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Clostridia Difficile Diarrhea

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1. Introduction

The term antibiotic associated diarrhea is usually reserved for diarrhea caused by infection with the organism Clostridia Difficile. Infection is thought to take place after the normal intestinal flora is altered by antibiotic use allowing for proliferation of Clostridia Difficile. Worryingly, the incidence and severity of illness caused by Clostridia Difficile is on the increase.

2. Pathophysiology

Clostridia difficile is a gram positive, spore forming anaerobic bacilli[1] Infection occurs when the organism is ingested. Though initially thought of as a nosocomial infection, community acquired clostridia difficile infection is increasingly recognized.[2]
Clostridia Difficile produces a variety of toxins, toxin A (enterotoxin) and B (cytotoxin) are the toxins most frequently linked to disease. They cause inflammation and disrupt cell cytoskeleton synthesis leading to colonic cell disruption.[3,4,5] A new strain, termed NAP1 or BI or 027 (depending on the technique used to identify it) was identified in the early 2000s the cause of selected outbreaks. This strain of clostridia difficile is associated with clinically more severe disease, innate resistance to quinolones and higher amounts of toxin production.[6]

3. Epidemiology

Clostridia difficile infection was linked to the development of pseudomembranous colitis in the 70's.[7] Initial cases were mostly linked to clindamycin but since then the range antibiotics linked with development of Clostridia Difficile has widened and cephalosporins and floroquinolones are thought to be the major causes.[8]
Though less often thought of as a cause of diarrhea in developing countries, pathogenic C. Difficile has been noted in South Africa[9] and India.[10]
The incidence rate of C. Difficile infection in the US was about 30 to 40 cases per hundred thousand.[11]
One research group noted an increasing rate of colectomies following C. Difficile infection.[12]
Canadian authors noted a four fold increase in background prevalence of C. Difficile between when the period before 2002 was compared to 2003.[13]

4. Clinical presentation

Presentation may range from asymptomatic carrier state[14] to fulminant colitis.[15]
Symptomatic patients typically present with watery diarrhea and lower abdominal pain.[16] Severe diarrhea with leucocytosis, fever, abdominal pain and distention occurs in the severely ill[16,17]. Surgical management with colectomy may be required in severe cases[18]. C. Difficile colitis was increasingly listed as the cause of death in an English population.[19]
Rises in white cell count to above 30,000 or a doubling of serum creatinine have been suggested as harbingers complicated disease.[20]

5. Diagnosis

C. Difficile diagnosis is usually done with laboratory testing in a patient suspected to be having the infection.
One of the most sensitive and specific tests available is the cell cytotoxycity assay, which had a sensitivity of 98% and specificity of 99% when compared to clinical and laboratory criteria.[21] This test is unfortunately technically demanding and may not be the first choice of many laboratories.
Many laboratories will use EIAs for detection of toxin A and B. These tests are insensitive when compared to cell culture or cytotoxicity assay but they are cheaper and produce results in hours rather than days.[22] Due to the lower positive predictive value of these tests a 2 step approach with a sensitive screening test followed by confirmation by culture or cell cytotoxicity may be appropriate.[23]
Testing for glutamate dehydrogenase, an enzyme produced by C. Difficile is sensitive (96 to 100%) [24], cheap, and rapid but it only detects presence of organism rather than toxin production.
Though its usually unnecessary, direct visualization of colitis by endoscopy is virtually diagnostic as they are few other infections that would cause pseudomembrane formation.[25] Endoscopy carries the risk of perforation in fulminant colitis.

6. Treatment

First line therapy for C. Difficile infection has long been considered to be a choice between metronidazole or vancomycin. Resolution of disease was seen in over 90% of patients taking a 10 day course of either therapy.[26]
More recently, metronidazole has been associated with therapeutic failure rates as high as 50 percent if persistence of disease and recurrence are conbined.[27] That said, oral metronidazole at a dose of 500mg, three times daily for ten to fourteen days remains the initial recommended therapy for mild disease.[28] Oral or rectal vancomycin (500mg four times a day) is recommended for more severe disease.[28] Patients who cannot tolerate oral therapy may be treated with intravenous metronidazole.[29]
Up to 25% of patients may have recurrent infection[16] believed to occur because of germination of spores or ingestion of new spores.
Many approaches have been taken to recurrent symptomatic C Difficile infection. A tapered or pulsed course of oral vancomycin may reduce recurrence rates[30].

Other approaches include fecal transplants[31], immunization against C difficile toxins[32], cholestyramine[33], rifampin[34] or probiotics[35]. There isn't sufficient data to recommend any of these approaches.

Recently fidaxomicin (200 mg oral, twice daily for ten days), a macrolide antibiotic, was shown to be non inferior to vancomycin.[36] During the trial referenced, patients were noted to have a lower recurrence rate when they were treated using fidaxomicin rather than vancomycin (13.3% vs. 24.0%)

7. Prevention

Judicious use of antibiotics has been shown to reduce the rates of C. difficile infection.[37, 38] Washing hands with soap and water, using gloves when touching patients and use of disposable thermometers have been recommended as control measures with good quality evidence of efficacy.[39] Alcohol hand washing gels are not effective in preventing disease spread.[40]

8. References

[1] Ryan KJ, Ray CG (editors) (2004). *Sherris Medical Microbiology* (4th ed.). McGraw Hill. pp. 322–4. ISBN 0-8385-8529-9.

[2] Epidemiology of community-acquired Clostridium difficile-associated diarrhea. Hirschhorn LR, Trnka Y, Onderdonk A, Lee ML, Platt R. J Infect Dis. 1994 Jan;169(1):127-33.

[3] Just I, Selzer J, Wilm M, von Eichel-Streiber C, Mann M, Aktories K. Glucosylation of Rho proteins by Clostridium difficile toxin B. Nature. 1995;375(6531):500.

[4] Clostridium difficile toxin A. Interactions with mucus and early sequential histopathologic effects in rabbit small intestine. Lima AA, Innes DJ Jr, Chadee K, Lyerly DM, Wilkins TD, Guerrant RL. Lab Invest. 1989;61(4):419.

[5] Clostridium difficile toxin-induced inflammation and intestinal injury are mediated by the inflammasome. Ng J, Hirota SA, Gross O, Li Y, Ulke-Lemee A, Potentier MS, Schenck LP, Vilaysane A, Seamone ME, Feng H, Armstrong GD, Tschopp J, Macdonald JA, Muruve DA, Beck PL. Gastroenterology. 2010 Aug;139(2):542-52, 552.e1-3. Epub 2010 Apr 13.

[6] Toxin production by an emerging strain of Clostridium difficile associated with outbreaks of severe disease in North America and Europe. Warny M, Pepin J, Fang A, Killgore G, Thompson A, Brazier J, Frost E, McDonald LC. Lancet. 2005;366(9491):1079

[7] Role of Clostridium difficile in antibiotic-associated pseudomembranous colitis. Bartlett JG, Moon N, Chang TW, Taylor N, Onderdonk AB. Gastroenterology. 1978;75(5):778.

[8] Narrative review: the new epidemic of Clostridium difficile-associated enteric disease. Bartlett JG Ann Intern Med. 2006;145(10):758.

[9] PCR detection of Clostridium difficile triose phosphate isomerase (tpi), toxin A (tcdA), toxin B (tcdB), binary toxin (cdtA, cdtB), and tcdC genes in Vhembe District, South

Africa. Samie A, Obi CL, Franasiak J, Archbald-Pannone L, Bessong PO, Alcantara-Warren C, Guerrant RL. Am J Trop Med Hyg. 2008 Apr;78(4):577-85.

[10] Dhawan B, Chaudhry R, Sharma N. Incidence of Clostridium difficile infection: a prospective study in an Indian hospital. J Hosp Infect. 1999;43:275-280. Abstract

[11] McDonald LC, Owings M, Jernigan JB. Clostridium difficile infection in patients discharged from US short-stay hospitals, 1996 to 2003. Emerg Infect Dis 2006;12:409-415 Ricciardi R, Rothenberger DA, Madoff RD, Baxter NN.

[12] Increasing prevalence and severity of Clostridium difficile colitis in hospitalized patients in the United States. Arch Surg. 2007;142:624-631; discussion 631.

[13] Pepin J, Valiquette L, Alary ME, et al. Clostridium difficile-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. CMAJ 2004;171:466-472

[14] Nosocomial acquisition of Clostridium difficile infection. McFarland LV, Mulligan ME, Kwok RY, Stamm WE. N Engl J Med. 1989;320(4):204.

[15] Severe Clostridium difficile colitis. Rubin MS, Bodenstein LE, Kent KC. Dis Colon Rectum. 1995;38(4):350.

[16] Clostridium difficile Colitis. Ciaran P. Kelly, Charalabos Pothoulakis, and J. Thomas LaMont. N Engl J Med 1994; 330:257-26

[17] Leukocytosis as a harbinger and surrogate marker of Clostridium difficile infection in hospitalized patients with diarrhea. Bulusu M, Narayan S, Shetler K, Triadafilopoulos G. Am J Gastroenterol. 2000;95(11):3137.

[18] Fulminant Clostridium difficile: An Underappreciated and Increasing Cause of Death and Complications. Ramsey M. Dallal, Brian G. Harbrecht, Arthur J. Boujoukas, Carl A. Sirio, Linda M. Farkas Kenneth K. Lee,Richard L. Simmons, Ann Surg. 2002 March; 235(3): 363–372.

[19] United Kingdom national statistics. Newport, United Kingdom: Office for National Statistics, UK Statistics Authority. (Accessed October 6, 2008, at http://www.statistics.gov.uk.)

[20] Predictors of Serious Complications Due to Clostridium difficile Infection. D. Gujja; F. K. Friedenberg. Alimentary Pharmacology & Therapeutics. 2009;29(6):635-642.

[21] Connor D, Hynes P, Cormican M, Collins E, Corbett-Feeney G, Cassidy M. Evaluation of methods for detection of toxins in specimens of feces submitted for diagnosis of Clostridium difficile–associated diarrhea. J Clin Microbiol 2001;39:2846-9.

[22] Clinical Recognition and Diagnosis of *Clostridium difficile* Infection. John G. Bartlett and Dale N. Gerding. Clin Infect Dis. (2008) 46 (Supplement 1): S12-S18. doi: 10.1086/521863

[23] Planche T, Aghaizu A, Holiman R, et al. Diagnosis of Clostridium difficile infection by toxin detection kits: a systematic review. Lancet Infect Dis 2008;8:777-784

[24] Ticehurst JR, Aird DZ, Dam LM, Borek AP, Hargrove JT, Carroll KC. Effective detection of toxigenic Clostridium difficile by a two-step algorithm including tests for antigen and cytotoxin. J Clin Microbiol 2006;44:1145-9.

[25] Kawamoto S, Horton KM, Fishman EK. Pseudomembranous colitis: spectrum of imaging findings with clinical and pathologic correlation. Radiographics 1999;19:887-97.

[26] Wenisch C, Parschalk B, Hasenhundl M, Hirschl AM, Graninger W. Comparison of vancomycin, teicoplanin, metronidazole, and fusidic acid for the treatment of *Clostridium difficile*-associated diarrhea [published correction appears in Clin Infect Dis 1996;23:423]. *Clin Infect Dis*. 1996;22:813–8.

[27] Musher DM, Aslam S, Logan N, et al. Relatively poor outcome after treatment of Clostridium difficile colitis with metronidazole. Clin Infect Dis 2005;40:1586-1590

[28] Shea-idsa guideline. Clinical Practice Guidelines for Clostridium difficile Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Stuart H. Cohen, Dale N. Gerding, Stuart Johnson, Ciaran P. Kelly, Vivian G. Loo, L. Clifford McDonald, Jacques Pepin, Mark H. Wilcox. Infect Control Hosp Epidemiol 2010; 31(5):000-000

[29] Bolton RP, Culshaw MA. Faecal metronidazole concentrations during oral and intravenous therapy for antibiotic associated colitis due to Clostridium difficile. Gut 1986;27:1169-1172

[30] McFarland LV, Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent Clostridium difficile disease. Am J Gastroenterol 2002;97:1769-1775

[31] Aas J, Gessert CE, Bakken JS. Recurrent Clostridium difficile colitis: case series involving 18 patients treated with donor stool administered via a nasogastric tube. Clin Infect Dis 2003;36:580-585Tedesco FJ. Treatment of recurrent antibiotic-associated pseudomembranous colitis. Am J Gastroenterol 1982;77:220-221

[32] Leung DY, Kelly CP, Boguniewicz M, Pothoulakis C, LaMont JT, Flores A. Treatment with intravenously administered gamma globulin of chronic relapsing colitis induced by Clostridium difficile toxin. J Pediatr 1991;118:633-637

[33] Zimmerman MJ, Bak A, Sutherland LR. Treatment of Clostridium difficile infection. Aliment Pharmacol Ther 1997;11:1003-1012

[34] Buggy BP, Fekety R, Silva J Jr. Therapy of relapsing Clostridium difficile-associated diarrhea and colitis with the combination of vancomycin and rifampin. J Clin Gastroenterol 1987;9:155-159

[35] Probiotics for treatment of Clostridium difficile-associated colitis in adults. Anjana Pillai, Richard L Nelson. Intervention review, The Cochrane Library. DOI: 10.1002/14651858.CD004611.pub2

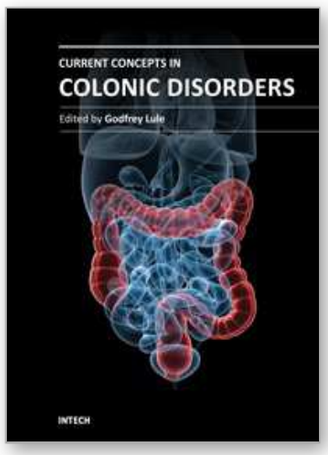
[36] Fidaxomicin versus Vancomycin for *Clostridium difficile* Infection. Thomas J. Louie, Mark A. Miller, Kathleen M. Mullane, D.O., Karl Weiss, Arnold Lentnek, Yoav Golan, Sherwood Gorbach, M.D., Pamela Sears, Youe-Kong Shue. N Engl J Med 2011; 364:422-431

[37] Carling P, Fung T, Killion A, Terrin N, Barza M. Favorable impact of a multidisciplinary antibiotic management program conducted during 7 years. *Infect Control Hosp Epidemiol*. 2003;24:699–706.

[38] Climo MW, Israel DS, Wong ES, Williams D, Coudron P, Markowitz SM. Hospital-wide restriction of clindamycin: effect on the incidence of *Clostridium difficile*-associated diarrhea and cost. *Ann Intern Med*. 1998;128(12 pt 1):989–95.

[39] Prevention of Endemic Healthcare-Associated *Clostridium difficile* Infection: Reviewing the Evidence. J Hsu, C Abad, M Dinh, N Safdar. *Am J Gastroenterol* 6 July 2010; doi: 10.1038/ajg.2010.254

[40] Leischner J, Johnson S, Sambol S, Parada J, Gerding DN. Effect of alcohol hand gels and chlorhexidine hand wash in removing spores of Clostridium difficile from hands [abstr]. In: Program and abstracts of the 45th interscience conference on antimicrobial agents and chemotherapy. Washington, DC: American Society for Microbiology, 2005:LB-29.



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The 21st Century has seen a resurgence of research of the gastrointestinal tract, especially since it was established that it plays a central role as an immune system organ and consequentially has a huge impact on causation, impact and transmission of most human ailments. New diseases such as the Acquired Immunodeficiency Syndrome, hepatitis and tumours of the gastrointestinal tract have emerged and they are currently subjects of intensive research and topics of scientific papers published worldwide. Old diseases like diarrhea have become extremely complex to diagnose with new and old pathogens, drugs, tumours and malabsorptive disorders accounting for the confusion. This book has set out algorithms on how to approach such conditions in a systematic way both to reach a diagnosis and to make patient management cheaper and more efficient. "Current Concepts in Colonic Disorders" attempts to put all the new information into proper perspective with emphasis on aetiopathogenesis and providing rational approach to management of various old and new diseases. As the book editor, I have found this first edition extremely interesting and easy to understand. Comments on how to improve the content and manner of presentation for future editions are extremely welcome.

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