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

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>AAD FROM C. DIFFICILE</th>
<th>INFECTION AAD FROM OTHER CAUSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most commonly implicated antibiotics</td>
<td>Clindamycin, cephalosporins, penicillins, fluoroquinolones</td>
<td>Clindamycin, cephalosporins, ampicillin, or amoxicillin-clavulanate</td>
</tr>
<tr>
<td>History</td>
<td>Usually no history of antibiotic intolerance</td>
<td>History of diarrhea with antibiotic therapy is common</td>
</tr>
<tr>
<td>Clinical Features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>May be florid; evidence of colitis with cramps, fever, and fecal leukocytes is common</td>
<td>Usually moderate in severity (nuisance diarrhea) without evidence of colitis</td>
</tr>
<tr>
<td>Findings on CT or colonoscopy</td>
<td>Evidence of colitis is common; pseudomembranes often are present</td>
<td>Usually normal</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------------------------------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Complications</td>
<td>Hypoalbuminemia, anasarca, toxic megacolon; relapse can occur after treatment with metronidazole or vancomycin</td>
<td>Usually none except occasional cases of volume depletion</td>
</tr>
<tr>
<td>Results of assay for <em>C. difficile</em> toxin</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Epidemiologic pattern</td>
<td>May be epidemic or endemic in hospitals or long-term care facilities</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrawal of implicated antibiotic</td>
<td>Condition can resolve but often persists or progresses</td>
<td>Condition usually resolves</td>
</tr>
<tr>
<td>Antiperistaltic agents</td>
<td>Contraindicated</td>
<td>Often useful</td>
</tr>
<tr>
<td>Oral metronidazole or vancomycin</td>
<td>Prompt response</td>
<td>Not indicated</td>
</tr>
</tbody>
</table>
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

Antibiotic therapy

- Altered colonic microflora
  - C. Difficile exposure and colonisation
    - Toxin production
      - Asymptomatic carriage
      - Diarrhea/colitis
Antimicrobial Agents That Predispose to *Clostridium difficile*-Associated Diarrhea and Colitis

<table>
<thead>
<tr>
<th>Most Frequently</th>
<th>Rarely or Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin and amoxicillin</td>
<td>Bacitracin</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Carbapenems</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Daptomycin</td>
</tr>
<tr>
<td></td>
<td>Metronidazole</td>
</tr>
<tr>
<td></td>
<td>Parenteral aminoglycosides</td>
</tr>
<tr>
<td></td>
<td>Rifampin</td>
</tr>
<tr>
<td></td>
<td>Rifaximin</td>
</tr>
<tr>
<td></td>
<td>Tetracyclines</td>
</tr>
<tr>
<td></td>
<td>Tigecycline</td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Less Frequently</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrolides (including erythromycin)</td>
<td></td>
</tr>
<tr>
<td>Other penicillins</td>
<td></td>
</tr>
<tr>
<td>Sulfonamides</td>
<td></td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td></td>
</tr>
</tbody>
</table>
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