ARTICULO DE REVISION

Basic and Clinical Aspects of Clostridium Difficile Colitis

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RESUMEN

El Clostridium difficille, un bacilo anaeróbico, descrito con ese calificativo "difícil" en 1935, por ser su aislamiento y cultivo complicado ha tomado una gran importancia en los últimos años, por ser un contaminante nosocomial común en pacientes o en guarderias. Se le ha identificado como habitante de la flora bacteriana normal en 1% de la población saludable y en 20% de las personas que viven en guarderias o casas de reposo.
Su patogenicidad esta relacionada a ciertos factores en el huésped.
La entidad clásica por la que el C. difficile ha sido mejor identificado es la colitis seudomembranosa; un proceso inflamatorio del colon en el que diarrea con moco e inclusive sangre aparece en pacientes que han estado consumiendo antibióticos de amplio espectro.
La patogenicidad del C. difficile esta relacionado a la producción de 2 tóxinas que destruyen el citoesqueleto de los enterocitos y balonan estas células. La toxina A, una enterotoxina, y la toxina B, una citotoxina 1,000 veces más potente que la tóxina A en cultivos celulares, pero que no es enterotóxica.
El tratamiento de pacientes con antibióticos de amplio espectro es el factor desencadenante de esta infección; sin embargo, ni el número de antibióticos utilizados, ni la duración de la terapia, fueron determinantes para el desarrollo de la infección. Se cree que componentes de la flora normal, como el Lactobacilli y los Bacteroides, suprimen el crecimiento o colonización del C. difficile; aspecto que suprimido por el uso de los antibióticos, predispone el desarrollo del cuadro clínico.
Las seudomembranas son prácticamente diagnósticas de la enfermedad, pero solo se ven en el 50% de los casos. El colon izquierdo es el más afectado, pero no hay que olvidar que el rectosigmoides puede estar respetado.
La sintomatología es muy variable, desde molestias leves hasta infecciones severas con diarreas acuosas profusas y sanguinolentas, retortijones, fiebre, deshidratación, leucocitosis e hipoalbuminemia.
El examen que sigue siendo el "estándar de oro", en el diagnóstico de la colitis por C. difficile es la determinación de citotóxina en heces; con una sensibilidad de 94%, y una especificidad de 99%. El cultivo de C. difficile en medio con cicloserina, cefoxitima y fructosa es sensible, pero poco específico, desde que hay cepas de C. difficile no toxigénicas.
La terapia de hidratación y suspender los antibióticos, mejora a 30% de los pacientes. En los más tóxicos o no respondedores el tratamiento con metronidazol o vancomicina solucionará el problema en 95% de los pacientes, luego de 10 días de tratamiento.
En el caso de la aparición de megacolon tóxico como complicación del C. difficile, la colectomia total puede ser salvadora.
La mortalidad actual por C. difficile alcanza el 3-4% de los casos.

PALABRAS CLAVE: Clostridium difficille, Colitis seudomembranosa

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SUMMARY

Clostridium difficile, a gram-positive anaerobic bacillus dubbed as the difficult clostridium because it resisted early attempts of isolation and cultura. After some decades in the dakness, it became famous, when in 1978, a cytotoxin of the C. difficile was found the responsable of the pseudomembranous colitis. We review in this paper aspects of the epidemiology of the C. difficile in health and disease. Also the importance of C. difficile as a cause of nosocomial infections. We review the caracheristics of the toxins A and B produced by the pathogenics strains of C. difficile. Finally, clinical aspects of infection with C. difficile in special in the pseudomembranosa colitis. The diagnosis, medical therapy, complications and surgical indications are briefly described.

KEY WORDS: Clostridium difficille, Pseudomembranosa colitis

INTRODUCTION

Clostridium difficile (C. difficile) infection has been identified as a common pathogen and has become a nosocomial threat in recent years[1]. This gram-positive anaerobic bacillus was dubbed «the difficult clostridium» in 1935, because it resisted early attempts at isolation and grew slowly in culture[2]. The bacteria were initially considered a harmless commensal, since infected infants showed no signs of illness. C. difficile subsequently passed into obscurity. In 1978, C. difficile reappeared as the source of the cytotoxin in the stools of patients with pseudomembranous colitis[3]. C. difficile forms spores that persist in the environment for months or years. Ingested orally, these spores survive the acid environment of the stomach and convert to vegetative form in the colon. Patients with mild diarrhea may require only discontinuation of antibiotic therapy[4]. This study was reviewed to access the incidence and implication of C. difficile colitis.

EPIDEMIOLOGY

C. difficile colitis has increased exponentially during the past 10 years[5]. The carriage rate of C. difficile was as high as 50%-70% in several longitudinal studies of healthy infants less than one year of age[6]. Newborns acquire C. difficile from the hospital environment. Many infants carrying C. difficile have high titers of toxin in the stools but are completely asymptomatic. This suggests that host factors required for pathogenesis is are lacking in the first year of life. Sites specific to C. difficile toxins are absent in the newborn rabbit intestine and are only expressed after weaning[7]. Thus one possible explanation is that the infant intestine lacks specific receptors for these toxins, which develop later in life. Because serum antibodies are found in 60% of children[8], it is also believed that infants are protected from the toxins by maternal antibodies.

C. difficile is an anaerobic bacillus that has been cultured as a component of the normal intestinal flora in 2%-3% of healthy adult subjects[9]. The prevalence of asymptomatic carriage varies widely depending on setting; rates of 1% in healthy subjects to over 20% in a long-term care facility have been documented[10]. Treatment of asymptomatic carriers with antibiotics is not recommended, since it does not permanently reduce the rate of carriage[11].

BACTERIOLOGY

Pathogenic strains of C. difficile produce two toxins: toxin A which is a 308 kDa enterotoxin, and toxin B, which is a 250-270 kDa cytotoxin[12]. Toxin A causes fluid secretion, mucosal damage, and intestinal inflammation when injected into the rodent intestine[13]. Toxin B is approximately 1000 times more potent than toxin A as a cytotoxin in tissue culture, but is not enterotoxic in animals; Both toxins (1) are lethal when injected parenterally in animals; (2) stimulate release of cytokines such as interleukin (IL) 1, IL-6 and tumor necrosis factor[14]; (3) act on mast cells to release histamine and may affect leucocyte endothelial cells and platelet interactions through upregulation of adhesion molecules[15]; and (4) act as enzymes to glucosylate a threonine residue on GTP-binding rho proteins[16].

Toxin A is a chemoattractant for neutrophils[17]. A specific glycoprotein receptor for toxin A have been identified on enterocyte membranes, and this toxin A receptor is linked to a guanine nucleotide regulatory protein in rabbits[18]. After binding to its receptor, toxin A induces the disaggregation of actin filaments, collapse of the cytoskeleton, and cell rounding [19]. Toxin B causes an identical rounding of cultured cells. C. difficile strains have been classified by their bacterial proteins, but these classifications have little clinical utility except to track hospital outbreaks[20].

PATHOGENESIS

Therapy with broad-spectrum antibiotics is the key precipitating factor for infection. C. difficile colitis has been shown to develop in patients taking antibiotics; however, neither the number of antibiotics nor the duration of therapy was a factor in predisposing patients to infection[21]. Infection occurs via the fecal-oral route. The spores resist stomach acid

and develop into a vegetative form in the colon. C. difficile toxins bind to specific receptors to stimulate fluid secretion and necrosis of the mucosa associated with an inflammatory infiltrate.

C. difficile forms heat-resistant spores that may persist in the environment for months or even years, and spores of the organism are resistant to all hospital disinfectants except alkaline glutaraldehyde. Spores have been isolated from furniture, sinks, toilets, floors, bedding, mops, bedpans and other surfaces, particularly, in hospitals and long-term care facilities[22,23].

C. difficile can colonize the bowel after a disturbance of the ecology of the intestinal flora[24]. The oral inoculation of hamsters with small doses of C. difficile is sufficient to cause colitis after treatment with antibiotics[25]. This fact suggests that certain organisms in the normal flora prevent colonization by C. difficile. Presumably, some components of the normal intestinal flora, such as lactobacilli and bacteroides, suppress the growth or prevent the colonization of C. difficile, and antibiotics confer a predisposition to disease by inhibiting these competing organisms.

Pseudomembranous colitis

Pseudomembranous colitis (PMC) was first recognized as a clinical entity in the 1950s. The advent of broad-spectrum antibiotics in the 1960s led to a marked rise in the numbers of PMC patients. It soon became clear that C. difficile could be isolated from the stools of PMC patients. PMC is the classical and dramatic manifestation of C. difficile infection. It is now accepted that C. difficile is responsible for virtually all antibiotic-associated colitis.

The histologic features of pseudomembranous colitis are divided into three types[26]. Type I, the earliest lesion, is characterized by patchy epithelial necrosis accompanied by an exudation of fibrin and neutrophils into the colonic lumen. The type II lesion has a more prominent exudate that erupts as a «volcano» or «summit» lesion from a focus of epithelial ulceration; the surrounding mucosa remains intact. The type III lesion is characterized by a pseudomembrane consisting of mucin, fibrin, leukocytes, and cellular debris.

The presence of pseudomembranes at endoscopy is diagnostic, but such presence can only be detected in about 50% of cases[27]. The left colon is most commonly affected, but the rectosigmoid is spared in 60% of cases and in 10% the disease is confined to the right colon. On sigmoidoscopic inspection, pseudomembranes appear as yellow or off-white raised plaques of 2-20 mm in diameter scattered over a hyperemic intervening mucosa. Exposure of the human colon to C. difficile toxins is followed by shedding of cells from the basement membrane into the lumen leaving a shallow ulcer. The serum protein, mucus and inflammatory cells flow outward from the ulcer, creating the typical colonic pseudomembrane. The spewing forth of the inflammatory exudate from the mucosal ulcerations produces the typical «volcano» or «summit» lesions of C. difficile colitis.

CLINICAL PRESENTATION

Manifestations of C. difficile colitis can vary from asymptomatic colonization to a life-threatening infection[1]. Profuse watery or bloody diarrhea, cramping abdominal pain, fever, leukocytosis, dehydration, and hypoalbuminemia are the hallmarks of C. difficile colitis[28]. In mild form, C. difficile produces abdominal discomfort and presents just as colitis without a pseudomembrane.

Patients with C. difficile occasionally present with an acute abdomen and fulminant colitis. Colonic muscular tone may be lost, resulting in toxic dilatation or megacolon. The development of a paralytic ileus and colonic dilatation can result in a paradoxical decrease in diarrhea. Such patients are acutely ill, with hypovolemic shock, toxic megacolon and perforation and the condition can be lethal despite aggressive medical or surgical treatment[29,30].

DIAGNOSIS

The gold standard for the laboratory diagnosis of C. difficile infection is the stool-cytotoxin test. This is a tissue culture assay based on the induction of cell rounding by C. difficile toxins in stool filtrate. A few picograms of toxin B is sufficient to induce the rounding of cultured cells, and the specificity of the assay is established by the addition of specific neutralizing antiserum[31]. This test is both extremely sensitive (94%) and specific (99%)[32]. In addition, enzyme immunoassays have recently been introduced and detect toxin with good sensitivity (85%-95%) and specificity (99%)[33,34]. Since they are quicker and simpler to perform, the enzyme immunoassays are a good alternative to the stool-cytotoxin test. C. difficile strains can be categorized as low, medium and high toxin producers, but disease severity does not appear to correlate with the concentration of toxin in the stools[35,36].

C. difficile is readily cultured on agar media containing cycloserine, cefoxitin, and fructose[37]. Colonies of C. difficile exhibit a characteristic yellow-green fluorescence under ultraviolet light. Cultures are the most sensitive method of detecting C. difficile, whereas cytotoxin assay is the most specific[38]. Stool culture for C. difficile is a less specific method for establishing a diagnosis, since some strains of C. difficile are non-toxigenic.

There is often substantial mucosal edema of the colon, which may leave thumbprint appearance on abdominal film[39]. Computed tomography may reveal «clover leaf» or «accordion» signs, the latter thought to be pathognomonic of PMC, in less than 20% of cases. Bowel wall thickening, pericolic streaking and ascites are noted in over half the patients[40]. These appearances cannot be distinguished from those of obstruction or ischemia.

The differential diagnosis should include Crohn's disease, ulcerative colitis and infections with intestinal pathogens such as Salmonella, Shigella, Entamoeba histolytica, Campylobacter, Yersinia, Strongyloides, and Staphylococcus. Cytomegalovirus (CMV) infection is also included in the differential diagnosis of PMC, especially in immunocompromised patients. Beaugerie

reported five cases of toxic megacolon in patients with human immunodeficiency virus infection; two cases were related to C. difficile infection and three to CMV[41]. The latter were macroscopically and histologically indistinguishable from the former.

TREATMENT

Initial Management

Initial treatment of C. difficile colitis includes discontinuation of the antibiotic therapy and the replacement of lost fluid. About 30% of patients improve within a few days after these measures[42,43]. Enteric isolation precautions should be taken. If the patients have not been, they should be treated with specific antimicrobial therapy.

Although therapy with antiperistaltic or antidiarrheal agents may appear to reduce diarrhea, such agents are generally contraindicated in C. difficile colitis, because they may lead to intestinal stasis, retention of toxins, and the development of complications[44].

Antibiotic Therapy

C. difficile rarely invades the colonic mucosa, and therapy exerts its beneficial effects within the lumen of the colon by stopping production of the toxins. Prompt therapy with metronidazole or vancomycin may control the colitis. Symptomatic improvement can be expected within 3-4 days, and colitis resolves completely in more than 95% of patients after 10 days of treatment. The diarrhea and fever, however, can take more than an additional week to resolve, probably because inflammation may persist after toxin production is stopped.

Metronidazole is less expensive than vancomycin, and is the drug of first choice. Vancomycin is reserved for patients with severe disease or for those who fail to respond to metronidazole. A randomized prospective trial comparing the two drugs showed them to be equally effective. Vancomycin had the same efficacy whether given at a high or low dose[45]. Oral vancomycin is ideal for the treatment of C. difficile colitis, since the drug is not appreciably absorbed or metabolized but is excreted unchanged in the stool[46]. However, vancomycin may accumulate in significant amounts in patients with renal impairment[47].

In terms of intravenous administration, only metronidazole appears to be effective, since it is excreted in the bile and exudes from the colon[48]. Patients who cannot tolerate oral medication, such as those with ileus, can be treated with intravenous metronidazole. Metronidazole sometimes causes nausea and a metallic taste, and in conjunction with alcohol it can cause a disulfiram-like effect. There have also been reports of diarrhea induced by metronidazole. And it is important to note that metronidazole-resistant strains of C. difficile have been isolated.

The absence of significant improvement after 48-72 hours of antibiotic therapy may indicate a more serious infection. It is important to realize that medical therapy is not always effective, and surgical intervention can be lifesaving in advanced or refractory cases[49].

Immunoglobulin

Rapid improvement has been reported following immunoglobulin administration for patients with C. difficile colitis[50]. Intravenous immunoglobulin treatment for unresponsive C. difficile colitis may be justified for patients with coexisting medical problems. Although surgery is lifesaving in severe circumstances, patients wondering surgery should be aware that surgical treatment still has a high mortality rate[30,51].

Secondary Infection

A substantial proportion (10%-20%) of patients have a relapse of diarrhea from C. difficile[52]. The relapse usually occurs within 1-3 weeks after the termination of initial therapy[53]. The diagnosis of recurrent diarrhea should be confirmed by a stool-toxin assay. It is not necessary, however, to test patients routinely for persistent C. difficile infection, since many of those who continue to have positive toxin test are asymptomatic. Symptomatic relapse should be treated in the same way as primary infection. Further antibiotic therapy is not required to precipitate a relapse, since these patients often resolve spontaneously. This conservative approach makes a subsequent relapse far less likely and the majority of patients may be expected to respond to a repeat course of vancomycin or metronidazole.

It has been assumed that relapse is due to reactivation of spores that have persisted in the colon, as many patients continue to excrete C. difficile long after the clinical illness has passed. Recently, by DNA typing of C. difficile from patients with recurrence of symptoms, Wilcox confirmed that 50% of the recurrences of symptoms were due to reinfection rather than relapse[54]. A significant proportion of relapses must be due to nosocomial infection with a second strain of C. difficile, which is a failure of infection control, not of treatment.

Outbreak management

Close monitoring of antibiotics is important so that patients are not needlessly exposed to a long drug course. Prophylactic treatment with oral metronidazole has not reduced the incidence of C. difficile colitis in patients undergoing bowel preparation[55].

C. difficile is associated with substantial morbidity and mortality and the financial burden to hospitals is large and increasing[55]. As many as 20% of hospital patients are colonized by C. difficile and up to 30% of these develop diarrhea[57]. C. difficile spores may become dormant and act as an infective source for months or years to come: this is the missing co-factor to prescription of antibiotics that allows hospital outbreaks[58].

Treatment should be based on positive toxin assays, though patients may be treated blindly for C. difficile infection while the results of the assay are awaited. However, the consequences of such blind treatment may have serious consequences in terms of morbidity due to drug side effects and the possibility of overlooking other causes of diarrhea. Such a policy creates hospital disruption. Finally, patients with diarrhea should be isolated until formed stools are obtained, whether or not they are positive for C. difficile toxins.

SURGERY

Surgical Patients

There has been a marked increase in the number of surgical patients developing C. difficile infection[59,60,61]. This is considered due to heightened awareness of the condition, better diagnostic methods, more widespread use of broad-spectrum antibiotics, and the increasing proportion of patients who are elderly and immunocompromised[28,55]. Most of C. difficile patients are over 65 years in age. Age is an independent risk factor, not simply a reflection of increase antibiotic usage, as natural immunity appears to wane. Rubin studied 710 patients over a 38-month period; factors that significantly predisposed to the development of C. difficile colitis included malignancy, chronic obstructive lung disease, laxatives, steroids, renal failure and administration of clindamycin[30].

Patients undergoing preoperative bowel preparation are at increased risk of C. difficile colitis, since alterations in the normal intestinal flora allow the overgrowth of nosocomial bacteria. C. difficile colitis is an important cause of morbidity and a significant contributor to death in patients undergoing major surgery, although C. difficile may be a trivial and self-limiting condition in healthy persons. In a recent series of surgical patients with C. difficile colitis[62], the only factor that discriminated those who died was length of time from symptoms to treatment, 6 days for survivors versus nearly 11 days for non-survivors. The mortality rate was 3%-4% of cases. Prompt diagnosis and treatment are crucial, if morbidity and mortality rates are to be minimized. Early treatment of diarrhea is recommended in surgical patients while awaiting the results of the stool toxin assay[63]. Prophylactic treatment of surgical patients undergoing bowel preparations should be considered.

Surgical Intervention

The first presentation of C. difficile infection may be as a surgical emergency associated with toxic megacolon and perforation[64]. Patients sometimes require extensive colectomy, i.e., a total abdominal colectomy, ileostomy, and mucous fistula[65,66]. Lipaett reported 13 adults who underwent operation for C. difficile colitis; the mortality rate was 38%[67]. All four patients undergoing left hemicolectomy died, compared with 14% of those patients who underwent total colectomy with ileostomy. The authors emphasized that the external appearance of the colon may be deceptively normal, and this should not tempt the surgeon to perform a limited resection and primary anastomosis, rather than total colectomy.

On the other hand, operative intervention may be inappropriate, because of the high mortality rate associated with surgery itself. In some patients, such as those without free perforation, diffuse peritonitis or toxic dilatation, there is no alternative to laparotomy. Once the organism is eradicated, the mucosal surface returns to normal even in severe C. difficile colitis.

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