Mechanisms and Management of Antibiotic-Associated Diarrhea

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Diarrhea is a frequent adverse effect of antibiotics. Diarrhea can be defined by any of the following criteria: mushy or watery stool, per-day stool weight of >200 g, or stool frequency of more than three per day [1]. However, antibiotic-associated diarrhea (AAD) has been suggested to be clinically significant when there are three mushy or watery stools per day [2]. Diarrhea can develop from a few hours up to 2 months after antibiotic intake [3]. The incidence of AAD differs with the antibiotic and varies between 5% and 25% [4].

The mechanisms by which antibiotics lead to AAD are disturbance of the composition and function of the normal intestinal flora, overgrowth by pathogenic microorganisms, and allergic and toxic effects of antibiotics on intestinal mucosa or pharmacologic effects on motility. Although in recent years discussions of AAD have centered on *Clostridium difficile*—associated diarrhea (CDAD), only 10%–20% of all AAD cases are positive for toxigenic *C. difficile* [2, 5, 6]. Understanding the different mechanisms that cause AAD may help to prevent AAD, improve medical care, and reduce costs.

**Infectious Origins of AAD**

**Clostridium difficile**

The normal bowel flora suppresses the growth of *C. difficile* [7]. Antimicrobial agents, most frequently cephalosporins, aminopenicillins, and clindamycin, are presumed to make the bowel more susceptible to infection with *C. difficile* because of alterations in the intestinal flora and amino acid contents [4, 8]. Any other antibiotic, including vancomycin and metronida-}

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Clinical Infectious Diseases 1998;27:702–10
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be cultured from the hands of 20% of the hospital staff caring for these patients. In the same study, 21% of 399 hospitalized patients had acquired *C. difficile* infection during the hospital stay [11].

**Clostridium perfringens**

Borriello et al. reported 11 patients with AAD in whom *C. perfringens* and its enterotoxin could be detected [17]. Ten of these patients had received antibiotics within 3 weeks before the onset of diarrhea. All cases were sporadic, and most *C. perfringens* serotypes found were different from those serotypes commonly found in food poisoning. Three patients with *C. perfringens*—associated diarrhea had bloody stools and four underwent colonoscopy, but there was no evidence of PMC. All cases were self-limited. According to this study, one *C. perfringens*—positive patient with AAD can be expected for every 10 *C. difficile*—positive patients with AAD [17]. These observations were confirmed in another 39 patients when the study was continued [18].

*C. perfringens* spores are present in the hospital environment [19]. Nosocomial, non-food-poisoning intestinal infections with *C. perfringens* occur mostly in elderly patients after antibiotic treatment. However, nosocomial *C. perfringens* infections in patients who have not had previous antibiotic treatment have also been reported [18, 20].

**Staphylococcus aureus**

In the 1950s and 1960s, *S. aureus* was thought to be responsible for antibiotic-associated PMC. A few reports still suggest that *S. aureus* can cause AAD. Methicillin-resistant *S. aureus* (MRSA) was found in the feces of 10 patients with diarrhea after antimicrobial treatment. All stool specimens were negative for *C. difficile* and its toxins [21]. One untreated patient died of generalized MRSA infection. Nine patients were treated with antistaphylococcal drugs (bacitracin or vancomycin), and the feces were cleared of MRSA after treatment in eight patients. In five patients the diarrhea resolved after four days of antistaphylococcal treatment; however, another patient died on the fourth day of treatment [21].

In other studies MRSA could be isolated from the stool of patients with AAD, and the authors suggest that antibiotic treatment is a predisposing factor for MRSA-induced enterocolitis [22–24]. The validity of *S. aureus* as a cause of enterocolitis is controversial, but there are reports suggesting that *S. aureus* can cause enterocolitis, albeit rarely [3, 25].

**Acute Segmental Hemorrhagic Penicillin-Associated Colitis**

Acute segmental hemorrhagic colitis is a rare complication of oral treatment with penicillin or penicillin derivatives that was first described in 1978 [26]. Typical symptoms are acute hemorrhagic diarrhea and painful abdominal cramps starting after a mean duration of 4 days of oral penicillin therapy. The patients usually are negative for *C. difficile*. Colonoscopic findings include submucosal hemorrhage, diffuse mucosal edema, and (in some cases) erosions or ulcerations, mostly located in the colon, but pseudomembranes are not present [27–29]. Penicillin must be discontinued immediately.

Allergic vasculitis or hypersensitivity of the colonic mucosa was hypothesized to cause this disease, but recent studies suggest that *Klebsiella oxytoca* and its cytotoxin are involved [30–33]. All *K. oxytoca* strains were resistant to ampicillin [34], and in the acute phase of hemorrhagic colitis, abnormally high numbers of *K. oxytoca* (10^7 cfu per gram of feces) were found [35]. This suggests overgrowth of *K. oxytoca* during penicillin therapy.

A cytotoxin-producing strain was isolated from a patient with hemorrhagic diarrhea after amoxicillin therapy [30]. Both the toxin alone and the *Klebsiella* strain induced fluid accumulation in the colon and bloody fluid accumulation in the ileum in a rabbit intestinal-loop model. Damage to the ileal mucosa, but not to the colonic mucosa, was demonstrated histologically after luminal administration of cytotoxin. A non-toxin-producing strain of *K. oxytoca* had no effect on the intestinal loops [30].

**Drug-Resistant Salmonella Species**

Holmberg et al. reported 18 patients with diarrhea caused by multidrug-resistant *Salmonella newport* (resistant to ampicillin, carbenicillin, and tetracycline). The source of infection was contaminated beef from cattle fed with subtherapeutic doses of chlorotetacycline. Twelve patients had taken antibiotics (penicillin or amoxicillin) 24–48 hours before onset of the symptoms. It seems likely that these patients had asymptomatic infection with drug-resistant *S. newport* before they took antibiotics and that antibiotics selected the pathogenic drug-resistant *Salmonella* species [36]. This is the only report on *Salmonella* as a cause of AAD, and the condition seems to be very rare.

**Candida Species**

Overgrowth of *Candida* species in feces (≥10^5 cfu/mL) was demonstrated in seven of 24 patients (29%) with *C. difficile*–negative AAD. *Candida albicans* was found in the stool of six patients and *Candida tropicalis* in the stool of one patient. After discontinuation of antibiotic therapy, the *Candida* species counts fell to <10^4 cfu/mL and diarrhea resolved in two patients. The other 5 patients were successfully treated with oral nystatin while antibiotic therapy was continued. The mean age of these patients was 74 years.

Candidal overgrowth was not seen in any of the patients of a matched control group, which had also received antibiotics but had no diarrhea [37]. Significant fecal candidal overgrowth was reported in 67 of 175 pediatric patients with AAD (49%) [38] and in 9 of 41 adult patients with AAD (22%) [39]. In
another study, eight of 10 hospitalized patients had Candida-associated, predominantly secretory diarrhea after multiple antibiotic courses [40]. The yeast overgrowth is presumed to be due to suppression of the normal fecal flora by the antibiotics.

The mechanism by which Candida causes diarrhea is not fully understood. Candida can depress lactase activity in the rabbit intestine, which might lead to lactose intolerance [40]. Candida has also been shown to stimulate net secretion of water, sodium, and potassium into the jejunal lumen in rats. This effect has been hypothesized to be mediated by endotoxin-like substances [40, 41].

Risk factors for Candida-associated diarrhea, besides antibiotic therapy, are age, hospitalization, endocrine abnormalities, immune dysfunction, chemotherapy, neoplasm, and steroid therapy. Typical symptoms noted with Candida-associated diarrhea are abdominal pain, cramping, and rectal irritation [42]. In an autopsy study of cancer patients, invasive intestinal candidiasis was associated with ulcers, erosions, and pseudomembranes, but no evidence of diarrhea was noted prior to death [43]. Other investigators of immunosuppressed patients have reported invasive or disseminated candidiasis associated with gastrointestinal symptoms and diarrhea [44–46]. The association of Candida and diarrhea is still controversial, but a critical review of the literature supports the theory that Candida can cause diarrhea in selective clinical settings [42].

**Disturbances in the Function of the Normal Bacterial Flora**

**Colonic Carbohydrate Metabolism**

It has been suggested that in normal subjects, as much as 70 g of carbohydrates reaches the colon per day. The colon cannot absorb carbohydrates, but colonic bacteria metabolize carbohydrates as an energy source. Anaerobic bacterial metabolism of carbohydrates results in production of lactic acid and short-chain fatty acids (SCFAs) such as acetate, butyrate, and propionate [47]. The colon has a high capacity for absorption of SCFAs.

SCFA absorption is accompanied by the absorption of fluids and electrolytes [48]. A small proportion of these organic acids remains in the colon. Together with cations bound by the anionic nature of organic acids and with carbohydrates, the remaining SCFAs exert an osmotic effect [1]. In carbohydrate malabsorption, osmotic diarrhea is caused by intraluminal accumulation of organic acids, cations, and carbohydrates that overwhelm the metabolic capacity of the colonic flora [49].

Decreased bacterial carbohydrate metabolism due to antibiotics may result in functional disturbances of colonic mucosa. In the distal colon, the SCFA n-butyrate is an important source of energy for the mucosa through cellular oxidation [50, 51]. Reduction in SCFA production may deprive the colonic mucosa of an energy source, as demonstrated by the clinical model of “exclusion colitis” in patients with exclusion of distal parts of the colon from the fecal stream [52].

Various antibiotics have been shown to reduce colonic bacterial carbohydrate metabolism. However, the development of diarrhea seems to be dependent on the quantity of poorly absorbable dietary carbohydrates (dietary fibers, fructose, or sorbitol) in the food. An in vitro study simulating luminal contents of the proximal colon has demonstrated that clindamycin reduces anaerobes (Clostridium and Bacteroides species), decreases fecal carbohydrate metabolism, and decreases concentrations of SCFA [53]. Ampicillin reduces colonic bacterial carbohydrate fermentation, as shown by a decreased breath-hydrogen response and by the presence of carbohydrates in stool.

These functional changes contribute to the development of diarrhea, as indicated by an increase in frequency and stool weight in subjects who ingested a subdiarrheal dose of lactulose [54, 55]. Reduced colonic carbohydrate fermentation has also been shown to occur in healthy subjects following oral administration of ampicillin and metronidazole [56, 57]. Patients with diarrhea associated with pivampicillin, dicloxacillin, erythromycin, or ampicillin plus netilmicin had reduced fecal concentrations of SCFA. In the same study another group of patients who were treated with erythromycin, dicloxacillin, or a combination of ampicillin, netilmicin, and metronidazole also had reduced fecal concentrations of SCFA but did not develop diarrhea. However, monotherapy with penicillin or pivampicillin did not reduce fecal SCFA concentrations or result in diarrhea [58].

In another study, SCFA concentrations were measured in the stool of 15 liver-transplanted patients who received bowel flora-suppressing antibiotics consisting of cefuroxime, tobramycin, and nystatin. Thirteen of them developed *C. difficile*–negative diarrhea, and the levels of SCFA in the stools were very low, possibly because of nearly complete suppression of the colonic bacterial fermentation. The diarrhea resolved before cessation of antibiotic therapy and normalization of the fecal SCFA levels [59].

Discrepancies between suppression of carbohydrate metabolism and manifestation of diarrhea [58, 59] suggest that disturbed carbohydrate metabolism was not the only mechanism responsible for diarrhea. A possible reason for the observed discrepancies may be an adaptive increase in colonic transit time. Hammer et al. have shown that colonic transit time in osmotic diarrhea increases in the descending colon [60]. This may provide more time for absorption of SCFA, water, and electrolytes.

**Decreased Metabolism of Bile Acids**

Primary bile acids that escape absorption in the small bowel are deconjugated and then dehydroxylated to secondary bile acids by bacteria in the colon (figure 1). Dihydroxy bile acids, such as the primary bile acid chenodeoxycholic acid and the secondary bile acid deoxycholic acid, are potent colonic secre-
Figure 1. The primary bile acids are dehydroxylated by colonic anaerobic bacteria to secondary bile acids. This step can be inhibited by antibiotics.

Contractions of rabbit and human duodenal smooth-muscle strips [65] but inhibits peristaltic motility in the guinea pig ileum [66]. Erythromycin, like motilin, induces a specific pattern of contractions called interdigestive migrating contractions in dogs [67]. Erythromycin also raises the plasma concentration of motilin in dogs.

Patients with cholesterol gallstones who had excessively elevated levels of deoxycholic acid (secondary bile acid) in the serum were treated with ampicillin for 5 weeks. After treatment a significant reduction of the postprandial deoxycholic acid serum level was shown, which indicated reduced 7α-dehydroxylation by colonic microorganisms. There was a trend toward an increase in serum levels of Chenodeoxycholic acid, although this was not statistically significant. Fecal levels of the bile acid composition were not measured in this study, and stool habits were not reported [64].

Data on the possible role of decreased bile acid dehydroxylation for AAD are sparse, but Hofmann et al. reported four patients who had diarrhea after receiving clindamycin, in whose stool primary bile acids were predominant [61].

The effects of antibiotics in decreasing carbohydrate metabolism and dehydroxylation of bile acids may be synergistic because decreased carbohydrate metabolism results in higher fecal pH, which increases the solubility of dihydroxy bile acids [59].

Direct Effects of Antibiotics

Erythromycin

Erythromycin has been shown to act as a motilin receptor agonist [65]. Motilin is a gastrointestinal peptide that stimulates contraction in the antrum and duodenum. Erythromycin induces contractions of rabbit and human duodenal smooth-muscle strips [65] but inhibits peristaltic motility in the guinea pig ileum [66]. Erythromycin, like motilin, induces a specific pattern of contractions called interdigestive migrating contractions in dogs [67]. Erythromycin also raises the plasma concentration of motilin in dogs.

Other erythromycin-induced motor effects, such as retrograde giant contractions, giant migrating contractions, and intestinal amyogenesis in dogs, cannot be explained by the motilin-agonistic effect. It has been suggested that these effects induce symptoms such as diarrhea, abdominal cramping, and vomiting after erythromycin administration [68]. Although these erythromycin effects are found mainly in the upper gastrointestinal tract [69], acceleration of gastric emptying may also cause diarrhea, as has been shown in patients with functional diarrhea [70].

Amoxicillin/Clavulanate

The effects of amoxicillin/clavulanate on intestinal motility were examined in six male volunteers. Amoxicillin/clavulanate increased nocturnal but not diurnal motility of the small intestine, as measured by duodeno-jejunal manometry. Two of the volunteers suffered from watery diarrhea after administration of amoxicillin/clavulanate. However, this study yielded no conclusive evidence that a change in motility pattern is responsible for the abdominal effects.

From this study it also remains unclear whether the effects were due to the combination or to an individual substance [71]. It seems more likely that the discussed intestinal effects are due to clavulanate, since a prolonged mouth-to-cecum transit time after administration of ampicillin could be demonstrated in one study [54], and other authors showed only a minimum or no effect of ampicillin on intestinal motility [72, 73].
data about the mechanism by which amoxicillin/clavulanate induces AAD are sparse, and further studies are necessary to elucidate this association.

Neomycin

Orally administered neomycin at a dosage of 3–12 g/day causes gastrointestinal symptoms and malabsorption [74]. Seven to 11 days following oral administration of neomycin (6 g/day) in healthy subjects, morphologic alterations of the intestinal mucosa were noted, such as shortening of intestinal villi; infiltration of the lamina propria with plasma cells, eosinophils, and pigment-containing macrophages; damage of the epithelial crypt cells; and increased mitosis. The test subjects developed symptoms and had steatorrhea, decreased serum levels of cholesterol and carotene, and reduced urinary excretion of Co60-labeled vitamin B12 [74].

Diagnostic Approach to Patients with Antibiotic-Associated Diarrhea

Patients with severe symptoms (stool frequency of greater than three per day, watery or bloody stool, abdominal cramping, dehydration, stool leukocytes, peripheral leukocytosis, hypalbuminemia, or fever) require immediate diagnostic workup [2, 4] (figure 2).

The tissue culture test for toxin B is still considered the “gold standard” for the diagnosis of CDAD and has a high positive and negative predictive value [3, 75]. EIAs for toxins A and B are performed more rapidly than the tissue culture assay. The sensitivity of the EIA ranged widely when evaluated in different laboratories. Therefore, a negative EIA for toxins A and B does not rule out the diagnosis of CDAD. However, the specificity of the EIA was generally very good [3].

Stool cultures alone are not sufficient for the diagnosis of CDAD. They may be false-positive because of coincidental carriage (where C. difficile is not the cause of diarrhea) and because C. difficile can be nontoxicigenic [3, 4]. The latex agglutination test, which has formerly been believed to detect toxin A, detects glutamate dehydrogenase and cross-reacts with proteins from nontoxicogenic strains of C. difficile and from non-pathogenic clostridia. Compared with the EIA, the latex agglutination test is not as specific but is similarly sensitive. Positive results should be confirmed by another test.

Because none of these tests, when performed alone, is sensitive and specific enough for the definitive diagnosis of CDAD, a combination of tests should be considered. Many laboratories perform a rapid test (e.g., EIA or latex test) plus a second specific test for the presence of the toxin or the organism (tissue culture test or culture for toxigenic C. difficile). Stool specimens have to be tested immediately or kept on ice after passage, because the toxins are inactivated rapidly by enzymes present in the feces. Freezing may decrease the toxin titers [76, 77]. For patients with severe diarrhea and risk factors for C. difﬁcile-associated diarrhoea, quantitative tests for Candida in stool should be performed. For the diagnosis of Candida-associated diarrhoea, ﬁndings of ≥10⁷ cfu/mL and mycelial forms in the stool are required [37, 42].

If stools are negative for C. difﬁcile toxins and for candidal overgrowth in patients with severe symptoms, S. aureus, C. perfringens, Klebsiella, Salmonella or other conventional enteric pathogens should be considered as rare but possible causative agents [3] (figure 2).

Colonoscopy can be considered for patients with severe AAD who are negative for C. difﬁcile toxin. Colonoscopy can detect the typical changes of pseudomembranous colitis, segmental hemorrhagic colitis, or other causes of diarrhoea-like ulcerative colitis or diverticulitis. Sigmoidoscopy cannot rule out PMC and segmental hemorrhagic colitis because the rectum and sigmoid can be spared [78]. Morphologically evident PMC is caused by C. difﬁcile in most cases [79] but can rarely occur with chemotherapy, leukopenia, hematologic malignancies, intestinal obstruction, ischemic colitis, Crohn’s disease, cardiovascular diseases, shock, spinal fracture, exposure to certain agents like diclofenac or heavy metal (poisoning), Escherichia coli O157-H7 infection (hemolytic-uremic syndrome), and shigellosis, as well as Plesiomonas shigelloides, cytomegalo virus, and other severe infections [80, 81].

Disturbances of carbohydrate metabolism or bile acid metabolism can be detected by analysis of fecal carbohydrates, SCFAs, or bile acids, although availability of these tests is limited to laboratories with a special research interest. Because of the self-limited nature of diarrhoea caused by these functional disturbances, no special effort in routine diagnostic evaluations should be made to detect these changes. Although fecal pH is usually lower than 5.5 in carbohydrate-induced diarrhoea, the suppression of bacterial carbohydrate metabolism by antibiotics makes it unlikely that fecal pH will be low in antibiotic-associated disturbances of colonic carbohydrate metabolism resulting in diarrhoea [49].

Prophylaxis

The risk of diarrhoea caused by disturbances of carbohydrate metabolism can be reduced by avoidance of poorly absorbable carbohydrates, such as fructose and sorbitol, or metabolizable dietary fibers, like pectin and guar gum. Fructose and sorbitol are present in fruits and also are used as sweeteners in soft drinks, candy, and chewing gum. Metabolizable fibers are present in vegetables such as carrots, cabbage, and peas [82]. Ingestion of milk products should be avoided by patients with documented lactose malabsorption or in populations with a high prevalence of lactose malabsorption, such as descendants of African, Asian, and Mediterranean populations. Tube feeding is associated with an increased risk of AAD, most likely because of carbohydrate content [83].
Various probiotics have been tested for the prevention of antibiotic-associated diarrhea. *S. boulardii* has been shown to reduce the risk of developing diarrhea associated with the use of various antibiotics, although the risk for acquiring *C. difficile* was not reduced [83]. The mechanism by which this prophylactic effect is achieved is unknown. Antagonistic activity against bacterial pathogens and *Candida* species as well as increased disaccharidase activity of the intestinal mucosa are suspected to play a role [83]. *S. boulardii* is commercially available in some European countries (Perenterol, Thiemann, Waltrop, Germany) but not in the United States.

In a multicenter double-blind, placebo-controlled trial, lactic acid–producing *Enterococcus* SF68 was effective in reducing the incidence of AAD [84]. *Enterococcus* SF68 is available in Europe as Bioflorin (Ab Cernelle, Engelholm, Sweden); the daily cost of therapy is \$1 (U.S.).

**Treatment**

Discontinuation of antibiotic therapy withdraws the offending agents but is often not appropriate if the indication for such therapy was correct. An alternative is to change to antibiotics that do not belong to the high-risk groups for the induction of CDAD, such as quinolones, sulfonamides, parenteral aminoglycosides, co-trimoxazole, metronidazole, or tetracycline [6].

Severe cases of *C. difficile*–positive diarrhea require oral antibiotic treatment. Vancomycin (125 mg four times daily), metronidazole (250 mg three times daily), bacitracin (25,000 units four times daily), teicoplanin (200 mg daily), or fusidic acid (500 mg once daily) can be used for a 7–14-day treatment course [2, 4, 85, 86]. Teicoplanin and fusidic acid are currently not available in the United States.

Vancomycin is associated with emerging resistance in enterococci and staphylococci and is 20 times more costly than metronidazole, which is the least expensive alternative for treating *C. difficile* infection. Metronidazole is suggested as the first-line drug for the treatment of *C. difficile* infection. Metronidazole, vancomycin, teicoplanin, fusidic acid, and bacitracin have similar initial therapeutic benefits; however, different relapse rates have been reported. Teicoplanin is associated with the lowest relapse rate but is the most expensive for a treatment regimen.
In a recent study, clinical symptoms recurred in 7% of patients using teicoplanin, 16% using metronidazole, 16% using vancomycin, and 28% using fusidic acid [85]. A relapse can be treated with a second course of the same antibiotic or with one of the other antibiotics. *S. boulardii* has been shown to be an effective and safe adjunct therapy in relapses [87]. Antibiotic treatment can be followed by use of *Lactobacillus* (1–2 g daily) for 4 weeks [4, 88]. If the patient has no diarrhea or if the diarrhea subsides after discontinuation of the inducing antibiotics, treatment of *C. difficile* with specific antibiotics is not recommended [4, 5, 6].

Single rooms with private bathrooms should be provided whenever possible for patients with *C. difficile* diarrhea, at least until the diarrhea has stopped [3]. The use of gloves and hand-washing between contacts with patients is mandatory [3].

Candidal overgrowth can be treated with nystatin (250,000 to 1,000,000 U orally three to four times daily), and response to antifungal therapy can be expected within 3–7 days [37, 40, 42].

Patients with mild diarrhea not caused by *C. difficile* may not need any specific treatment. Particularly in children and the elderly, lost fluids and electrolytes have to be substituted. Poorly absorbable dietary carbohydrates should be avoided. In a small study, yogurt containing *Bifidobacterium longum* has been shown to reduce erythromycin-induced diarrhea [89]. Another study suggests that a *Lactobacillus* preparation reduces ampicillin-induced diarrhea [90].

Acknowledgments

The authors thank D. Bruckner, Sc.D., and B. Bearson, Ph.D. (both of UCLA), as well as K. Tamussino, M.D. (of Graz), for their critical review of this manuscript.

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