Evidence suggests that drug-induced gastrointestinal (GI) injury is common, with a wide range of medications implicated, but an accurate estimate of the incidence of adverse GI reactions to drugs is difficult to obtain. Data from the United States (Food and Drug administration) show that 18 percent of all adverse reactions reported to that agency were related to the GI tract. Diarrheal episodes are classically distinguished into acute and chronic (or persistent) based on their duration. Acute diarrhea is thus defined as an episode that has an acute onset and lasts no longer than 14 days; chronic or persistent diarrhea is defined as an episode that lasts longer than 14 days. The distinction, supported by the World Health Organization (WHO), has implications not only for classification and epidemiological studies but also from a practical standpoint because protracted diarrhea often has a different set of causes, poses different problems of management, and has a different prognosis.

Drugs can induce intestinal injury or dysfunction through single or multiple mechanisms. The more common mechanisms of drug induced bowel injury are listed below. This discussion covers antibiotic agents that have been associated with some effect.

**ADVERSE EFFECTS OF DRUGS ON THE GASTROINTESTINAL TRACT**

- Suppression of cell turnover
- Mucosal inflammation
- Malabsorption
- Altered enteric flora
- Intestinal pseudo-obstruction
- Ischemia
- Hemorrhage
Causes

Although infectious agents are by far the most common cause for sporadic or endemic episodes of acute diarrhea, one should not dismiss other causes that can lead to the same presentation.

Causes of diarrhea with acute onset include the following:

- Infections
  - Enteric infections (including food poisoning
  - Extraintestinal infections

- Drug-induced
  - Antibiotic-associated
  - Laxatives
  - Other drugs

- Food allergies or intolerances
  - Cow’s milk protein allergy
  - Soy protein allergy
  - Multiple food allergies
  - Methylxanthines (caffeine, theophylline)

- Disorders of digestive/absorptive processes
  - Glucose-galactose malabsorption
  - Sucrase-isomaltase deficiency
  - Late-onset (adult-type) hypolactasia, resulting in lactose intolerance

- Surgical conditions
  - Acute appendicitis
  - Intussusception

ANTIBIOTIC-ASSOCIATED DIARRHEA

Diarrhea is a frequent adverse effect of antibiotics, occurring in between 5 percent and 25 percent of cases, depending on the antibiotics in use. Antibiotic-associated diarrhea (AAD) can be divided broadly into 2 types: uncomplicated diarrhea (not associated with *Clostridium difficile* infection) and *Clostridium difficile* disease, the best known antibiotic-associated diarrhea, accounts for only 10 to 20 percent of all cases of AAD and is discussed below. Antibiotics can cause diarrhea by at least three major mechanisms: disturbances of enteric flora, altered metabolic impact of these flora, and a direct effect of the antibiotic on the intestine. Generally, broad-spectrum antibiotics disturb flora more than those with a
narrow spectrum, and antibiotics that are poorly absorbed from the colon or are secreted in bile (clindamycin, ceftriaxone or cefixime) are associated with relatively high rates of AAD. Short chain fatty acid (SCFA) metabolism is also important in the pathogenesis of AAD. Carbohydrates that reach the colon are metabolized by colonic anaerobic bacteria to lactic acid and SCFA which are then absorbed by the colon and serve as an energy source, while driving absorption of water and electrolytes. Diarrhea in this setting can be due to the lack of SCFA driven water absorption or an osmotic diarrhea, depending on the amount of poorly absorbable carbohydrates (dietary fibers, fructose, sorbitol) in the diet. Broad spectrum antibiotics that disturb normal flora are particularly associated with disturbances of SCFA synthesis in the colon. In this situation, diarrhea is self limiting, and resolves despite continuing low SCFA levels, suggesting an adaptive process of water absorption in the colon. Bile acid deconjugation by colonic bacteria is also disturbed by broad spectrum antibiotics, and an increase in the levels of these bile acids in the colonic lumen may contribute to the development of diarrhea. In addition, several antibiotics including erythromycin, amoxicillen/clavulanate, and neomycin can have a direct impact on the gut. Erythromycin is a motilin receptor agonist that stimulates contraction in the antrum and duodenum. Erythromycin can alter intestinal motility via a non motilin mechanism, which may account for the diarrhea, abdominal cramping, and vomiting associated with its use. Amoxycillin/clavulanate often causes diarrhea, as it also increases small intestinal motility. These effects are probably secondary to clavulanate, as amoxicillin alone does not alter intestinal motility. Neomycin, at a dosage of 3 to 12 grams per day, causes GI symptoms and malabsorption. Morphologic changes in the small intestine have been demonstrated with neomycin as described above; they include blunting of intestinal villi, crypt cell damage, increased crypt mitosis, and infiltration of the lamina propria with plasma cells, eosinophils and macrophages.

Treatment of AAD involves discontinuation of the offending antibiotic, if that is possible, or choosing an antibiotic from a low risk group, such as the quinalones, sulfonamides, parenteral aminoglycosides, cotrimoxazole, metronidazole, or tetracyline (in the older patient). Oral nystatin may be useful for the treatment of antibiotic associated Candida.

Probiotic agents may be useful in simple antibiotic associated diarrhea and in Clostridium difficile infection. Lactobacillus casei GG has been found to reduce the duration of simple and Clostridium difficile antibiotic associated diarrhea, although larger studies are needed to confirm these findings.

CLOSTRIDIUM DIFFICILE

Even though Clostridium difficile is now recognized as the single most common cause of bacterial diarrhea in hospitalized patients, its role as a pathogen had not been established as recently as the late 1970s. Clostridium difficile has the ability to become established in the gastrointestinal tract once the natural microflora have been modified by antibiotic therapy. The organism causes intestinal disease ranging from mild diarrhea to fatal pseudomembranous colitis (PMC). While C. difficile is associated with almost all cases of PMC, only 25 percent of antibiotic associated diarrheas are due to this pathogen. Clostridium difficile spreads from patient to patient and tends to persist in the environment because of the formation of spores. The micro-organism is not only present in the infected
patient and soiled linens but can be isolated from bookshelves, curtains, and floors of rooms of infected patients where it can persist for as long as 5 months. The organism is spread primarily by health care workers; up to 60 percent of personnel attending patients infected with C. difficile in one study had the organism on their hands. Several outbreaks of C. difficile infection have been reported in the United States and throughout the world, and the incidence continues to rise. Whether this increase represents a true increment or represents an increased awareness of the disease is not clear at this stage.

Infections with C. Difficile range in severity from asymptomatic forms to clinical syndromes, such as severe diarrhea, PMC, and toxic megacolon, and can even lead to death. The onset of symptomatic forms usually begins several days after starting antibiotic therapy up to 2 months following cessation of treatment. Diarrhea and abdominal cramps are usually the first symptoms, followed by the development of fever and chills in severe cases.

Diagnosis and Treatment.

Mild forms of colitis, with bloody stools and mucus, particularly if they are preceded by antibiotic treatment, should be considered suspicious for C. difficile infection. Clinical microbiologists face an array of methods and commercial tests when considering what procedure to use for the detection of C. difficile and its toxins. Culturing of the organism, latex agglutination, tissue culture assay, and enzyme-linked immunosorbent assay (ELISA) are all used as aids for the diagnosis of C. difficile infection. In many instances, C. difficile disease is self-limiting, and the patient may respond simply to the withdrawal of the offending antibiotic. In more severe forms, particularly if complicated by PMC, antibiotic treatment with either oral vancomycin (5 to 10 mg/kg, maximum 500 mg, given every 6 hours for 7 days) or metronidazole (5 to 10 mg/kg per day, maximum 500 mg, given every 8 hours for 7 days) is recommended. Despite pharmacologic treatment, the rate of relapse is significant (up to 40 to 50% of cases). In these complicated patients, the use of probiotics, particularly Lactobacillus GG and Saccharomyces boulardii, has been associated with a significant eradication of C. difficile and a substantial decrease of recurrence of the infection.

CONCLUSION

Despite the tremendous increase in knowledge of bacterial pathogenesis experienced during the past decade, gastrointestinal infections remain a major cause of disease and death, particularly in the pediatric population of the Third World. Widespread travel to developing countries has brought diseases transmitted by contaminated food and water to immunologically naive populations. However, the widespread use of oral rehydration solutions has revolutionized the way this plague is being fought, and more positive results are anticipated from the development of safe enteric
vaccines. Some probiotic formulations appear to be safe and modestly effective for preventing antibiotic-associated diarrhea. However, many unanswered questions remain regarding the use of probiotics for this indication. There are no evidence-based guidelines or consensus statements regarding probiotics for this use. However, the American Academy of Pediatrics issued a Clinical Report on the use of probiotics and prebiotics in children in 2010 that discussed a wide variety of conditions for which these agents have been used, including antibiotic-associated diarrhea. Additionally, the optimal dose, duration, and mode of delivery for probiotics has not been fully elucidated.

Although various probiotics are marketed, only those formulations evaluated in controlled clinical trials should be recommended. Patient selection criteria would at a minimum include immunocompetent patients with a history of antibiotic-associated diarrhea. Further studies should delineate which patients benefit most from probiotics.

References
