Antibiotic-Associated Diarrhea, *Clostridium difficile*-Associated Diarrhea and Colitis

ANTIBIOTIC-ASSOCIATED DIARRHEA

- Disturbance of the normal colonic microflora
- Leading to alterations in bacterial degradation of nonabsorbed carbohydrates and bile salts
- Multiple mechanisms

Differences between Antibiotic-Associated Diarrhea from *Clostridium difficile* Infection and from Other Causes

CHARACTERISTIC	AAD FROM *C. DIFFICILE*	INFECTION AAD FROM OTHER CAUSES
Most commonly implicated antibiotics	Clindamycin, cephalosporins, penicillins, fluoroquinolones	Clindamycin, cephalosporins, ampicillin, or amoxicillin-clavulanate
History	Usually no history of antibiotic intolerance	History of diarrhea with antibiotic therapy is common
Clinical Features		
Diarrhea	May be florid; evidence of colitis with cramps, fever, and fecal leukocytes is common	Usually moderate in severity (nuisance diarrhea) without evidence of colitis

Findings on CT or colonoscopy	Evidence of colitis is common; pseudomembranes often are present	Usually normal
Complications	Hypoalbuminemia, anasarca, toxic megacolon; relapse can occur after treatment with metronidazole or vancomycin	Usually none except occasional cases of volume depletion
Results of assay for *C. difficile* toxin	Positive	Negative
Epidemiologic pattern	May be epidemic or endemic in hospitals or long-term care facilities	Sporadic
Treatment		
Withdrawal of implicated antibiotic	Condition can resolve but often persists or progresses	Condition usually resolves
Antiperistaltic agents	Contraindicated	Often useful
Oral metronidazole or vancomycin	Prompt response	Not indicated

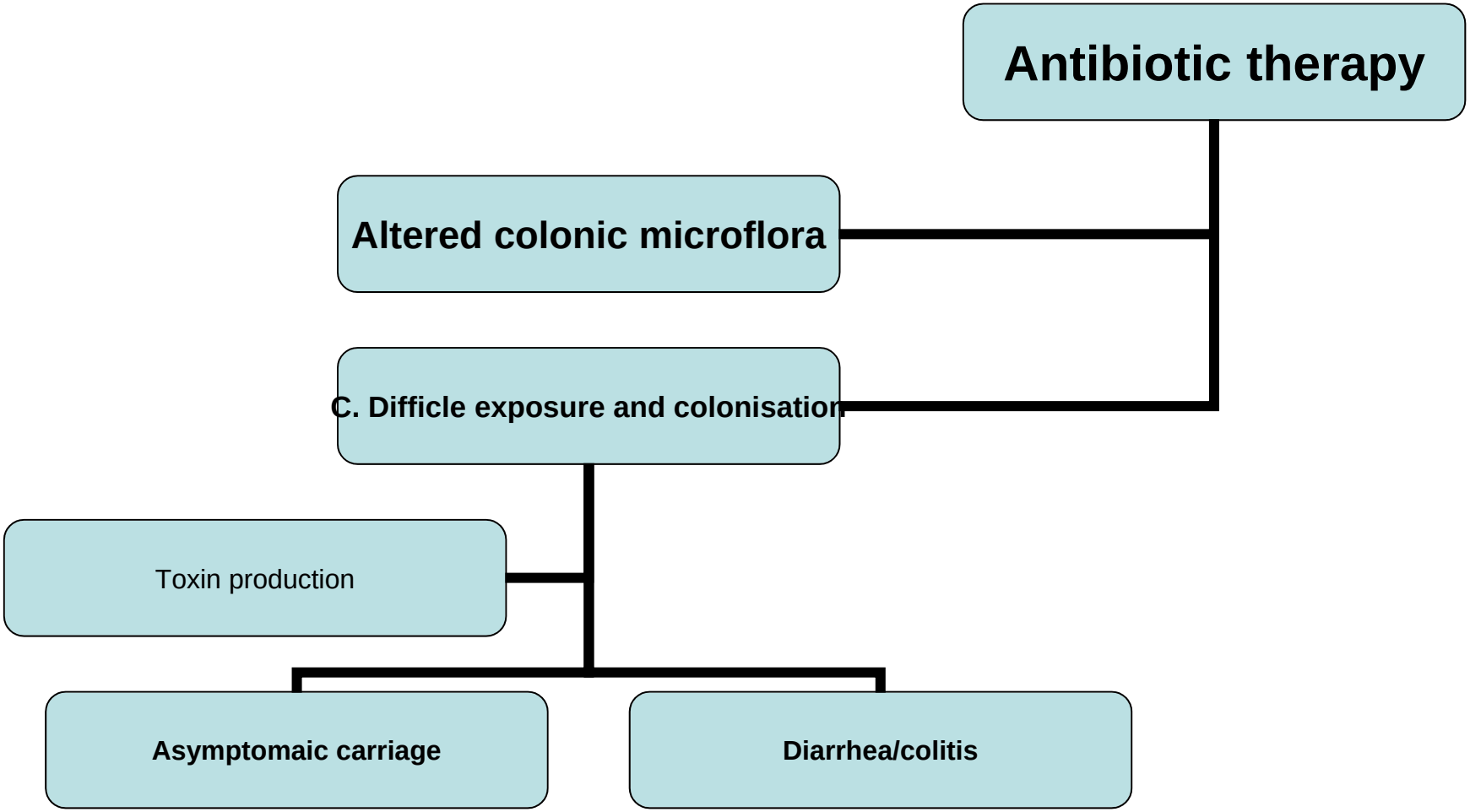
TREATMENT (of simple AAD)

- Discontinuing the inciting antibiotic
- Antiperistaltic agents (e.g., loperamide)
- Probiotic agents (treatment and prevention)

CLOSTRIDIUM DIFFICILE-ASSOCIATED DIARRHEA AND COLITIS

- *C. difficile*, an anaerobic, Gram-positive, spore-forming, toxigenic bacillus

PATHOGENESIS



Antimicrobial Agents That Predispose to *Clostridium difficile*-Associated Diarrhea and Colitis

Most Frequently

- Ampicillin and amoxicillin
- Cephalosporins
- Clindamycin
- Fluoroquinolones

Less Frequently

- Macrolides (including erythromycin)
- Other penicillins
- Sulfonamides
- Trimethoprim/sulfamethoxazole

Rarely or Never

- Bacitracin
- Carbapenems
- Chloramphenicol
- Daptomycin
- Metronidazole
- Parenteral aminoglycosides
- Rifampin
- Rifaximin
- Tetracyclines
- Tigecycline
- Vancomycin

Hospital Epidemiology of *Clostridium difficile* Infection

- Chronic intestinal carriage rates of *C. difficile* in healthy adults are low (0% to 3% in American and European populations)
- In contrast, hospital inpatients treated with antibiotics have reported colonization rates of 10% to 21%

Practice Guidelines for the Prevention of *Clostridium difficile* Diarrhea

- Limit the use of antimicrobial drugs
- Wash hands between contacts with all patients
- Use enteric (stool) isolation precautions for patients with *C. difficile* diarrhea
- Wear gloves when contacting patients with *C. difficile* diarrhea or their environment
- Disinfect objects contaminated with *C. difficile* with sodium hypochlorite, alkaline glutaraldehyde, or ethylene oxide
- Educate the medical, nursing, and other appropriate staff members about the disease and its epidemiology

Toxins

- Toxin A
- Toxin B
- Toxin B is a major virulence factor in human disease.
- A minority (less than 10%) of *C. difficile* clinical isolates produce the third toxin—binary toxin
- The NAP-1/BI or epidemic strain is binary toxin positive, however, thereby raising renewed suspicion that this toxin might enhance the effects of toxins A and B.

Other Risk Factors for *Clostridium difficile* Infection

- Increasing age and
- Use of a nasogastric tube
- Gastrointestinal procedures
- Intensive care unit stay
- Length of hospital stay
- HIV
- Patients with inflammatory bowel disease (IBD)
- The role of acid suppression in *C. difficile* infection is unclear

CLINICAL FEATURES

Range -

Asymptomatic carriage

Mild or moderate diarrhea

Life-threatening pseudomembranous colitis.

DIAGNOSIS

- History of recent or current antimicrobial therapy, development of diarrhea or other evidence of acute colitis
- Tests for *Clostridium difficile* Infection
- Testing of solid or formed stools for *C. difficile* toxin is not recommended because only patients with diarrhea require treatment

- Cytotoxin assay
- Enzyme immunoassay

Sigmoidoscopy and Colonoscopy

- Neither sigmoidoscopy nor colonoscopy is required for diagnosis in most patients
- Endoscopy is helpful, however, when the diagnosis is in doubt or when disease severity demands rapid diagnosis
- The finding of colonic pseudomembranes in a patient with AAD is virtually pathognomonic for *C. difficile* colitis

Pseudomembranes appear as yellow, gray, or white plaques 2 to 5 mm in diameter, and in some areas they can coalesce to cover large portions of the mucosal surface

Histologic image of an endoscopic biopsy specimen from a patient with pseudomembranous colitis showing a summit or volcano lesion. Focal ulceration of the colonic mucosa is evident (*lower arrow*), with exudation of a pseudomembrane made up of inflammatory cells, fibrin, and necrotic debris (*upper arrow*

TREATMENT

- Discontinue the inciting antibiotic if possible
- Confirm the diagnosis
- Prescribe specific therapy if symptoms are moderately severe or persistent:

  Metronidazole orally for 10-14 days (drug of choice for mild-to-moderate disease)

  Vancomycin orally for 10-14 days if
  Diarrhea and colitis are severe
  Diarrhea does not improve during metronidazole treatment
  Patient cannot tolerate metronidazole
  Patient is pregnant or younger than 10 yr of age

Approach to Management of Recurrent *Clostridium difficile* Colitis

First Relapse

Confirm diagnosis
Symptomatic treatment if symptoms are mild
10- to 14-day course of metronidazole if symptoms are moderate
10- to 14-day course of vancomycin if symptoms are severe

Second Relapse

Confirm diagnosis
Vancomycin-taper regimen 125 mg every 6 hr for 10 to 14 days
125 mg every 12 hr for the next seven days
125 mg daily for the next seven days
125 mg every other day for the next eight days
125 mg every three days for the next 15 days

Third Relapse

10- to 14-day course of vancomycin followed by a 14-day course of oral rifaximin 400 mg twice a day

Additional Options

Therapy with microorganisms, e.g., bacteriotherapy, *Saccharomyces boulardii,* or *Lactobacillus* spp. in combination with and following metronidazole or vancomycin

or

Intravenous immunoglobulin 400 mg/kg two or three times with a three-week interval between doses

or

Vancomycin 125 mg every 6 hr plus cholestyramine 4 g twice daily*

or

Vancomycin 125 mg every 6 hr and rifampicin 600 mg twice daily

Bacteriotherapy

- Stool transplantation