of CDI infections in 2000 and 2006 doubled. Currently, about 500,000 cases are detected there every year, among them 15-20 thousand patients die [9]. CDI related to healthcare is 12% of all HAIs [10].

The incidence of CDI in European hospitals varies. Calculated on 10,000 man-days, it is from 0 in Luxembourg to 19.1 in Finland. Differentiation also applies to the 30-day mortality caused by CDI (from 2.8 to 29.8%). In a study conducted in 2008 involving 106 laboratories in 34 European countries, the weighted average was 4.1 per 10,000 patient-days PD [11]. In the Czech Republic, the average incidence of CDI was 5.2 per 10,000 PD in 27 hospitals in 2015 [12]. In pan-European studies in which three hospitals participated, the

incidence of CDI was significantly different (3.8-36.3 / 10000 man-days, average 12.5 / 10000 man-days) [10]. A multi-center PPS Point Study - EU HAI & AU (Point Prevalence Survey of Healthcare-Associated Infections and Antimicrobial Use in Acute Care Hospitals) for several years in European countries showed that gastrointestinal infections constitute 8.5% in the EU and 11.6% in Poland [13]. In the hospital in Tarnów, hospital infections of the gastrointestinal tract moved from the fifth to the first position for ten years and accounted for 26.2% of all infections. The predominant etiologic factor of these infections was *Clostridium difficile* [14]. This anaerobic bacterium is dangerous from an epidemic, therapeutic and economic point of view. CDI recurrences relate to 10.8% of those infected [12]. The morbidity caused by *Clostridium difficile* is on average 2-3 cases per 1,000 hospitalizations, and in the group of patients over 65 years of age it is twice as much as three times more often [15].

Risk factors

Human intestines are colonized by microorganisms referred to as intestinal microbiota. This biocenosis constantly strives to maintain homeostasis, showing a positive effect on the health of the host [16]. Intestinal microbiome is shaped during childbirth, it depends on the way of feeding a small child and diet in the subsequent years of life. Important factors disturbing the balance are: pharmacotherapy (mainly antibiotics, steroids, proton pump inhibitors) and previous inflammation and procedures of the gastrointestinal tract. These are situations favoring the occurrence of diarrhea symptoms and *Clostridium difficile* infection.

The most important risk factor for the development of the disease is ongoing or past treatment with antibiotics, which disturbs gastrointestinal microbiome and promotes the proliferation of *Clostridium difficile*. The occurrence of CDI associated with hospital care depends, inter alia, on the amount of antibiotics used in a given hospital and ranges from 1-10 per 1000 patients [4,17,18]. The probability of infection depends on the type of preparation. Treatment with second or third generation cephalosporins, fluoroquinolone, clindamycin, amoxicillin and clavulanic acid carries a high risk of CDI. Less frequently, this disease is caused by: ampicillin, amoxicillin, macrolides, cotrimoxazole, carbapenems. The lowest risk of antibiotic-associated diarrhea relates to drugs such as penicillin, first generation cephalosporins, tetracyclines, aminoglycosides, rifampicin, cloxacillin, vancomycin and metronidazole. In hospitals with a high endemic incidence on CDI even a single dose of antibiotic used as a result of perioperative prophylaxis may lead to the development of CDI [19,20,21].

The following types of drugs may also predispose to the occurrence of CDI: non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPI), H2 receptor antagonists, antacids and immunosuppressant drugs [22,23,24,25,26,27,28, 29]. All these drug groups have a greater or lesser impact on quantitative and qualitative changes in the intestinal microflora. Studies have shown that underweight (BMI <19) or morbid obesity (BMI > 40) was associated with an increased risk of in-hospital mortality in patients with CDI [30].

CDI recurrence is promoted by factors such as: reduced immunity, exposure to other antibiotics, renal failure, age over 65 years, severe underlying disease, long hospitalization, intensive care unit (ICU) stay and infection with hypervirulent *C. difficile* strain [31].

Identification of persons belonging to the high risk group of CDI development enables faster diagnosis and treatment.

Diagnostics, clinical picture and treatment

The diagnosis of CDI is necessary for proper management of patients and for correct infection control. In recent years, there has been a significant improvement in the access to *Clostridium difficile* microbiological diagnostics. The main task of the laboratory is to quickly

detect a pathogen in a stool sample taken from a patient with diarrhea. It is estimated that 2 out of 3 CDIs have not been identified or are poorly diagnosed due to the use of low sensitivity or no clinical suspicion [32]. Inadequate diagnostic methods mean that potentially 23% of those hospitalized with CDI are undiagnosed [33, 34].

CDI is an inflammation of the colon with varying degrees of severity: from mild to severe, with high mortality [35,36]. The most severe form of diarrhea associated with CDI is pseudomembranous colitis occurring more often in adults than in children [37]. The spectrum of clinical course of gastrointestinal infection includes cases of: asymptomatic carriers, mild spontaneous diarrhea, colitis, pseudomembranous colitis, as well as colitis fulminant. The most serious, life-threatening complications are: paralytic intestinal obstruction, toxic colon distension, sepsis and shock. A serious problem is relapses that occur in 20% of cases [38].

The basic drugs used to treat diarrhea of the aetiology of clostridium difficile are metronidazole and vancomycin [39]. The vast majority of clostridium difficile strains isolated in the world are sensitive to these antibiotics. The sensitivity to other drugs is varied. In Poland there are clostridium difficile strains with high resistance to drugs used in hospital treatment such as: clindamycin erythromycin and new fluoroquinolones [40]. A new drug recommended at every stage of CDI treatment is fidaxomicin. It has a special application in the case of recurrence of infection and in severe infections [41].

Prevention

In the prevention of infections, the rational use of antibiotics, as well as compliance with hygiene rules and isolation or cohortation of patients treated in a hospital setting are of utmost importance. Antibiotics should be used only in justified cases - in accordance with the applicable antimicrobial treatment standards and the characteristics of the given medicinal product. The selection of antibiotics should be preceded by microbiological diagnostics and the correct interpretation of the results obtained. An important role in the prevention of CDI infections is also played by the identification of Clostridium difficile reservoirs in the hospital environment. It is recommended to use the guidelines provided by the experts of SHEA / IDSA (Society for Healthcare Epidemiology of America / Diseases Society of America) and ESCMID (European Society of Clinical Microbiology and Infectious Diseases) [42, 43]. According to the guidelines provided by experts:

- use standard definitions of Clostridium difficile infection;
- constantly monitor the epidemiological situation;
- use personal protection equipment;
- take care of hand hygiene, using appropriate means (soap), excluding the use of an alcohol preparation in the first stage;
- isolate or cohort patients with CDI;
- regularly clean and disinfect hospital surfaces, using, if possible, processing agents (sodium hypochlorite, alkaline glutaraldehyde);
- avoid carrier testing, among other things, because eradication of C. difficile in carriers is ineffective.

Summary

With the increase in life expectancy, the average age of hospitalized patients increases. Old age is associated with the occurrence of multiple disorders, increased consumption of drugs, including antibiotics - the phenomenon of polypragmasy [44]. Clostridium difficile infection is associated with prolonged hospitalization and increased costs of treatment, which undoubtedly puts Clostridium difficile infection at the forefront of growing and very important public health problems. Introduction and adherence to rational antibiotic policy in hospitals and limiting the consumption of antibiotics in outpatient

clinics and adherence to the principles of isolation can effectively limit the increase in the number of symptomatic CDIs.

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