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Clostridium Difficile Infection: An Overview of the Disease and Its Pathogenesis, Diagnosis, Treatment, Prevention And Management

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ABSTRACT

Clostridium difficile was thought to be nonpathogenic until 1978, when Bartlett et al. identified C. difficile as the source of cytotoxin in the stools of patients with pseudomembranous colitis, a disorder frequently associated with antimicrobial use C. difficile is responsible for both hospital-acquired and community-acquired diarrhea. Clostridium difficile is transmitted via the fecal–oral route, disruption of the gut flora, typically by antibiotics, allows C. difficile to proliferate, thus resulting in infection C. difficileexerts its pathogenic effect mainly through the production of two exotoxins, toxin A and B. Usually, exposure to both antimicrobials andtoxin-producing C. difficile strains is necessary for the development of CDI. Host factors may be as important. CDI has a wide range of manifestations, causing a self-limited mild diarrheal illness to a fulminant life-threatening colitis. The two main risk factors for CDI are antibioticexposure and age older than 65 but other factors shouldalso be considered like the use of laxatives, proton pump inhibitors or H2 histamine as gastric protection, chemotherapy, renal failure, gastrointestinal surgery, nasogastric tube, mechanical ventilation, prolonged hospital stay. The most widely used diagnostic test for the diagnosis of CDI is the enzyme immunoassay (EIA) for toxin A or toxins A and B. Other methods include:an antigen test that detects the mitochondrial enzyme glutamate dehydrogenase (GDH) within C. difficile, used for screening, stool culture, the cytotoxicity cell assay, another highly sensitive and specific method is polymerase chain reaction(PCR), sensitivity being higher than 90% and specificity of 100%. Colonoscopy and flexible sigmoidoscopyalso used in certain situations, abdominal X-ray is used in cases of ileus or toxic megacolon. For treatment different antibiotics are used: metronidazole, Vancomycin is recommended in severe cases, other treatment options include: fidaxomicin, Nitazoxanide, rifaximin, Teicoplanin, tigecycline, bacitracin,andfusidic acid. Probiotics are found in fermented milk, yogurt, powders and capsules as lactobacillus, bifidobacteria and Saccharomyces boulardii. They act by inhibiting bacterial adhesion to the intestinal mucosa.There are case reports according to which the use of intravenous unspecific immunoglobulin will benefit patients in recurrence, but there is little data in the literature. While the effectiveness of immunoglobulins remains controversial, monoclonal antibodies directedagainst toxins A and B have been shown to be protective against further relapses when compared to placebo, leaving the door open for future research. Fecal transplants or fecal bacteriotherapy is very promising, with success rates greater than 90% in patients with recurrent infections. In this approach, the stool may be introduced by esophagogastroduodenoscopy, colonoscopy or enema [89].In patients with fulminant infection, early surgery is important. Surgery showed a benefit compared to medical therapy, especially in patients with serum lactate ≥5 mmol/L and/or leukocytosis ≥50 x109/L. Cl.difficile can cause different rare cases including: inflammatory bowel disease (IBD), pseudomembranous colitis (PMC) that lead to death of a 22-year-old female university student following clindamycin treatment for coverage of a tooth extraction due to a dental abscess, the emergence of multidrug-resistant C. difficile PCR ribotype 046 may be detrimental to anti-tuberculosis chemotherapy, a case of C. difficile bacteremia in a patient who had underwent loop ileostomy is reported, mycoticaneurysm causedby C. difficile is also reported, the use of fecal transplantation as a safe and highly effective treatment for recurrent Clostridium difficile infection is repoterd, Clostridium difficile Infection in Infants and Children is reported also, Clostridium difficile is reported to be the first identified autotrophic bacterial pathogen[104], and Clostridium difficile enteritis is also reported.

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INTRODUCTION

Clostridium difficile, a spore-forming gram-positiveanaerobic bacillus, was initially detected in the fecalflora of healthy newborns in 1935 [1]. Clostridiumdifficile was thought to be nonpathogenic until 1978, when Bartlett et al [2] identified C. difficile asthe source of cytotoxin in the stools of patients with pseudomembranous colitis, a disorderfrequently associated with antimicrobial use [3].

C. difficile is responsible for both hospital-acquired and community-acquired diarrhoea,it is now recognized as the leading cause of infectious nosocomial diarrhoea among adults in industrialized countries [4], as well as being responsible for outbreaks of infectious diarrhoea in hospitals all over the world [5]. Colonization ofthe gastrointestinal tract occurs via the faecal oral route following environmental exposure to C. difficile spores or from contact with an infected person or healthcare worker, who acts as a vector.

Clostridium difficile is transmitted via the fecal–oral route, although evidence of airborne spread is emerging. [6]. Although C. difficile can be cultured from the stool of healthy adults, mostpeople remain asymptomatic. Disruption of thegut flora, typically by antibiotics, allows C. difficile to proliferate, thus resulting in infection.
The incidence of infection with C. difficile has fallen in recent years in several countries, including England [7], with a corresponding fall in mortality. However, infection with C. difficile remains a major problem for hospitals[6].

During the past decade, a great deal of knowledge about the disease is known and new methodsfor CDI diagnostic testing have emerged [8–10].

This article highlights the key strategies for the pathogenesis, diagnosis, treatment, prevention
and management of C. difficile.

PATHOGENESIS

CD transmission is fecal-oral, from person to person,from fomites, and from hospital furniture[11]. Spores remain in the environment for long periods and are resistant to the use of commercial disinfectants, favoring propagation at hospitals [12].

The spores resist the acidity of the stomach and germinateinto the vegetative form in the small intestine. Disruption of normal gut flora, typically by exposure to antimicrobials, allows C. difficile to proliferate, causing a broad spectrum of clinical manifestations that can range from asymptomatic carriage to diarrhea of varying severity to fulminant colitis and even death [13].

In addition to toxins A and B, some strains also produce a third toxin known as binary toxin. The role of binary toxin in the pathogenesisof C. difficile remains unclear; however, the presence of thistoxin among BI/NAP1/027 epidemic strains has raised concernsabout its synergism with toxins A and B in causingsevere colitis [12].

Asymptomatic patients

The only natural reservoir for CD is human beings[15]. However, C. difficile is reported to be ubiquitous in the environment. obtained from river (87.5%) and seawater (44%) samples, but it was also isolated from swimming pools (50%) and main tap water (5.5%). In private residences, the organism was present in 12 (2.2%) of 550 samples, whereas 2.4% of 300 raw-vegetable samples were positive. Therate of carriage of C. difficile in 524 fecal samples from assorted farm animals was 1%, while rates were 10% in dogs and 2% in cats. C. difficile has also been found in calves, ostriches, chickens, elephants, dogs, horses, and pigs, but its role in infection and its pathogenesis in animals are largely poorly understood and possibly underestimated [16].Many patients are colonized by CD and do not have symptoms[15]. Although colonization of healthy nonhospitalized adults is uncommon (ie, rate <5%), colonization among hospitalized patients and especially nursing home residents may range from 25% to 55% [17,18]. It has been shown that asymptomatic carriers of C. difficile have higher serum concentrations of antibodies against toxin A compared to symptomatic patients and that such carriers have a lower risk of developing clinically active disease [19-20]. Moreover, individuals with low levels of anti-toxin A IgG are at an increased risk of developing active infection with C. difficile and are also at increased risk of recurrent disease [21, 22]. The trigger for growth of CD is the release of toxins and the use of antibiotics[23]. There is no benefit in treating those people, since after a few weeks of treatment for CD, most patients will recolonize [24].

RISK FACTORS

The two main risk factors for CDI are antibiotic exposure and age older than 65 but other factors should also be considered.Use of laxatives, proton pump inhibitors orH2 histamine as gastric protection, chemotherapy, renal failure, gastrointestinal surgery, nasogastric tube, mechanical ventilation, prolonged hospital stay [25, 26].

The presence of spores of C. difficile in the hospital environment and long term care facilities is relatively high, this may explane why the rate of asymptomatic colonization is significantly higher in hospitalized patients when compared to the general population [27].

Usually, exposure to both antimicrobials and toxin-producing C. difficile strains is necessary for the development of CDI. However, host factors also appear to play an important role in CDI development because some patients with both exposures do not become symptomatic[24,28].

Whilst colonized individuals may have an important role in the spread of the microorganism and therefore in ongoing transmission events, they rarely develop clinically evident disease. This observation may be attributable to a greater antibody response induced by the chronic carrier state[20, 29].

CLINICAL MANIFESTATIONS

CDI has a wide range of manifestations, causing a self-limited mild diarrheal illness to a fulminant life-threatening colitis [30]. The onset of CDI symptoms may range from 1 day

to up to 10 weeks after antibiotics are administered; however most cases begin within 3 and 7 days of exposure [31-34]. Stools are usually watery and malodourous, but macroscopic bloody stools are rare [35]. The watery diarrhea of CDI is usually accompanied by low gradefever and cramping abdominal pain. Although standard definitions of disease severity are lacking, systemic symptoms generally increase with the degree of colitis. [31-34].

Notably, however, clinical disease can be present without a diarrhea illness and presence of constipation and abdominal pain as the main presenting features make the diagnosis more “difficile” [36].

This is due to atony and thinning of the intestinal mucosa, characterized by toxic megacolon that may progress to perforation [37].

Leukocytosis, increased creatinine, hypoalbuminemia, signs of a systemic inflammatory response, increased lactate and abdominal distension are associated with a more severe clinical picture [36].

DIAGNOSISSIS

The most widely used diagnostic test for the diagnosis of CDI is the enzyme immunoassay (EIA) for toxin A or toxins A and B. [38].The detection of toxin in stool culture is less sensitive than traditional stool culture and its sensitivity is 70%[39]. The test is rapid, with results in up to 2 hours and with high specificity but due to lack of sensitivity up to 40% of diagnoses can be missed [35, 40]. Recently, an antigen test that detects the mitochondrial enzyme glutamate dehydrogenase (GDH) within C. difficile has been used. This test has a good sensitivity (96-100%) but is not able to distinguish between toxigenic and non-toxigenic strains; therefore it is used predominantly as a screening test [41, 42].

The laboratory gold standard for detection of C. difficile toxins in the stool is the cytotoxicity cell assay. When filtered diarrheal stool that contains C. difficile toxins is added to cultured fibroblasts a characteristic cytopathic effect is seen. The cytotoxicity cell assay is largely considered too impractical for routine use due cost, time delays, and need for cell culture equipment, and has been replaced by enzyme linked immunosorbant assays (ELISAs) in most centers [43]. Characteristic cytopathic effect of C. difficile is seen after 24-48 hours. A specific antitoxin is used to identify the characteristic cytopathic effect of C. difficile[44].

Stool culture is the gold-standard for diagnosis, with sensitivity close to 100% but it is not used due to its cost, to being labor intensive, and to the fact that the results take long to be obtained (mean of 48 hours).False positive results occurs in 10% of cases, including asymptomatic carriers [39]. However, this is the only method that allows the isolation of the strain that can then be used for further studies within the scientific research community[38].

Another highly sensitive and specific method is polymerase chain reaction (PCR), sensitivity being higher than90% and specificity of 100%.[39].

Despite a high sensitivity, this method detects presence of the gene only and cannot confirm or refute whether the toxin is being expressed and hence causing disease.

Variations in the design of the PCR primers allows such methods to also identify with high specificity, the presence of specific strains of C. difficile e.g. certain PCR assays can identify the “hypervirulent” strain NAP1/027/BI by amplification of the deletion in the tcdC gene [46].

It must be stressed that abdominal imaging can be useful in defining clinical cases or characterizing subsequent complications but is not a tool of fundamental importance in the acute diagnostic setting[38]. In the uncommon event that the diagnosis of CDI cannot be established through stool testing or compatible clinical syndrome, endoscopy may be a useful adjunct if the diagnosis cannot be delayed. The goal of endoscopy is to visualize the nearly pathognomicpseudomembrane, however colonic edema, erythema, and mucosal ulcerations may also be consistent with thediagnosis [47,48].

Endoscopy is generally contraindicated in patients with confirmed disease or in patients with fulminant colitis, as there is a risk of perforation with the procedure. Endoscopic features include the presence of pseudomembranes, which are yellow-white raised plaques with localized edema and hyperemia, surrounded by intervening areas of normal mucosa. Pseudomembranes are seen in roughly 50% of patients, but because they may be right-sided, evaluation by flexible sigmoidoscopy might miss the diagnosis. It is important to note that C difficile can infect the small bowel as well, so the absence of a colon does not exclude the diagnosis[49].
Colonoscopy is the procedure of choice to detect pseudomembranous colitis, as up to one third of patients have only involvement of the proximal colon only, which would be missed by sigmoidoscopy[50, 51].

Rectal sparing occurs in up to 25% of patients, but most lesions will be visible within 60 cm from the anus so either flexible sigmoidoscopy or colonoscopy are acceptable methods [64]. Although intestinal perforation appears uncommon in patients with CDI that undergo flexible sigmoidoscopy, this remains an associated risk in severe disease so endoscopic confirmation of the diagnosis should be performed with caution [48].

Colonoscopic investigation very specific but with low sensitivity (51%). Furthermore, in cases of fulminant colitis, colonoscopy has a risk of bowel perforation.Diagnosis can also be made by flexible sigmoidoscopy. This may be indicated if there is a high degree of suspicion regarding a patient whose test results for C difficile toxin were negative or in patients requiring a rapid diagnosis that would preclude a delay in laboratory testing [52].

Computed tomography (CT) is rarely used in the diagnosis of CDI; however it may reveal patterns consistent with colitis and can also be used as supportive evidence for the diagnosis. Findings of colonic wall thickening > 4 mm, {the “sign of the accordion”, the “sign of the double halo” (alternatively known as the “target” sing)} wall nodularity, pericolonic stranding, and ascites, the latter being suggestive of hypoalbuminemia, are common in CDI [64,65]. In one study using CT scan, the sensitivity was 52% and specificity was 93% compared to stool toxin assays [52,53].
Computed tomography (CT) of the abdomen can be helpful in the diagnosis of pseudomembranous colitis or fulminant CDI [52].

Abdominal X-ray is unspecific and are usually normal in patients with CDI, but they can provideuseful information, for example, in cases of ileus or toxic megacolon [55].

TREATMENT OF CDI

Treatment of CDI should be based on the severity of the disease. Unfortunately, standardized definitions for disease severity are lacking and current divisions are somewhat subjective and artificial given the illness varies along a continuous spectrum of symptoms. In general, symptoms of CDI can be grouped into three categories: mild to moderate, severe, and severe disease with complications [56,57].

Mild to moderate CDI consists only of diarrhea and abdominal cramping unaccompanied by systemic symptoms. Patients with abundant diarrhea, abdominal pain, leukocytosis, and fever or other systemic symptoms should be considered to have severe CDI. Individuals suffering from severe disease with complications may have any degree of gastrointestinal symptoms that are also accompanied by paralytic ileus, toxic megacolon, or other life threatening conditions. The disease may become progressively more
serious even after treatment has been initiated so assessment of disease category must remaina dynamic process [58].

On suspicion of CDI, management should include the discontinuation of antibiotic therapy where possible or changing antibiotic therapy to a narrower spectrum agent.This approach aloneis clinically effective for a small percentage of patients, without the need for further interventions. In the majority of patients however, pharmacological treatment is needed and the recommended antibiotics for the initial episode are metronidazole and oral vancomycin [38].

Aditionaly, correct any fluid and electrolyte imbalances, avoid antiperistaltic agents, initiat contact precautions to limit spread, and treatment of patients with antibiotics if there is evidence of colitis (fever, elevated white blood cell (WBC) count [49].

The advantage of metronidazole is low cost, good availability, and few side effects. Nevertheless, failure with relapse occurs in 28% of all cases, specially due to the NAP1/ BI/027 strain. The main factors associated to relapse are patients with diabetes mellitus, sepsis, and previous surgery [59].

For all severities of CDI, cessation of the inciting antibiotic is the first step in treatment whenever possible. This should theoretically allow for recovery of the normal colonic flora to help combat the overgrowth of C. difficile. Prior to the NAP1 epidemic, stopping the administration of antibiotics resulted in the resolution of diarrhea in nearly one-quarter of patients with CDI [60,61].

Metronidazole is first line for mild to moderate CDI (first and/or second episode) and is used in mild to moderate disease in either oral or intravenous formulation at a dosage of 500 mg 3 times a day orally for 10-14 days [62]. In cases of severe CDI, the use of metronidazole is not recommended due to the high rate of treatment failures reported [63].

Vancomycin is no longer considered the treatment of choice for mild CD, since it has the same efficacy as metronidazole. There is the risk, during treatment,of having vancomycin-resistant Enterococcus spp. It is indicated in patients with severe infection or who relapse [67].

Vancomycin tablets are more expensive than metronidazole tablets: For inpatient hospital setting in the US, in 2010, a 500 mg metronidazole tablet costs 7 cents and a 250 mg tablet of vancomycin cost $29. However, C difficile has become more refractory to treatment with metronidazole, and there is a new, less-expensive liquid form of vancomycinavailable [49].

In patients with complicated CD, the cure rate with metronidazole was 76% and with vancomycin, 97%. Also the recurrence rate was higher in the patients who used metronidazole [63].

Vancomycin is recommended in severe disease. It is administered orally since it does not reach appropriate concentrations in the lumen of the colon when administered intravenously. As it is not absorbed though the intestinal lumen, oral vancomycin reaches faecal concentrations far above the MIC of C. difficile[68].Vancomycin is given orally at a dose of 125 mg 4 times per day for 10-14 days and is considered the drug of choice for an initial severe episode [62].

Metronidazole remains the treatment of choice for mild to moderate infection with C. difficile,[62].but oral or rectal vancomycin is more effective for severe cases (raised white blood cell count, acutely rising serum creatinine level, temperature > 38.5°C or severe colitis). [63].

OTHER TREATMENT OPTIONS

Fidaxomicin

Fidaxomicin (OPT-80) is an antibiotic more active invitro than vancomycin, even for treating NAP1/BI/027 strains. The recommended dose is of 200 mg/day every 12 hours, for 10 days. It has minimal intestinal absorption, high fecal concentration, and does not change intestinal microbiota. Response rate is similar to vancomycin with lower recurrence in strains other than NAP1/BI/027 (16.9 versus 29.2%)[66, 67].

Nitazoxanide (a drug often used for intestinal parasites) was reported to be at least as effective as oral vancomycin for the treatment of CDI, but the small size of sample patients enrolled in this study precludes definitive conclusions about its effectiveness [68].

Rifaximin

Derived from rifamycin, it is active against Gram negative, Gram-positive, and anaerobic agents. It is not absorbed by the intestine, has high colonic concentration, is highly active against CD, and has a lower relapse rate . The recommended dose is 400 mg, TID, for 10 days [64]. Fidaxomicin was associated with a significantly lower rate of recurring

infection. [69]. Teicoplanin, tigecycline, bacitracin, fusidic acid and rifampicin have all been used for infections caused by C. difficile both in vivo and in vitro but with discordant results [70-72].

Anti-peristaltic agents such as loperamide, is contraindicated in patients with CDI (especially in the elderly) as theyincrease the risk of toxic megacolon [65,73].

Probiotics

Probiotics are found in fermented milk, yogurt, powders and capsules as lactobacillus, bifidobacteria and Saccharomyces boulardii. They act inhibiting bacterial adhesion to the intestinal mucosa. The efficacy of this agent in prevention is controversial, since the studies are heterogeneous. It is still inconclusive whether they are effective in prevention or could be used as adjuvant treatment in primary infection or in relapse episodes. [23].Probioticsare not recommended by current guidelines since their effectiveness is yet to be proven [62].

Immunotherapy

There are case reports according to which the use of intravenous unspecific immunoglobulin will benefit patients in recurrence, but there is little data in the literature [12]. However, An injection of human monoclonal antibodies againstC. difficile toxins A and B has been shown to reduce recurrences.[75].

RECURRENCE

Reported recurrence rates vary from 5% to 50% and typically are around 20% [76]. Although it is suspected that noncompliance by patients and misdiagnosis contribute to recurrence, the true etiology of recurrence remains unknown.Once the diagnosis has been confirmed, the case is managed either by tapered (125 mg four times a day for one week, then twice a day for one week, once a day for one week, every other day for one week, and finally, every three days for one week), or pulse vancomycin regimen (given on alternate days initially, then every 3 days and so on) and should last several weeks on the basis of the concept that persistent spores convert to toxin producers and are killed when antibiotics are given repeatedly over time. [77,78].

Recurrence of disease may represent reinfectionor relapse. A meta-analysis of 12 studies involving 1382 patients with C. difficile infectionfound that continued use of the causative antibiotic agent(s) afterdiagnosis, the use of antacidmedication and older age were all significantlyassociated with increased risk of recurrence.[79].

Recurrence can arise either from a relapse of the original infection or following re-infection with a new strain of C. difficile from an exogenous source. Current treatment guidelines, including those from the ESCMID, argue that it is impossible in daily clinical practice to distinguish between relapse and re-infection, and ‘recurrence’ is therefore used as a generic term for both[63,62].

Recurrence occurs more often during the first or secondweek after the end of the treatment. Around 25%of patients may relapse, even after being treated withvancomycin. If the patient has more than two relapses,the risk for a new episode increases to 50 to 65%.[11].Recurrence occurs due to the spores that remainin the intestinal lumen and due to the inability of the immune system to eradicate the agent [11, 15].

Patients treated with metronidazole relapse more than those treated with vancomycin (21.2 versus 16.7%, respectively) [80, 15]. Therefore, in cases of the recurrence cases, the same treatment may be used or vancomycinbe preferred [15].

The main risk factors for relapse are advanced age, chronic kidney disease, previous episodes of CD,leukocytes (≥ 15 × 109/μL) and the use of systemic antibiotics concurrent to treatment for CD[15].

It remains unresolved if disease relapse is secondary to reactivation of latent C. difficlespores, reacquisition of the organism from the environment, or a combination of both scenarios [81].

Prolonged use of metronidazole is not recommended because of the potential side effects such as peripheral neuropathy. In patients with CDI refractory to standard doses of metronidazole and/or vancomycin, vancomycin can be given at higher doses (2 g per day) which has been effective in some cases [82,83].

It was reported that 79% of rifaximin treated patients had no relapse at follow-up and 64% was also reported in another study. These results need to be confirmed on large acales [84-86].

The same confirmation is needed for nitazoxanide that gave 54% initial cure rate in patients not responding to metronidazole [87]. While the effectiveness of immunoglobulins remains controversial, monoclonal antibodies directed againsttoxins A and B have been shown to be protective against further relapses when compared to placebo, leaving the door open for future research [88].

Fecal transplants or fecal bacteriotherapy is very promising, with success rates greater than 90% in patients with recurrent infections . In this approach,the stool may be introduced by esophagogastroduodenoscopy, colonoscopy or enema[89,90].

Surgery

The need for colectomy in patients with C difficile colitis has increased in parallel with the increasing incidence of fulminant colitis and toxic megacolon. Fulminant colitis typically manifests as severe lower quadrant pain or diffuse abdominal pain, diarrhea, abdominal distension, fever, hypovolemia, lactic acidosis, and marked leukocytosis (WBC count of ≥40,000/μL)[91, 92].

In patients with fulminant infection, early surgery is important. Surgery showed a benefit compared to medical therapy, especially in patients with serum lactate ≥5 mmol/L and/or leukocytosis ≥50 x 109/L [93].

The timing of an earlier surgical intervention must weigh the potential advantages of reduced surgical mortality against the possibility that surgery might not have been necessary. This decision requires careful judgment and experience and is made easier by vigilant monitoring of the patient's clinical course, by frequent serial examinations, and by a high level of suspicion, as the patient's condition may rapidly deteriorate [94].
The treatment of choice in patients with CDI requiring surgery is the subtotal colectomy with ileostomy formation [95].

Rare cases of Cl.difficile

The role of microbial dysbiosis in initiation of C. difficile infection and inflammatory bowel disease (IBD), and the role of specific pathogens, particularly C. difficile, as causative agents of IBD is reported in this review [96]. Orville reported a case of a 22-year-old female university student who was admitted to the University Hospital of the West Indies, Jamaica with a presumptive diagnosis of pseudomembranous colitis (PMC). She presented with a 5-day history of diarrhoea following clindamycin treatment for coverage of a tooth extraction due to a dental abscess. Her clinical condition deteriorated and progressed from diarrhoea to toxic megacolon, bowel perforation and Gram-negative sepsis. Clostridium difficile NAP12/ribotype 087 was isolated from her stool while blood cultures grew Klebsiellapneumoniae. Despite initial treatment intervention with empiric therapy of metronidazole and antibiotic clearance of Klebsiella pneumonia from the blood, the patient died within 10 days of hospital admission.[97].

P. Obuch-Woszczatyński& G. Dubiel& C. Harmanus suggested that: patients who are treated with anti-tuberculosis agents, especially rifampicin, who developed acute diarrhea during or after therapy should be evaluated for CDI, also, treatment with rifampicin can lead to high-level resistance to rifampicin in C. difficile strains, finally, the emergence of multidrug-resistant C. difficile PCR ribotype 046 may be detrimental to anti-tuberculosis chemotherapy. [98].

Jae-Lim Choi and his colleagues reported a case of C. difficile bacteremia in a patient who had underwent loop ileostomy because of rectal obstruction following metastatic colon cancer originated from prostate cancer. [99]. Two rare case of mycotic aneurysm caused by C. difficile were reported [100, 101].

Alexander Kleger reported that Fecal transplantation as a safe and highly effective treatment for recurrent Clostridium difficile infection. [102]. PEDIATRICS Volume 131, Number 1, January 2013 197 published an article about Clostridium difficile Infection in Infants and Children. [103]. Michael Ko¨ pke and his colleagues presented data showing C. difficile (both clinical and rumen isolates) able to grow on CO2+H2 as sole carbon and energy source, thus representing the first identified autotrophic bacterial pathogen.[104].
Sean P Dineen and his colleagues reported two cases Clostridium difficileenteritis [105].

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CONCLUSION

Despite our knowledge regarding diagnosis, treatment, risk factors and infection control, Cl.difficile infection weather nosocomial or community acquired remains a prevalent health concern. Optimal treatment strategies need further investigation. Vigilance of hospitalized patients to prevent and rapidly treat the disease is a priority. Prevention prevail over cure and prudent antibiotic prescribing , effective environment cleaning in hospitals and minimizing duration of hospital admission remain important in reducing morbidity and mortality caused by this disease.

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