frequently 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 antibiotics associated with CDI. The second- and third-generation cephalosporins, particularly cefotaxime, ceftriaxone, cefuroxime, and ceftazidime, are frequently responsible for this condition, and the fluoroquinolones (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 antibiotics, including vancomycin and metronidazole (the agents most commonly used to treat CDI), carry a risk of subsequent CDI. Rare cases are reported in patients without prior antibiotic exposure.

C. difficile is acquired exogenously—most frequently in the hospital or nursing home, but also possibly in the outpatient setting—and is carried in the stool of both symptomatic and asymptomatic patients. The rate of fecal colonization is often ≥20% among adult patients hospitalized for >1 week; in contrast, the rate is 1–3% among community residents. Community-onset CDI without recent hospitalization, nursing home residence, or outpatient health-care contact probably accounts for ≤10% of all cases. The risk of *C. difficile* acquisition increases in proportion to the length of hospital stay. Asymptomatic fecal carriage of *C. difficile* in healthy neonates is very common, with repeated colonization by multiple strains in infants (<1 year old), 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 strains 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 implicated these agents in patients who are not already receiving antibiotics.

PATHOLOGY AND PATHOGENESIS

Spores of toxigenic *C. difficile* are ingested, survive gastric acidity, germinate in the small bowel, and 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 guanosine triphosphate (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 is the more important virulence factor. This possibility, if confirmed, might account for the occurrence of clinical disease caused by toxin A–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 pathogenesis 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 intervening mucosa appears unremarkable, but, as the disease progresses, the pseudomembranes coalesce to form larger plaques and become confluent over the entire colon wall (Fig. 161-1). 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 neutrophil 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. At least three events are proposed as essential for the development of CDI (Fig. 161-2). Exposure to antimicrobial agents is the first event and establishes susceptibility to *C. difficile* infection, most likely through disruption of the normal gastrointestinal microbiota. 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 events include exposure to a *C. difficile* strain of particular virulence, exposure to antimicrobial agents especially likely

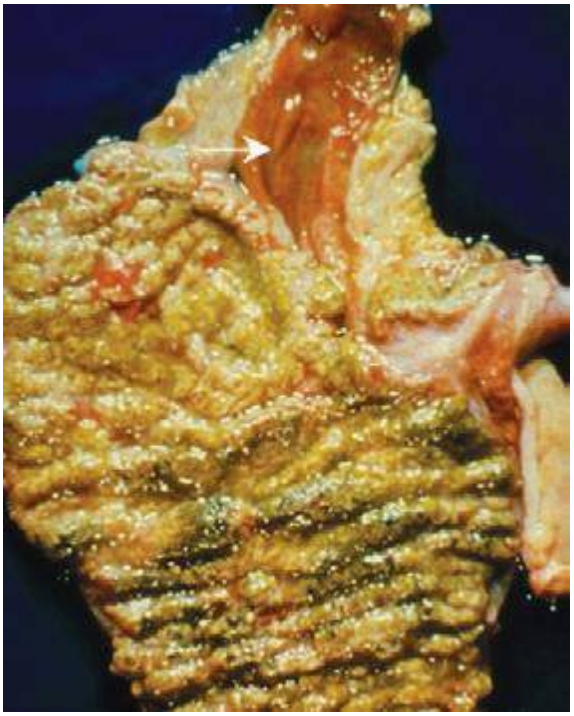

FIGURE 161-1 Autopsy specimen showing confluent pseudomembranes covering the cecum of a patient with pseudomembranous colitis. Note the sparing of the terminal ileum (*arrow*).

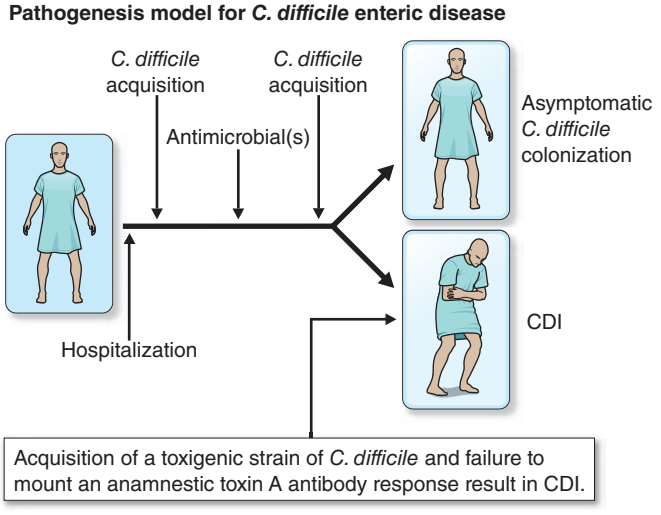

FIGURE 161-2 Pathogenesis model for hospital-acquired *Clostridium difficile* infection (CDI). At least three events are integral to *C. difficile* pathogenesis: (1) Exposure to antibiotics establishes susceptibility to infection. (2) Once susceptible, the patient may acquire nontoxigenic (nonpathogenic) or toxigenic strains of *C. difficile* as a second event. (3) Acquisition of toxigenic *C. difficile* may be followed by asymptomatic colonization or CDI, depending on one or more additional events (e.g., an inadequate host anamnestic IgG response to *C. difficile* toxin A).