to cause CDI, and an inadequate host immune response. The host anamnestic serum IgG antibody response to toxin A of *C. difficile* is the most likely third event that determines which patients develop diarrhea and which patients remain asymptomatic. In all probability, the majority of people 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, serum levels of IgG antibody to toxin A increase more in response to infection in individuals who become asymptomatic carriers than in those who develop CDI. For persons who develop CDI, development of increasing levels of antitoxin A during treatment correlates with a lower risk of recurrence of CDI. A clinical trial using monoclonal antibodies to both toxin A and toxin B in addition to standard therapy showed rates of recurrence significantly lower than those obtained with placebo plus standard therapy.

GLOBAL CONSIDERATIONS

Rates and severity of CDI in the United States, Canada, and Europe increased markedly after the year 2000. Rates in U.S. hospitals tripled between 2000 and 2005. In 2005, hospitals in Montreal, Quebec, reported rates four times higher than the 1997 baseline, with directly attributable mortality of 6.9% (increased from 1.5%). An epidemic strain, variously known as toxinotype III, REA type BI, polymerase chain reaction (PCR) ribotype 027, and pulsed-field type NAP1 and thus collectively designated NAP1/BI/027, is thought to account for much of the increase in incidence and has been found in North America, Europe, and Asia. It is now recognized that two clones of NAP1/BI/027 originated in the United States and Canada and spread to the United Kingdom, Europe, and Asia. The epidemic organism is 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 a third toxin (binary toxin CDT); and (3) high-level resistance to all fluoroquinolones. New strains have been and probably will continue to be implicated in outbreaks, including a strain (toxinotype V, ribotype 078) commonly found in food animals that also carries binary toxin and has been associated with high mortality risk in human infections. In the past 5 years, rates of CDI in the United Kingdom have markedly decreased, and the frequency of the NAP1/BI/027 strain in the countries of the European Union has likewise decreased. However, there has been no evidence of decreased rates of CDI or a decreased incidence of NAP1/BI/027 in North America; the latter strain still causes 25–35% of all CDIs in most regions of the United States.

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. Patients may have as many as 20 bowel movements per day. 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 *C. difficile* infection, particularly toxic megacolon and sepsis.

C. difficile diarrhea recurs after treatment in ~15–30% of cases, and this figure may be increasing. 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 fecal-microbiota disruption 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 recognized cause plus (2) toxin A or B detected in the stool, toxin-producing *C. difficile* detected in the stool by PCR or culture, or pseudomembranes seen 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*. 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.

Despite the array of tests available for *C. difficile* and its toxins (Table 161-1), no single traditional test has high sensitivity, high specificity, and rapid turnaround. Most laboratory tests for toxins, including enzyme immunoassays, lack sensitivity. However, testing of multiple additional stool specimens is not recommended. Nucleic acid amplification tests, including PCR assays, have now been approved for diagnostic purposes and appear to be both rapid and sensitive while retaining high specificity. Testing of asymptomatic patients is not recommended except for epidemiologic study purposes. In particular, so-called tests of cure following treatment are not recommended because >50% of patients continue to harbor the organism and toxin after diarrhea has ceased and test results do not always predict recurrence of CDI. Thus these results should not be used to restrict placement of patients in long-term-care or nursing home facilities.

TREATMENT *CLOSTRIDIUM 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 current epidemic strain and the associated rapid clinical deterioration of some patients,

TABLE 161-1 RELATIVE SENSITIVITY AND SPECIFICITY OF DIAGNOSTIC TESTS FOR *CLOSTRIDIUM DIFFICILE* INFECTION (CDI)

Type of Test	Relative Sensitivity[a]	Relative Specificity[a]	Comment
Stool culture for *C. difficile*	++++	+++	Most sensitive test; specificity of ++++ if the *C. difficile* isolate tests positive for toxin; with clinical data, is diagnostic of CDI; 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 toxin A or 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; rapid results
Nucleic acid amplification tests for *C. difficile* toxin A or B gene in stool	++++	++++	Detect toxigenic *C. difficile* in stool; newly approved for clinical testing, but appears to be more sensitive than enzyme immunoassay toxin testing and at least as specific
Colonoscopy or sigmoidoscopy	+	++++	Highly specific if pseudomembranes are seen; insensitive compared with other tests

[a]According to both clinical and test-based criteria. ++++, >90%; +++, 71–90%; ++, 51–70%; +, ~50%.