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CLOSTRIDIUM DIFFICILE: EPIDEMIOLOGY, DIAGNOSIS AND TREATMENT

SUMMARY

Clostridium difficile is a Gram-positive, spore-forming, anaerobic bacillus widely distributed in the environment. However, it is found as a part of the normal large intestine flora in approximately 2% of normal adults. C. difficile is now thought to be responsible for a wide range of diseases from asymptomatic colonization, to diarrhea of varying severity, life-threatening colitis, often as a consequence of antibiotic exposure. This spectrum has become known as "C. difficile associated disease (CDAD)". Effective control of CDAD in the hospital requires both antibiotic control and prevention of environmental seeding and bacterial spread. Epidemic C. difficile strains are widely distributed in the hospital environment, both as a cause and result of nosocomial diarrhea. Current treatment options are antibiotic-based, which is less than ideal. The use of various biotherapeutic preparations was not as efficient as we expected.

Key words: **Clostridium difficile, hospital infection, diarrhea**

INTRODUCTION

Clostridium difficile is a Gram-positive, spore-forming, anaerobic bacillus widely distributed in the environment. However, it is found as part of the normal large intestine flora in approximately 2% of normal adults. This percentage increases with age and the elderly have colonization rates of 10-20%, depending on recent antibiotic exposure and the time spent in an institution. It is still unknown whether the (asymptomatic) carriage rate of C. difficile, particularly in the elderly, is increasing. Vegetative forms of the bacterium die rapidly while being exposed to air, but spores are produced when it encounters unfavorable conditions. Clostridial spores can survive for many months and, possibly, years, and most probably are infective. The hospital environment is variably contaminated (20-70% of sampled sites) with C. difficile spores, depending on the level of hygiene and degree of fecal soiling. There is little information available on the distribution of C. difficile in the intensive care unit setting. C. difficile has also been isolated from farmyards and domestic animals such as horses, cows, pigs, dogs and cats. Interestingly, rates of colonization in neonates, who have a less complex gut flora, may be very high (up to 70% depending on the degree of spread of the bacterium within individual units), although babies are very seldom symptomatic. These rates fall to the normal level in children from 2 to 3 years of age (1). The organism is now thought to be responsible for a spectrum of largely but not exclusively hospital-acquired disease, ranging from asymptomatic colonization, diarrhea of varying severity, life-threatening colitis, often as a consequence of antibiotic exposure. This spectrum has become known as C. difficile associated disease (CDAD). Pseudomembranous colitis (PMC) was first reported in 1893, but came to prominence during the 1950 following the widespread introduction of antibiotics into clinical practice. It was not until 1970, however, that

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toxigenic C.difficile was identified as the cause of PMC in humans (2).

EPIDEMIOLOGY

During the first month of life up to two thirds of infants become colonized with C. difficile. As childhood progresses, carriage rates decline to adult levels, while both sporadic and outbreak CDAD begin to appear.

Presence of C. difficile in feces can be demonstrated in up to 2% of healthy adults. Rates of colonization and infection increase markedly beyond the age of 65. C. difficile is the predominant enteric pathogen among people in this age group. Asymptomatic presence has been reported in about 7% in residents of long-term care facilities, 14% of hospitalized elderly patients on acute medical wards, and 20% of elderly patients on chronic care wards, in whom it is between three and five times more common than symptomatic disease(3).

Apart from age, the main risk factors are antibiotic administration (particularly third generation of cephalosporins, clindamycin, trimethoprim / sulfamethoxazole, although virtually all antibiotics have been implicated including vancomycin and metronidazole. Risk factors include and underlying morbidity such as abdominal surgery, cancer, chronic renal disease and tube feeding. Significant risk factors for severe C. difficile diarrhea included functional disability, cognitive impairment and recent endoscopy (4).

The incidence of C. difficile diarrhea increased during the 1980s and 1990s. In one study in the USA, between 1989 and 2000, the incidence of CDAD increased from 0.68 to 1.2% of hospitalized patients, with a corresponding double increase (1.6-3.2%) in the subset who developed life-threatening symptoms. CDAD is underdiagnosed in the community setting, but data from Sweden indicate that 42% of cases of C. difficile infection present in the community, half of which do not have a history of hospitalization within the previous month. In Ireland, 11% of cases presenting with cytotoxin positive C. difficile diarrhea had no hospitalization within the previous 60 days. CDAD can impact markedly on hospital activity; for example, ward closures occurred in 5% of UK hospitals in 1993, increasing to 16% in 1996(5).

MECHANISMS OF TRANSMISSION

Contaminated environmental surfaces and healthcare personnel hands are the two major mechanisms of C. difficile transmission in hospitals. C. difficile spores are detected on l0-50% of environmental surfaces (e.g., bedding, buzzers, floors, toilets) in rooms of patients with C.difficile diarrhoea, and less often in rooms of patients who are asymptomatically colonized, suggesting that diarrhea increases shedding of the organism into the environment (6). C. difficile is rarely found on environmental surfaces in rooms of patients who do not have positive stool cultures. Thus, it is easier to demonstrate that patients contaminate the environment than to show that acquisition occurs as a result of environmental contact. Several studies have documented the presence of C. difficile spores on healthcare workers' hands, usually at a frequency less than environmental contamination (7). Hand carriage is transient, and, in general, healthcare workers are not at risk for C. difficile gastrointestinal carriage or diarrhea unless they receive antibiotics. Contamination of hands is strongly associated with contact in rooms-with heavy environmental contamination (6). Molecular typing studies have linked personnel hand carriage with C. difficille transmission. In an experimental model, washing with chlorhexidine and bland soap were equally effective in lowering counts of C. difficile on hands. Removal of C. difficile by hand washing presumably occurs as a result of mechanical action because antimicrobial soaps are generally not bactericidal against clostridial spores. Ingestion of contaminated food or water is not a known mechanism for C. difficile acquisition. Investigators have been unable to link C. difficile infection with exposure to pets or other animals. However, a recent extensive study of environmental sources of C. difficile by Al-Saifand Brazier found that C. difficile frequently contaminates lake waters, soil, and swimming pools. The large number of community environmental sources of C. difficile may help explain acquisition of the organism by individuals outside of the healthcare setting (7).

PATHOGENESIS

The accepted model of the pathogenesis of CDAD involves disruption to the host defenses mediated by the indigenous microflora of the bowel. Healthy adults carry at least 500 recognized bacterial species in the colon, over 90% of them anaerobes. Within an individual, this complex population remains stable over time, and has an inhibitory effect on incoming, non-indigenous species. This phenomenon has been called 'colonization resistance'. In vitro and animal models have demonstrated that vegetative C. difficile cells become nonviable when exposed to normal colonic populations (8).

Colonization resistance is so effective that exogenous pathogens such as *Salmonella* sp. or *Campylobacter* sp. require specialized mechanisms

to circumvent it. However, if the normal flora is disrupted, colonization resistance is lost and organisms such as C. difficile may seize their opportunity. The most frequent reason for this is exposure to antimicrobial agents, and it is noteworthy that in general, the antibiotics that carry the greatest risk are those which exert the greatest effect on colonic bacteria. Moreover, colonic populations of bifidobacteria, which are thought to be protective, are known to decline naturally with advancing age. There is also an increasing evidence that humoral immunity is important in defense against progression to disease, if not prior to colonization, and this observation is likely to have a profound influence on our understanding of the disease (7,8).

The existence of specific outbreak strains implies that bacterial as well as host factors are important. Proposed virulence factors include an antiphagocytic capsule, fimbriae, hydrolytic enzymes, adhesins, and flagella, but our understanding of the relationship between virulence factors and pathogenesis is rudimentary. Toxins A and B are the best studied C. difficile virulence determinants, causing cell death by disrupting the actin cytoskeleton, inducing the production of inflammatory mediators and disrupting epithelial cell tight-junction proteins. The genes encoding C. difficile toxins A and B, and minor toxins C, D and E, are sited in a chromosomal pathogenicity locus; it was found that this locus was highly stable in 50 toxigenic C. difficile strains, whereas non-toxigenic isolates lacked the unit. Also, isolates with a defective pathogenicity locus were still able to cause clinical disease (9).

C. difficile toxin is found in the stools of up to 95% of patients with PMC, 30% of patients with antibiotic-associated colitis, but usually less than 5% of patients who are receiving antibiotics in general. The corresponding figures for C. difficile culture-positive feces are 95, 60 and 2040%. Hence, C. difficile culture positivity is a less specific_finding than the presence of toxin, and it is likely that C. difficile is not the only pathogen in antibiotic-associated diarrhea (AAD). While C. difficile is the most commonly identified pathogen causing hospital-acquired infective AAD, the cause(s) of the majority of such cases is unclear. Evidence suggests that enterotoxigenic C. perfringens may be pathogenic in some cases of nosocomial, antibiotic-associated diarrhea. A recent study of patients have suspected of having antibiotic-associated diarrhea (AAD) found that 8% of specimens were positive for C. perfringens enterotoxin, 16% were positive for C. difficile cytotoxin, and 2% tested positive for both C. perfringens and C. difficile toxins. Culture and PCR results confirmed the majority of ELISA results, although notably not for two (12.5%) reactive specimens which were weakly positive (10).

DIAGNOSIS OF C. DIFFICILE ASSOCIATED DISEASE

Non-microbiological methods

Clinical assessment: Clinical manifestations of CDAD include abdominal pain, profuse, foul-smelling, soft stools and fever. Infections may be complicated by electrolyte disturbances, hypoalbuminaemia, and paralytic ileus. These features are not specific, and it seems unlikely that the clinical picture can contribute greatly to diagnosis. A history of antibiotic administration might be a useful pointer, but antibiotic-induced CDAD may occur at any time up to two months after exposure, so that the association may go unrecognized. In such cases, it is possible that antimicrobial substances in food could have altered the individual's resistance to colonization. The clinical picture is also complicated by the fact that diarrhea may be completely absent, a presentation associated with the serious complication of toxic megacolon. It has been suggested that leukocytosis is particularly prominent in CDAD, but again, this alone is inadequate for diagnosis. A recent study highlighted that patients with CDAD often have raised peripheral white blood cell (WBC) counts. Of 400 patients with WBC counts $\geq 15 \cdot 10^9$/l, infection was documented in 207 (53%), and the latter 16% had confirmed CDAD (11). Furthermore, excluding those with hematological malignancy, CDAD was present in a quarter of patients with WBC counts $\geq 30 \cdot 10^9$/l. The plain abdominal radiograph is usually normal even in PMC, while the main CT finding is a thickened bowel wall, which is both insensitive and nonspecific (12).

Endoscopy. Pseudomembranous colitis per se is a pathological diagnosis and may be confirmed by endoscopy. Pseudo membranes are raised, yellowish nodules, sometimes coalescing to form plaques, which overlie the inflamed mucosa, but are easily dislodged from it. The appearance may be enough for macroscopic diagnosis, but biopsy allows histological confirmation of the 'summit' or 'volcano lesions' typical of PMC. In a small series, it has been shown that flexible endoscopy is more sensitive than rigid endoscopy, and colonoscopy more sensitive than sigmoidoscopy (13).

Faecal leukocytes and lactoferrin: It has been suggested that detection of fecal leukocytes, traditionally by methylene blue staining may be helpful in distinction between inflammatory and non-inflammatory causes of diarrhea. Fecal

lactoferrin, which can be detected using a latex agglutination test, has been validated as a stable marker of fecal leukocytes, but although there is evidence that this can be useful in the investigation of diarrheal diseases. Its role in CDAD remains to be defined (14).

Detection of C. difficile products

Glutamate dehydrogenase: A commercial latex agglutination test, Culturette Brand (Marion) was initially claimed to detect toxin A and seemed to yield promising results. Its credibility was diminished when this claim was refuted, but later, it was shown to detect the enzyme glutamate dehydrogenase (GDH), which is a moderately specific marker for C. difficile. Reevaluation suggested that the test might have a role when combined with other techniques, but that it was not sufficiently accurate to replace the prevailing cell cytotoxicity assay (15).

Volatile fatty acids: In vitro, C. difficile exhibits a fairly characteristic pattern of volatile fatty acid production, particularly isocaproic acid, isovaleric acid and para-cresol. During the 1980s, attempts were made to correlate conventional testing methods with the results of gas liquid chromatography (GLC) performed directly on stool samples (16).

Toxins: C. difficile toxins may be detected either by virtue of their biological properties (the cell cytotoxicity assay) or by immunological methods (latex agglutination, counter-immunoelectrophoresis, or immunoassay).

Cell cytotoxicity assay: Recognition that the stools of patients with antibiotic-associated colitis were toxic to cultured cell lines predated the discovery of C. difficile as the causative agent of this disease, and the cell cytotoxicity assay remains the standard by which other tests are measured. The assay is performed by exposing cell monolayers to stool filtrates, and observing the cell for evidence of cytopathic effect (CPE) (17).

Latex agglutination for toxin A: Development of the first rapid agglutination test for C. difficile was reported in 1984, using latex particles coated with a commercial antitoxin that could be shown to react with toxin A as well as other antigens that remained undefined. In comparison with the cell cytotoxicity assay, the latex test had a good negative predictive value, but suffered from a high rate of false positive reactions (18).

Counter-immunoelectrophoresis (CIE): This technique, by which toxins in fecal specimens can be detected as toxin-antitoxin precipitation lines in agarose gel, was investigated in the early 1980. Although relatively easy to perform, the technique suffered from the lack of standardization, and poorly defined antitoxins meant that it was never clear whether the assay was detecting toxin A, toxin B, both, or something else (19).

Immunoassay: Two types of immunoassay have been developed, the traditional enzyme immunoassay-EIA (in various formats), and the single-use membrane immuno-chromatography type. The first EIA to detect C. difficile toxin was described in the 1980, since when a large number have been developed, some detecting toxin A, others detecting both toxin A and toxin B. Most are marketed as kits but the principle has been adapted for automated equipment such as the Vidas system (20).

Detection of C. difficile gene sequences

16s rRNA: Primers targeting the C. difficile 16s rRNA gene have been used to detect the organism in fecal samples (21).

Toxin genes: Use of PCR to amplify parts of the toxin A gene from stool was first reported in 1993, and yielded results that were in complete accord with the cell cytotoxicity assay. Stool toxin B PCR was first reported in the same year (22).

Isolation and typing of C. difficile

Culture methods: The first satisfactory medium for the culture of C. difficile was cefoxitin-cycloserine fructose agar (CCFA). This has been extensively used since, although there has been debate about the optimal concentration of cycloserine. A preinoculation process of heat or alcohol shock has been shown to enhance the isolation of C. difficile. It has also been suggested that the medium should be anaerobically reduced before specimen inoculation. Egg yolk agar has been employed in an attempt to distinguish C. difficile (which is lecithinase and lipase negative) from other common colonic clostridia, but there are concerns that it can hamper the detection of fluorescence and it is not universally used. Some authorities recommend a broth enrichment step, which gives enhanced isolation of C. difficile, but it is debatable whether this is of clinical relevance (23).

Identification and toxin testing: Based on the appearance of culture, C. difficile can be identified by its characteristic smell, yellowgreen fluorescence under long wave ultraviolet light, and/or by a latex slide agglutination test which reacts with cell wall antigens. Identification according to p-cresol production on CCFA, and biochemical profile have been described but have not become widely accepted. It is also possible to determine whether or not the isolate is a toxin producer. This process has been called 'toxigenic culture'. Toxin production can

be demonstrated by putting broth culture filtrates through the same EIAs used for fecal specimens, and also by the cell cytotoxicity assay. Alternative methods reported include reversed passive latex agglutination (applied to toxin A), colony blot probe-hybridisation (applied to toxin B), and PCR (toxins A and B). These so-called 'second-look' cytotoxicity assays can be shown to detect toxigenic C. difficile in diarrheal specimens negative in the stool cytotoxicity assay, but the clinical significance of this finding requires confirmation (23).

Typing: Strain typing is important for outbreak investigation and descriptive epidemiology. As with other organisms, typing of C. difficile can be conveniently divided into phenotypic methods and genotypic methods. It is accepted that molecular methods are superior to the phenotypic methods, but debate continues about which format is best.

Antibiotic sensitivity testing: Antibiotic sensitivity testing of anaerobes is a specialized task, currently carried out by the UK Anaerobe Reference Unit, Cardiff. It is of the utmost importance that surveillance of the antibiotic sensitivity of C.difficile is maintained, but for surveillance and reference purposes, this is best done by a single national center.

TREATMENT

Treatment of CDAD has evolved little in recent years and there remain few proven therapeutic choices. The high recurrence rate following metronidazole and vancomycin therapy has stimulated interest in exploring new treatment options. However, progress in defining new treatments has been slow because of the varied etiology of diarrhea, spontaneous but unpredictable symptomatic resolution in approximately a quarter of cases of C. difficile infection, and inconsistencies in diagnosis. First-line treatment should, where possible, involve discontinuation of the precipitating antibiotic(s). In the critically ill patient, this is rarely possible. Specific treatment is indicated when the patient has a systemic illness with evidence of colonic inflammation, pseudomembranous colitis or persistent symptoms despite stopping the precipitating antibiotic. In practice, most patients are commenced on either vancomycin or metronidazole when the infection is diagnosed and before precipitating antibiotic(s) are ceased; the latter can be substituted with lower-risk agents, although this approach is of unproven benefit. C. difficile infection is treated with either oral vancomycin (125 mg) or oral metronidazole (400 mg or 500 mg) for 710 days. The mean duration of symptoms is shorter (mean 1.6 days) following vancomycin compared with metronidazole administration (24). Either antibiotic can be administered via the nasogastric route if it cannot be tolerated orally. For intravenous treatment both antibiotics should be administered together because of the unpredictable colonic concentrations of each agent. In practice, the first recurrence is usually treated with oral metronidazole. Courses of 46 weeks with tapering and pulsed doses of vancomycin have been used in theory to first kill the vegetative bacteria, to allow spores to germinate and then be killed (25).

Biotherapy aims to restore the commensal gut flora; probiotics are live organisms which, on ingestion, can either prevent or treat specific host pathology. The yeast Saccharomyces boulardii, has in particular been extensively examined and is commercially available as a freeze dried preparation. S. boulardii was found to prevent binding of toxin A in a rat ileal model (26). An area of concern with biotherapy remains the risks associated with the administration of live microorganisms to patients, particularly the frail elderly with inflamed gut mucosa. Cases of fungaemia have been reported in immunocompromised patients following administration of S. boulardii, and indeed one such case has also been reported in an immunocompetent patient treated with a commercial preparation of S. boulardii, highlighting the potential virulence of this yeast in humans (26). Several small series of patients have been treated for, or received prophylaxis against, antibiotic-associated diarrhea with biotherapy, including Lactobacillus acidophilus, Lactobacillus GG, Enterococcus faecium SF 68. Based on the previous experiences, we recommend the application of rectal biotherapy and enema as a dominant form of therapy (27).

There is continued interest in the role of vaccines and immunotherapy against C. difficile. Vaccines preventing CDAD in the elderly could potentially revolutionalize current therapeutic options. A toxoid vaccine has been shown to be safe and immunogenic in healthy volunteers, producing increased serum IgG and faecal IgA levels (28). A high molecular-weight toxin-binding polymer (GT160-246) is undergoing investigation for treatment of C. difficile diarrhea. It has no direct antimicrobial activity, but it binds toxins A and B and has been shown to protect C. difficile-infected hamsters from mortality, although not from initial development of colitis. The treatment has been shown to be well-tolerated in phase 1 trials, and may offer a promising alternative to the current limited choice of proven therapies (29).

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CLOSTRIDIUM DIFFICILE: EPIDEMIOLOGIJA, DIJAGNOZA I TERAPIJA

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SAŽETAK

Clostridium difficile je Gram-pozitivan bacil koji stvara sporu, raste u anaerobnim uslovima i široko je rasprostranjen u čovekovoj okolini. Može se naći u 2% zdravih ljudi kao deo normalne flore debelog creva čoveka. Clostridium difficile se danas smatra odgovornim za nastanak velikog broja oboljenja, asimptomatske kolonizacije, dijareje različite težine kliničke slike i po život opasnih kolitisa koji mogu nastati nakon primene antibiotika. Ova oboljenja su nazvana jednim imenom „bolesti povezane sa prisustvom C. difficile (CDAD)„. Efikasna kontrola CDAD u bolničkim uslovima zahteva primenu antibiotika i prevenciju širenja bakterija i spora. Epidemijski sojevi C. difficile su rasprostranjeni u bolnicama, gde mogu prouzrokovati hospitalne dijareje. Današnji terapijski pristup zasniva se na primeni antibiotika, koji nije idealan. Primena mnogih bioterapeutskih preparata nije dala željene efekte.

Ključne reči: **Clostridium difficile, bolničke infekcije, dijarea**