18 - 139 Clostridioides difficile Infection, Including Pseudomembranous Colitis

139 Clostridioides difficile Infection, Including Pseudomembranous Colitis

viral enteric pathogens. An effective rotavirus vaccine is available. Vac cines against V. cholerae are available and recommended in areas where active transmission is ongoing, although the protection they offer is incomplete and short lived. A typhoid conjugate vaccine is now recom mended by the World Health Organization for use in countries where typhoid is endemic. At present, there are no effective commercially available vaccines against pathogenic E. coli, Shigella, Campylobacter, nontyphoidal Salmonella, norovirus, or intestinal parasites.

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Clostridioides difficile

Infection, Including Pseudomembranous Colitis ■ ■DEFINITION Clostridioides difficile infection (CDI) is a unique colonic disease that is acquired most commonly in association with antimicrobial use and the consequent disruption of the normal colonic microbiota. The most commonly diagnosed diarrheal illness acquired in the hospital, CDI results from the ingestion of spores of C. difficile that vegetate, multi ply, and secrete toxins, causing diarrhea and, in the most severe cases, pseudomembranous colitis (PMC).

■ ■ETIOLOGY AND EPIDEMIOLOGY C. difficile is an obligately anaerobic, gram-positive, spore-forming bacillus whose spores are found widely in nature, particularly in the environment of hospitals and chronic-care facilities. CDI occurs fre quently in hospitals and nursing homes (or shortly after discharge from these facilities) where the level of antimicrobial use is high and the environment is contaminated by C. difficile spores. Clindamycin, ampicillin, and cephalosporins were the first antibiot ics associated with CDI. The second- and third-generation cephalospo rins, particularly cefotaxime, ceftriaxone, cefuroxime, and ceftazidime, are agents frequently responsible for this condition, and the fluoroqui nolones (ciprofloxacin, levofloxacin, and moxifloxacin) are the most recent drug class to be implicated in hospital outbreaks. Penicillin/

β-lactamase-inhibitor combinations such as ticarcillin/clavulanate and piperacillin/tazobactam pose significantly less risk. However, all anti biotics, including vancomycin (the agent most commonly used to treat CDI), have been found to carry a risk of subsequent CDI. A minority of cases, especially in the community, are reported in patients without documentation of prior antibiotic exposure. C. difficile is acquired exogenously—most often in the hospital or nursing home, but also in the outpatient setting—and is carried in the stool of both symptomatic and asymptomatic patients. The rate of fecal colonization increases in proportion to length of hospital stay and is often ≥20% among adult patients hospitalized for >2 weeks; in contrast, the rate is 1–3% among community residents. CDI is the most com mon health care–associated infection in the United States, with an esti mated 462,100 cases in 2017. Between 2011 and 2017, the total burden of CDI in the United States decreased by 24%, which was due primarily to decreases in health care–associated CDI. The estimated burden of community-associated CDI was unchanged, but it now approximates the health care–associated rate in the United States. Asymptomatic fecal carriage of C. difficile in healthy neonates is very common, with repeated colonization by multiple strains in infants <1–2 years of age, but associated disease in these infants is extremely rare if it occurs at all. Spores of C. difficile are found on environmental surfaces (where the organism can persist for months) and on the hands of hospital personnel who fail to practice good hand hygiene. Hospital epidemics of CDI have been attributed to a single C. difficile strain and to multiple different strains, introduced by patients on admission, that are present simultaneously. Other identified risk factors for CDI include older age, greater severity of underlying illness, gastrointestinal surgery, use of electronic rectal thermometers, enteral tube feeding, and antacid treatment. Use of proton pump inhibitors may be a risk factor, but this risk is probably modest, and

no firm data have impli cated these agents in patients who are not already receiving antibiotics. ■ ■PATHOLOGY AND PATHOGENESIS Spores of toxigenic C. difficile are ingested, survive gastric acidity, ger minate in the small bowel, and, in the presence of a disrupted micro biota, colonize the lower intestinal tract, where they elaborate two large toxins: toxin A (an enterotoxin) and toxin B (a cytotoxin). These toxins initiate processes resulting in the disruption of epithelial-cell barrier function, diarrhea, and pseudomembrane formation. Toxin A is a potent neutrophil chemoattractant, and both toxins glucosylate the GTP-binding proteins of the Rho subfamily that regulate the actin cell cytoskeleton. Data from studies using molecular disruption of toxin genes in isogenic mutants suggest that toxin B may be the more impor tant virulence factor, which is consistent with the well-documented occurrence of clinical disease caused by toxin A–negative strains but not by toxin B–negative strains. Disruption of the cytoskeleton results in loss of cell shape, adherence, and tight junctions, with consequent fluid leakage. A third toxin, binary toxin CDT, was previously found in only ~6% of strains but is present in all isolates of the widely recognized epidemic NAP1/BI/027 strain (see “Global Considerations,” below); this toxin is related to C. perfringens iota toxin. Its role in the pathogen esis of CDI has not yet been defined. The pseudomembranes of PMC are confined to the colonic mucosa and initially appear as 1- to 2-mm whitish-yellow plaques. The inter vening mucosa appears unremarkable, but, as the disease progresses,

FIGURE 139-1 Autopsy specimen showing confluent pseudomembranes covering the cecum of a patient with pseudomembranous colitis. Note the sparing of the terminal ileum (arrow). the pseudomembranes coalesce to form larger plaques and become confluent over the entire colon wall (Fig. 139-1). The whole colon is usually involved, but 10% of patients have rectal sparing. Viewed microscopically, the pseudomembranes have a mucosal attachment point and contain necrotic leukocytes, fibrin, mucus, and cellular debris. The epithelium is eroded and necrotic in focal areas, with neu trophil infiltration of the mucosa. Patients colonized with C. difficile were initially thought to be at high risk for CDI. However, four prospective studies have shown that colonized patients who have not previously had CDI actually have a decreased risk of CDI, possibly because many of these patients are colonized by nontoxigenic strains. At least three events are proposed as essential for the development of CDI (Fig. 139-2). Exposure to anti microbial agents is the first event and establishes susceptibility to CDI, most likely through disruption of the normal gastrointestinal micro biota. The second event is exposure to toxigenic C. difficile. Given that the majority of patients do not develop CDI after the first two events, a third event is clearly essential for its occurrence. Candidate third C. difficile exposure C. difficile exposure Antimicrobial(s) Healthcare Exposure (Increased chance of receiving an antibiotic and Increased chance of being exposed to spores of C. difficile) FIGURE 139-2 Pathogenesis model for Clostridioides difficile infection (CDI). At least three events are integral to C. difficile pathogenesis. Exposure to antibiotics establishes susceptibility to C. difficile infection. If susceptible, the patient may ingest nontoxigenic (nonpathogenic) or toxigenic strains of C. difficile as a second event. Acquisition of toxigenic C. difficile may be followed by asymptomatic colonization or CDI, depending on one or more additional factors, including the strain of C. difficile and an inadequate host anamnestic antibody response to C. difficile toxins.

events include exposure to a C. difficile strain of particular virulence, exposure to antimicrobial agents especially likely to cause CDI, and an inadequate host immune response. The host anamnestic immune response as has been shown for serum IgG antibody response to toxin A of C.

difficile is likely one factor in the third event that determines which patients develop diarrhea and which patients remain asymp tomatic. The majority of humans probably first develop antibody to C. difficile toxins when colonized asymptomatically during the first year of life or after CDI in childhood. Infants are thought not to develop symptomatic CDI because they lack suitable mucosal toxin receptors that develop later in life. In adulthood, there is evidence that serum antibodies to both toxin A and B protect against recurrent CDI. Two large clinical trials in which intravenous monoclonal antibodies to toxin A and toxin B were used together and as single agents in addi tion to standard antibiotic therapy showed that rates of recurrent CDI were significantly lower with the combination of antibodies and with the toxin B antibody alone than with placebo plus standard therapy. Antibody to toxin A alone was ineffective.

■ ■GLOBAL CONSIDERATIONS Rates and severity of CDI in the United States, Canada, and Europe increased markedly in the early 2000s. Rates in U.S. hospitals tripled between 2000 and 2005. Hospitals in Montreal, Quebec, reported rates in 2005 that were four times higher than the 1997 baseline, with directly attributable mortality of 6.9% (increased from 1.5%). An epi demic strain, variously known as toxinotype III, REA type BI, PCR ribotype 027, and pulsed-field type NAP1 (collectively designated NAP1/BI/027), likely accounted for much of the increase in incidence. Two clones of NAP1/BI/027 originated in the United States and Canada and spread to the United Kingdom, Europe, and Asia. This epi demic strain was characterized by (1) an ability to produce 16–23 times as much toxin A and toxin B as control strains in vitro, (2) the presence of binary toxin CDT, and (3) high-level resistance to all fluoroquino lones. National control policies instituted in England in 2006 resulted in a marked decline in CDI cases, and restriction of fluoroquinolones, in particular, was correlated with near elimination of fluoroquinoloneresistant strains of C. difficile (i.e., NAP1/BI/027) there by 2013. This epidemic strain has likewise decreased in the United States, with data from the Centers for Disease Control and Prevention showing a decrease among health care–associated isolates from 31% to 15% (and from 19% to 6% in community-associated isolates) between 2011 and 2017. New strains have been and will probably continue to be impli cated in outbreaks, including a strain commonly found in food animals that also carries binary toxin and has been associated with high mortal ity rates in human infections (toxinotype V, ribotype 078). Currently, the most frequently isolated community-associated strain in the United States is ribotype 106 (REA group DH), which was previously found to be epidemic in the United Kingdom. CHAPTER 139 Clostridioides difficile Infection, Including Pseudomembranous Colitis Asymptomatic C. difficile colonization CDI Acquisition of a toxigenic strain of C. difficile and presence of additional factor(s) result in CDI.

■ ■CLINICAL MANIFESTATIONS Diarrhea is the most common manifestation caused by C. difficile. Stools are almost never grossly bloody and range from soft and unformed to watery or mucoid in consistency, with a characteristic odor. Clinical and laboratory findings include fever in 28% of cases, abdominal pain in 22%, and leukocytosis in 50%. When adynamic ileus (which is seen on x-ray in ~20% of cases) results in cessation of stool passage, the diagnosis of CDI is frequently overlooked. A clue to the presence of unsuspected CDI in these patients is unexplained leukocytosis, with ≥15,000 white blood cells (WBCs)/μL. Such patients are at high risk for complications of CDI, particularly toxic megacolon and sepsis.

C. difficile diarrhea recurs after treatment in ~15–30% of cases and remains one of the most challenging treatment dilemmas. Recurrences may represent either relapses due to the same

strain or reinfections with a new strain. Susceptibility to recurrence of clinical CDI is likely a result of continued disruption of the normal fecal microbiota caused by the antibiotic used to treat CDI. ■ ■DIAGNOSIS The diagnosis of CDI is based on a combination of clinical criteria: (1) diarrhea (≥3 unformed stools per 24 h for ≥2 days) with no other rec ognized cause plus (2) detection of toxin A or B in the stool, detection of toxin-producing C. difficile in the stool by nucleic acid amplification testing (NAAT; e.g., polymerase chain reaction [PCR]) or by culture, or visualization of pseudomembranes in the colon. PMC is a more advanced form of CDI and is visualized at endoscopy in only ~50% of patients with diarrhea who have a positive stool culture and toxin assay for C. difficile (Table 139-1). Endoscopy is a rapid diagnostic tool in seriously ill patients with suspected PMC and an acute abdomen, but a negative result in this examination does not rule out CDI. PART 5 Infectious Diseases Despite the array of tests available for C. difficile and its toxins (Table 139-1), no single test has high sensitivity, high specificity, and rapid turnaround. Most laboratory tests for toxins, including enzyme immunoassays (EIAs), lack sensitivity. NAATs (including PCR) are widely used diagnostically and are both rapid and sensitive; however, concern has been raised that PCR may detect colonization with toxigenic C. difficile in patients who have diarrhea for a reason other than CDI. Confirmation of the presence of toxin in the stool in addition to NAAT or glutamate dehydrogenase (GDH) positivity is recommended in the European CDI guidelines for diagnosis of CDI, and inclusion of a stool toxin test is recommended in the U.S. guidelines when there are no prior criteria for stool submission. Test algorithms that include NAAT followed by toxin EIA for NAAT+ results, and GDH plus toxin EIA arbitrated by NAAT when the two initial test results do not agree, have become widely used; however, when results of individual algorithm tests are discrepant (NAAT+ or GDH+/toxin EIA–), most patients are nonetheless treated for CDI. TABLE 139-1 Relative Sensitivity and Specificity of Diagnostic Tests for Clostridioides difficile Infection (CDI) TYPE OF TEST RELATIVE SENSITIVITYa RELATIVE SPECIFICITYa COMMENT Stool culture for C. difficile ++++ +++ Most sensitive test; specificity of ++++ if the C. difficile isolate tests positive for toxin; turnaround time too slow for practical use Cell culture cytotoxin test on stool +++ ++++ With clinical data, is diagnostic of CDI; highly specific but not as sensitive as stool culture; slow turnaround time Enzyme immunoassay for toxins A and B in stool ++ to +++ +++ With clinical data, is diagnostic of CDI; rapid results, but not as sensitive as stool culture or cell culture cytotoxin test Enzyme immunoassay for C. difficile common antigen in stool +++ to ++++ +++ Detects glutamate dehydrogenase found in toxigenic and nontoxigenic strains of C. difficile and other stool organisms; more sensitive and less specific than enzyme immunoassay for toxins; requires confirmation with a toxin test; rapid results Nucleic acid amplification tests for C. difficile toxin A or B gene in stool ++++ +++ Detects toxigenic C. difficile in stool; widely used in United States for clinical testing; more sensitive than enzyme immunoassay toxin testing; marked increase in CDI diagnoses when implemented Colonoscopy or sigmoidoscopy + ++++ Highly specific if pseudomembranes are seen; insensitive compared with other tests aAccording to both clinical and test-based criteria. Note: ++++, >90%; +++, 71–90%; ++, 51–70%; +, ~50%.

Empirical treatment is appropriate if stool testing is delayed. Testing of asymptomatic patients is not recommended except for epidemio logic study purposes. In particular, so-called tests of cure following treatment are not recommended because >50% of patients continue to harbor the organism and its toxin after diarrhea has ceased and test results are not predictive of recurrence of CDI. The results of such tests should not be used to restrict placement of patients in long-term care or nursing home facilities. TREATMENT Clostridioides difficile Infection PRIMARY CDI When possible, discontinuation of any ongoing antimicrobial administration is recommended as the first step in

treatment of CDI. Earlier studies indicated that 15–23% of patients respond to this simple measure. However, with the advent of the NAP1/BI/027 epidemic strain and the associated rapid clinical deterioration of some patients, prompt initiation of specific CDI treatment has become the standard. General treatment guidelines include hydra tion and the avoidance of antiperistaltic agents and opiates, which may mask symptoms and possibly worsen disease. Nevertheless, antiperistaltic agents have been used safely with vancomycin or metronidazole treatment for mild to moderate CDI. Oral administration of fidaxomicin was suggested as firstline treatment for CDI in the 2021 Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) focused update guidelines on management of CDI in adults. However, because of resource availability issues, oral vancomycin remains an acceptable alternative. Oral metro nidazole is recommended only for mild or moderate CDI when fidaxomicin or vancomycin is not available. IV vancomycin is ineffective for CDI. Fidaxomicin is available only for oral admin istration. Two large clinical trials comparing vancomycin and fidaxomicin indicated comparable clinical resolution of diar rhea in ~90% of patients, and the rate of recurrent CDI was significantly lower with fidaxomicin. The largest randomized controlled trial of vancomycin versus metronidazole showed that the vancomycin cure rate was superior to the metronidazole cure rate (81% vs 73%; p = .034) for all patients with CDI, regardless of severity. Although the mean time to resolution of diarrhea is 2–4 days, the response to metronidazole may be much slower. Treatment should not be deemed a failure until a drug has been given for at least 6 days. On the basis of data for shorter courses of vancomycin and the results of four large clinical trials, it is recommended that vancomycin or fidaxomicin be given for at least 10 days. Metronidazole was never approved for CDI by the

TABLE 139-2 Recommendations for the Treatment of Clostridioides difficile Infection (CDI) CLINICAL SETTING TREATMENT(S) COMMENTS Initial episode, mild to moderate Fidaxomicin (200 mg bid × 10 d) or alternatively Oral vancomycin (125 mg qid × 10 d) Initial episode, severe Oral vancomycin (125 mg qid × 10 d) or alternatively Fidaxomicin (200 mg bid × 10 d) Initial episode, fulminant Vancomycin (500 mg PO or via nasogastric tube) plus metronidazole (500 mg IV q8h) plus consider Rectal instillation of vancomycin (500 mg in 100 mL of normal saline as a retention enema q6–8h) First recurrence Fidaxomicin (200 mg bid × 10 d) or Oral vancomycin (125 mg qid × 10 d) or Oral vancomycin followed by a taper-and-pulse regimena Multiple recurrences Oral vancomycin treatment followed by a taper-and-pulse regimen or Fidaxomicin (200 mg bid × 10 d or 200 mg bid × 5 d followed by every other day × 20 d) or Vancomycin (125 mg qid × 10 d), then stop vancomycin and start rifaximin (400 mg bid × 2 weeks) or Fecal microbiota replacement therapy (FMRT) Patients at high risk of recurrent CDI who are receiving vancomycin, fidaxomicin, or metronidazole Bezlotoxumab 10 mg/kg given IV Bezlotoxumab is adjuvant therapy (in addition to and during antibiotic treatment) for patients at high risk for recurrent CDI. Risk factors include age >65 years, immunocompromised host, severe CDI on presentation, and prior episode of CDI in the past 6 months. aA typical taper-and-pulse vancomycin regimen following a 10-day treatment course includes: 125 mg bid × 1 week, then daily × 1 week, then q2–3d for 2–8 weeks. U.S. Food and Drug Administration (FDA), and its use for CDI treatment declined markedly after publication of the 2017 IDSA/ SHEA CDI guidelines. It is important to initiate treatment with oral vancomycin or fidaxomicin for patients who appear seriously ill, particularly if they have a high WBC count (>15,000/μL) or creatinine level (≥1.5 mg/dL) (Table 139-2). Small randomized trials of nitazoxanide, bacitracin, rifaximin, and fusidic acid for treatment of CDI have been conducted. These drugs have not been extensively studied, shown to be superior, or approved by the FDA for

CDI, but they provide potential alternatives to vancomy cin and fidaxomicin. RECURRENT CDI Overall, ~15–30% of successfully treated patients experience recurrences of CDI following treatment. CDI recurrence is sig nificantly lower in patients treated with fidaxomicin than in those treated with vancomycin. Vancomycin and metronidazole have comparable recurrence rates, and metronidazole is not recom mended for treatment of recurrent CDI. Patients who have a first recurrence of CDI have an even higher rate of second recur rence. Fidaxomicin is superior to vancomycin in reducing further recurrences in patients who have had one CDI recurrence (Table 139-2). Recurrent disease, once thought to be relatively mild, has now been documented to pose a significant (11%) risk of seri ous complications (shock, megacolon, perforation, colectomy, or death within 30 days). There is no standard treatment for multiple recurrences, but the use of vancomycin in a tapering and pulsed dosing regimen every other day for 2–8 weeks has been used for years as a practical approach to treating these patients, and recent data suggest it is still effective. Other recommended treat ment options for patients with multiple CDI recurrences include fidaxomicin in standard or extended/pulsed dosing regimens, vancomycin followed by rifaximin, or fecal microbiota transplan tation (FMT) via nasoduodenal tube, colonoscope, enema, or oral capsules (Table 139-2). FMT has been widely used over the past decade, and the availability of stool banks and oral capsule formu lations made this approach more practical. Recently, the FDA has approved two microbiota replacement therapies and discontinued enforcement discretion for centralized donor stool banks. A fecal

Oral metronidazole is less effective than the other options and may necessitate a longer treatment course for response. Metronidazole (500 mg tid × 10–14 d) is recommended only if vancomycin or fidaxomicin is not readily accessible and for mild to moderate disease only. Indicators of severe disease may include leukocytosis (≥15,000 white blood cells/μL) and a creatinine level ≥1.5 mg/dL. Fulminant CDI is defined as severe CDI with the addition of hypotension, shock, ileus, or toxic megacolon. The duration of treatment may need to be >2 weeks and is dictated by response. Treatment for the initial episode may be considered when choosing treatment for the first recurrence. It is recommended that FMRT by fecal microbiota (Rebyota, live-jslm) given by enema or fecal microbiota spores (Vowst, live-brpk) given orally be considered only after appropriate antibiotic treatment for recurrent CDI. CHAPTER 139 microbiota suspension (Rebyota, live-jslm) and a suspension of live fecal microbiota spores for oral delivery (Vowst, live-brpk) are now approved for patients with recurrent CDI to prevent further recurrence. Both of these products are adjunctive treatments that are indicated for patients who have completed antibiotic treat ment for CDI. Clostridioides difficile Infection, Including Pseudomembranous Colitis In addition to antibacterial therapies, another adjunctive treat ment is now available for patients who are receiving standard-ofcare antibacterial agents and who are at high risk for recurrent CDI (rCDI). Bezlotoxumab, a monoclonal antibody directed against C. difficile toxin B, has been shown to reduce the risk of rCDI by an absolute rate of ~10% when administered to patients currently receiving vancomycin, fidaxomicin, or metronidazole. Risk factors for rCDI in the clinical trials included age >65 years, immunocom promise, severe CDI on presentation, and prior episode of CDI in the past 6 months. SEVERE COMPLICATED OR FULMINANT CDI Fulminant (rapidly progressive and severe) CDI presents the most difficult treatment challenge. Patients with fulminant disease often do not have diarrhea, and their illness mimics an acute surgical abdomen. Sepsis (hypotension, fever, tachycardia, leukocytosis) may result from fulminant CDI. An acute abdomen (with or with out toxic megacolon) may include signs of obstruction, ileus, colonwall thickening and ascites on abdominal CT, and peripheral-blood leukocytosis (≥20,000 WBCs/μL). With or without diarrhea, the differential diagnosis of an acute abdomen, sepsis, or toxic megaco lon should include CDI if the patient has

received antibiotics in the past 2 months. Cautious sigmoidoscopy or colonoscopy to visualize PMC and an abdominal CT examination are the best diagnostic tests in patients without diarrhea. Medical management of fulminant CDI is suboptimal because of the difficulty of delivering oral fidaxomicin, metronidazole, or vancomycin to the colon in the presence of ileus (Table 139-2). The combination of vancomycin (given orally or via nasogastric tube and by retention enema) plus IV metronidazole has been used with some success in uncontrolled studies, as has IV tigecycline in small-scale uncontrolled studies. Surgical colectomy may be life saving if there is no response to medical management. If possible,

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