INTRODUCTION

The spectrum of antibiotic associated diarrheal disorders ranges from antibiotic associated diarrhea (AAD), to the rare but dramatic presentation of hemorrhagic colitis and Clostridium difficile associated disease (CDAD). C. difficile is responsible for 10%–20% of cases of AAD, depending upon the type of antibiotic and individual susceptibility (1,2). In older adults CDAD has emerged as the most frequent nosocomial infection with substantial morbidity, mortality and economic burden to healthcare in the older adults since advanced age is a major risk factor for CDAD. Our review, an update and extension of many previous reviews on this topic, is aimed at discussing the epidemiology, risk factors, bacteriology, clinical manifestations, diagnostic modalities, prevention and treatment of CDAD especially in the older adults.

AAD is not synonymous with CDAD and is a frequent side effect of many antibiotics. AAD is usually self-limited or can be treated with empirical and supportive therapy, along with discontinuation of the offending antibiotic. Beta-lactum antibiotics and clindamycin are among the many antibiotics often noted to induce diarrhea in up to 25% of the patients (3,4). Most cases of AAD, not associated with any colonic mucosal lesions, are caused by alterations of gut micro flora resulting in mild diarrhea secondary to intestinal carbohydrate and / or bile acid metabolism (5). Antibiotic (ampicillin) associated hemorrhagic colitis has been recently recognized to be the result of Klebsiella oxytoca infection and will not be discussed in this review.

CDAD, the focus for discussion here, ranges from mild diarrhea to fulminant and fatal colitis, and is caused by toxins A and B, produced by a spore forming obligate anaerobic bacillus. It is part of the normal fecal flora in many infants, 5% of healthy adults, and 10% or more of hospitalized adults without diarrhea who have received antibiotics or chemotherapeutic agents (6). Since the understanding of C. difficile as the main etiologic factor for Pseudo membranous colitis (continued on page 11)
In a recent study from Israel, Moshkonitz et al found that the mortality among the elderly is high(35). The occurrence of CDAD in individuals without exposure to antibiotics is a puzzle in the new epidemic(16). There has been a notable rise in the number of community acquired cases in comparison to the nosocomial acquired infections in the past. CDAD results with a reduction in the natural gastrointestinal flora that allows for the toxin production and proliferation of C. difficile.

The epidemiological characteristics of CDAD vary markedly depending on the antibiotic prescribing patterns, endemic strains and criteria used to define CDAD (36). CDAD forms approximately 25% of the AAD and most cases of pseudo membranous colitis(37). The clinical index of suspicion associated with the frequency with which the presence of toxins A and B are assayed in stools of suspected patients influence the epidemiological studies (1,38–41,42).

RISK FACTORS FOR CDAD

See Table 1 for risk factors associated with CDAD.

Other than age, co-morbid conditions requiring treatment in the intensive care units, cancer, low albumin, COPD and chronic renal failure increase the risk for CDAD. Preadmission naso-gastric tube feeding, severe leukocytosis and hypoalbuminemia were associated with increased mortality whereas preadmission stay in nursing homes and acid reducing treatments were associated with increased risk of recurrence(35).

A few recent studies have looked at the role of prolonged proton pump inhibitor (PPI) therapy as an independent risk factor for CDAD (43–45). C. difficile diarrhea developed in 6.8% of the 1187 patients who received antibiotics while in the hospital; there was a significant association with the use of PPI (adjusted odd’s ratio [OR] 2.1, 95% CI 1.2–3.5), multiple (3 or 4) antibiotic use [OR 2.1, 95% CI 1.3–3.4] and admission to a medical ward [OR 4.1, 95% CI 2.3–7.3] (44,46–50).

Owens et al has recently reviewed the antimicrobial associated risk factors for CDAD(51). In earlier studies, CDAD was noted to be frequent with the use of ampicillin and other penicillin derivatives, cephalosporin and clindamycin. Less frequently impli-
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Table 1
Risk factors for C. difficile associated disease (2,16,35,43,45,51,112,113)

1. Advanced age

2. Co-morbid conditions and associated factors
   - Stay in the intensive care unit
   - Pre-admission Nursing Home stay
   - Pre-admission NG tube/enteral feeding (particularly post-pyloric)
     - Handling of tube feed by health care workers
     - Contamination of tube feeding formulas
     - Low fiber content of formulas
   - Enemas and stool softeners
   - COPD
   - Immunosuppressive states
   - Chronic renal failure
   - Cancer and anti-neoplastic drugs, particularly
     Doxorubicin, Cisplatin, Cyclophosphamide, 5-flourouracil, Chlorambucil, and Methotrexate
   - GI surgery
   - NSAID use

3. Reduced gastric acidity
   - Prolonged use of H2 receptor antagonists or PPIs

4. Anti-microbial agents
   - Frequently associated
     - Ampicillin
     - Amoxicillin
     - Cephalosporin
     - Clindamycin
     - Quinolones
   - Occasionally associated
     - Penicillins other than ampicillin
     - Sulfonamides
     - Erythromycin
   - Rarely or never associated
     - Parenteral aminoglycosides Tetracycline
     - Chloramphenicol
     - Metronidazole
     - Vancomycin

5. Failure to follow institution specific Infection Control Policies

6. Exposure to infected room-mate

C. difficile produces two cytopathic and enteropathic virulent factors, Toxin A (or Tcd A) and Toxin B (or Tcd B). Toxin A is an inflammatory enterotoxin that induces fluid secretion, increases mucosal permeability and causes enteritis and colitis. Toxin B is an extremely potent toxin. Toxins A and B are structurally similar and most pathogenic strains produce both toxins (59,60). These toxins are encoded by two genes, Tcd A and Tcd B that map to a 19.6 kb pathogenicity locus (Pa loc) consisting additional regulatory genes(61). Further, clinically relevant toxin A negative, toxin B positive (A–, B+) strains of C. difficile that cause diarrhea and colitis in humans have been isolated (62–65). A third toxin—a binary toxin designated CDT (Actin specific ADP-ribosyl transferase) is found in 1-16% of patients with CDAD, but its role in the pathogenesis of CDAD is not clear (66,67). Outbreaks demonstrating a toxic strain of C. difficile have been reported(7,68–71), influenced by antimicrobial use patterns, increased virulence or resistance among strains and failure in infection control measures.

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CDAD encompasses a wide spectrum of clinical manifestations ranging from symptomatic carriers to mild brief self limited diarrhea, severe diarrhea, diarrhea occurring as a complication of underlying inflammatory bowel disease (IBD), septic shock, toxic mega
colon and a need for total colectomy, to fatal CDAD. The onset of symptoms is usually within 48 hours of infection. Although hospitalized patients generally get infected within 3 weeks of hospitalization (38), delayed onset of symptoms up to 2–3 weeks after infection has also been reported (20,38,49). Toxic mega colon is to be suspected when the transverse colonic diameter is greater than 6 cm associated with systemic toxicity; here mortality can be as high as 64%. Severe CDAD mimics ischemic colitis, IBD, intra-abdominal sepsis and diverticulitis.

The pathogenesis of CDAD involves multiple steps. Initially there is disruption of the normal colonic bacterial flora by antibiotic use or antineoplastic agents, followed by colonization with toxigenic C difficile that elaborates the toxins A and B, which cause mucosal injury. In a study on the predictors of severity in patients with CDAD presenting to the emergency department, Andrews et al noted that the patients in the severe category were over 70 years old, with more co-morbid disease, and recurrent CDAD (72).

DIAGNOSIS

A. Demonstration of C. difficile Toxins

Diagnostic studies looking at toxins A and/or B include enzyme immunoassay (EIA) and cell culture toxicity assay performed on stool samples. EIA or tissue culture cytotoxicity assay has been considered the gold standard for diagnosis. EIA methods, although are less than optimal, have a low turn around time compared to cell culture cytotoxicity. The sensitivity of these tests ranges from 63% to 94% and specificity ranges from 75% to 100%. Both toxins A and B are to be tested and found in CDAD. Testing for CDAD may have to be repeated if clinical suspicion is strong. Atypical strains produce one of the two toxins. The absence of toxin in the stool in the initial assay does not rule out CDAD. Stool assays for C. difficile toxin have significant false negative rates. Detection of toxigenic C. difficile in stool samples by real time polymerase chain reaction (PCR) for the diagnosis of CDAD has turn around time of less than 4 hours and is more sensitive than EIA (73), however, the test is not available for routine use.

B. Sigmoidoscopy/Colonoscopy

Endoscopic examination is not mandatory in the diagnosis of CDAD. Sigmoidoscopy may be normal in mild cases or the characteristic pseudo membrane may be seen as yellow or white plaques 2–4 mm in diameter. Since pseudo membranes may be very proximal and beyond the reach of the sigmoidoscope, colonoscopy may be needed to detect proximal pathology (74,75). The histology in severe cases shows focal ulceration of the colonic mucosa associated with eruption of purulent material containing inflammatory cells and necrotic debris that covers the area of ulceration called “summit” or “volcano” lesions. Endoscopic pseudo membranes and the above histological abnormalities are not pre-requisites to diagnose CDAD.

According to the ACG guidelines (11), endoscopy is recommended in the following situations:
- When a rapid diagnosis is needed and test results are delayed or insensitive tests are used
- When the patient has an ileus and stool is not available
- When other colonic diseases that can be diagnosed with endoscopy are being considered

C. C. difficile Culture

Although in general, culture is not required to diagnose CDAD and is not specific for toxin producing strains (2), in special cases culture permits strain typing. The Society for Healthcare Epidemiology Association (SHEA) recommended continuing tissue culture cytotoxin typing with stool culture for optimal diagnostic sensitivity (culture) and specificity (Cytotoxin assays).

TREATMENT OF CDAD

Gerding et al have recently reviewed the topic on treatment of CDAD (76). This topic can be discussed under:
- a. Preventive measures
- b. Treatment of initial mild disease
- c. Treatment of recurrences
- d. Treatment of complications and Surgery in CDAD.

A. Preventive Measures

i. Institutional steps: Attempts to control CDAD require the prudent use of antimicrobials, preventive measures for nosocomial infection and ongoing sur-
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veillance. A step demonstrated to show considerable benefit in reducing the incidence of CDAD in health care facilities is the enforcement and practice of meticulous hand washing with soap and water by all health care providers and the practice of contact precautions using sterile gown and gloves during patient care (38,77,78). It needs to be emphasized that since CDAD is a disease spread by spores, alcohol-based hand sanitizers are not sufficient (79).

A well established hospital wide infection control program, phenolic disinfection for environmental cleaning, disinfection of rooms with a spore killing bleach, disposable medical equipments and periodic education programs are all mandatory steps for the control of CDAD (80). The incidence of CDAD can be substantially decreased as shown in the Quebec study. The decrease in the study was not as a result of changing pattern of specific anti-microbial use, rather the change followed specific modifications of infection control and cleaning procedures by governmental incentives. Extreme measures such as closure of medical units to control spread of infection may be at times necessary (32).

ii. Physician education: Education of physicians with regard to many issues discussed above and in particular with regard to a rational use of antibiotics is important. Clindamycin, cephalosporin and fluoroquinolones are the antibiotics determined to be associated with the highest risk for CDAD. Metronidazole, vancomycin and aminoglycosides have a lower risk (12,31,81). Restrictive antibiotic policies through antibiotic stewardship are a needed step (82,83). In a retrospective analysis, O'Connor et al studied a group of patients who were subjected to a new antibiotic policy from the period following July 2000 and compared them to patients hospitalized prior to July 2000 and not subjected to the new policy. Infections, antibiotic prescriptions and mortality rates were determined from case notes and C. difficile diarrhea rates from microbiological data. As a result of the new antibiotic use policy, IV cephalosporin use fell from 210 to 28 defined daily doses with a corresponding increase in piperacillin-tazobactum and moxifloxacin use. The new policy led to a significant reduction in C. difficile diarrhea cases in the elderly care service (84).

B. Treatment of Initial Disease

Treatment of CDAD is tailored to the severity of the disease; those with mild disease characterized by minimal diarrhea do not need any treatment, except discontinuation of the antibiotic, which may not always be possible. Those with more severe diarrhea may require oral metronidazole or vancomycin therapy with supportive measures. While oral vancomycin is the only FDA approved treatment for CDAD, metronidazole is the drug of choice because of its low cost and acceptable efficacy in most cases. Certainly, it is the recommended drug for mild to moderate cases. Metronidazole provides effective therapy with a reported response rate of 95–100%. The adult dose is 500mg oral three times a day or 250 mg oral four times a day for 10–14 days or 500 mg IV four times a day for 10–14 days. Documented hypersensitivity is a contraindication for metronidazole therapy. Metronidazole may increase adverse drug effects from interactions with anti-coagulants, lithium and phenytoin, drugs that older adults may be taking. Disulfiram reaction is known to occur from alcohol-metronidazole interaction. An important but difficult to answer question is whether and when to abandon the use of metronidazole as first line therapy for C. difficile diarrhea, both for initial and recurrent episodes (2,85).

Failure rate of metronidazole therapy has increased from less than 10% in 2003, to 28% recently and to 40% during the Canadian outbreak (86–90). The arrival of a new strain of C. difficile is associated with a decreased response to metronidazole and a high rate of recurrence (17,88,89,91–93). In severe cases vancomycin is more effective than metronidazole (30,92).

C. Treatment of Recurrences

Recurrent C. difficile infection is not related to the resistance of the organism to the individual medication used in the initial treatment (94). Recurrence is a result of reinfection with the same or a different strain of C. difficile from the environment (95). Although the mechanism of persistent carrier state is poorly understood(96), the diagnosis of recurrence should be confirmed with a stool toxin assay.

(continued on page 16)
CDAD recurs in about 20% of patients within 2–4 weeks of the remission of the first episode. Multiple recurrences may occur. It is the standard teaching to treat the first recurrence with a second course of the same drug used to treat the first episode. In view of the changing trends in the epidemiology, this approach needs to be reevaluated. A trend towards a better outcome with vancomycin in the first recurrence is reported. A recent issue of the medical letter has nicely summarized the treatment options available for recurrences and fulminant forms of CDAD (17).

Moshkowitz et al from Israel recently noted that the mortality from CDAD in the elderly is high, along with a high incidence of relapse. Of the 72 study patients (mean age 77 years), 47% were nursing home residents. Nearly 26% of the patients had received antacid therapy and 36% had been fed with a nasogastric tube. Twenty-one (29%) of the patients died within 30 days of hospitalization and 14 (19%) were re-hospitalized because of relapse. Multivariate analysis showed that leukocytosis \((20 \times 10^9/l)\), serum albumin level of less than 2.5 g/dl and pre-hospitalization nasogastric tube feeding were associated with high mortality. Treatment with acid reducing agents and residence at a nursing home facility were associated with a high relapse rate (35).

Prolonged tapering or pulsed dose of oral vancomycin 125 mg four times a day for 1 week followed by three times a day and every other day followed by every 3 days for 2 weeks is recommended. Other antimicrobials are investigational. Rifaximin 200 mg three times a day for 3 days (97), and nitazoxamide (17) are currently being evaluated. Other non-antibiotic agents which are investigational include Tolevamer, a toxin binding polymer. Low dose Tolevamer (3 grams per day) resolved diarrhea in 67% of patients and a higher dose (6 grams per day) in 83% of patients, but it was not superior to vancomycin (98) which helped in resolving diarrhea in 90% of patients. Anion binding resins, cholestyramine and colestipol have been used for initial infection as well as relapse. These resins have the advantage of not altering the normal colonic flora.

D. Surgery in CDAD

As the number of severe cases of CDAD is increasing, more and more patients are requiring colectomy. It is an extremely difficult decision to choose surgery for a disease which, until recently, was considered a medically manageable problem. Systemic signs of severe infection, such as fever, leukocytosis, severe abdominal pain, toxic mega colon, shock requiring vasopressors, a lack of response to medical therapy, peritoneal sepsis and perforation are indications for surgery (99–101).

The study by Lamontagne et al showed that mortality from fulminant \(C.\) difficile colitis is lower in patients who underwent colectomy (34). After adjusting for confounding variables, a significant survival benefit was shown for emergency colectomy (AOR 0.22, 95% CI 0.07–0.67). Colectomy did not give survival benefit to patients aged below 65 years or those with a leukocytosis \(<20 \times 10^9/l\) or a normal serum lactate level. A rising serum lactate level \(\geq 5\) mmol/l was associated with increased mortality. The study suggested that colectomy should be a consideration early in the course of severe disease in the 75+ age group. Commenting on the article, Surawicz stated that it might be prudent to consider early surgery in at risk patients such as those aged more than 65 years with co-morbidities and marked leukocytosis (102). Timing for surgery is important and it should not be delayed unnecessarily. The goal for surgical intervention is operating before serum lactate and white blood cell count rise and before multi-organ failure develops. Koss et al have noted that total colectomy is associated with a better outcome than hemi-colectomy (101).

PROBIOTICS

\(C.\) difficile, being an opportunistic infection, colonizes the colon only after the normal colonic bacterial flora has been altered by antibiotics. Probiotics are microorganisms which are non-pathogenic but with health benefits when ingested. They are reported to restore the balance of intestinal micro flora. The new field of probiotics estimated initially in the management of diarrheal diseases, is being currently studied as continuation therapy for CDAD (103). Although initial results are encouraging, they are currently not the primary agents in the treatment of CDAD. Treatment with \(Saccharomyces boulardii\) (\(S.\) boulardii) (1 gram per day for 4 weeks), and a non-pathogenic yeast, administered with oral vancomycin (2 gram daily for
10 days), produced a significantly lower rate of recurrence when compared to the group that received vancomycin with placebo (16.7% vs. 50%) (104).

Review of literature supports the efficacy of \textit{S. boulardii} in the prevention of antibiotic-associated recurrent CDAD in adults, whereas \textit{Lactobacillus rhamnosus} (LGG) is useful in the treatment of AAD in children. Although generally safe and well tolerated, both \textit{S. boulardii} and LGG should be used cautiously in immunocompromised patients (105–107). Using meta-analyses, McFarland recently concluded that three types of Probiotics (\textit{S. boulardii}, LGG, and probiotic mixtures) significantly reduced the development of AAD, but only \textit{S. boulardii} was effective for CDAD (108).

Administration of fecal enemas from healthy donors has been shown to reduce recurrences; however because of esthetic reasons and the fear of introducing unknown pathogens, it is not appealing (109). Based on the observation that recurrences are reflections of the host immune response, IV Immunoglobulin (IVIG) has been tried (110). A new vaccination has been developed to promote antitoxin A antibody (111).

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