Clostridium difficile: Pathogenesis and Host Response

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Pathogenesis of *Clostridium difficile* associated diarrhea (CDAD)

Antibiotic therapy

Disturbed colonic microflora

*C. difficile* exposure & colonization

Toxin A & Toxin B

Diarrhea & colitis
Pathogenesis of *Clostridium difficile* associated diarrhea (CDAD)

Antibiotic therapy

Disrupt “colonization resistance” of colonic microflora
• Antibiotic susceptibility of *C. difficile*
• Pharmacokinetics (colonic luminal concentrations)
• Effect on colonic microflora (colonization resistance)
### Antimicrobial agents that induce C. difficile-associated diarrhea and colitis

<table>
<thead>
<tr>
<th>Frequent</th>
<th>Infrequent</th>
<th>Rare</th>
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<tbody>
<tr>
<td>Ampicillin/amoxicillin</td>
<td>Chloramphenicol</td>
<td>Metronidazole</td>
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<tr>
<td>Cephalosporins</td>
<td>Macrolide</td>
<td>Parenteral aminoglycoside</td>
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<tr>
<td>Clindamycin</td>
<td>Sulfonamide</td>
<td>Vancomycin</td>
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<tr>
<td>Quinolones</td>
<td>Tetracycline</td>
<td>Trimethoprim</td>
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- Cytotoxic chemotherapy
- Colon preparation
- IBD (esp. Ulcerative colitis)

Adapted from Kelly et. al. NEJM 1994;330:257
Onset of *Clostridium difficile* associated diarrhea

- **> 80%** During antibiotic treatment  
  (typically after 4 - 5 days of therapy)

- **< 20%** After inciting antibiotic discontinued  
  most within 4 weeks  
  almost all within 12 weeks
Non-antibiotic associated *Clostridium difficile* induced diarrhea

- **Nosocomial:** Very rare

### Community acquired CDAD

- Less common than nosocomial
- Undocumented Abx use in community-based studies? **versus**
- “Spontaneous” CDAD more evident?

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JID 1994, 169:127  
JAMA 2005, 294:2989
Pathogenesis of *Clostridium difficile* associated diarrhea (CDAD)

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Disturbed colonic microflora

*C. difficile* exposure & colonization
**Clostridium difficile:**

**Environmental sources**

- **Hospital:**
  - Linens, toilet, bathroom floor, telephone

- **Personnel:**
  - Hands, fingernails, rings, stethoscopes

- **Home:**
  - Toilet, infant’s room, diaper pail, backyard

- **Other:**
  - Infants, adult carriers, animals
Hospital-acquired 28 (10%)

Colonized on admission 19 (7%)

Colonized on admission 18 (7%)

Hospital-acquired 19 (7%)

Cases 47 (17%)

Colonized by C. difficile 84 (31%)

Carriers 37 (14%)

Hospital patients (Acute medical ward) LOS > 2 days Receiving antibiotic

540 evaluated 311 eligible

271 enrolled

CDAD rate: (Jan to Jun) 7 per 1,000 admissions


Nosocomial C. difficile associated diarrhea and asymptomatic carriage are common
Pathogenesis of *Clostridium difficile* associated diarrhea (CDAD)

- Antibiotic therapy
- Disturbed colonic microflora
  - *C. difficile* exposure & colonization
    - Toxin A & Toxin B
**Clostridium difficile** toxins: Is A=B?

**Toxin A**
- “The Enterotoxin”
  - Enterotoxic to animal intestine (>>) toxin B
  - Toxin A immunization protective in animals (toxin B not)

**Toxin B**
- Not an enterotoxin?
  - In animals - correct
  - BUT: Enterotoxic in humans!
    - Colonic explants
    - Intestinal xenografts
    - ToxA-/ToxB+ strains

- Toxin A important
- Toxin B probably also important
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Diarrhea & colitis
CDAD: Host factors

- Age
- Co-morbidity / disease severity
- Immune response
  - Innate e.g. IL-8 SNPs
  - Adaptive e.g. Anti-toxin IgG response
C. difficile toxin-induced Pseudomembranous colitis
Histopathology of pseudomembranous colitis

“Volcano” lesion in PMC

CDAD: Host innate immune response

- PMN leukocytosis characteristic & prognostic
- Blocking PMN recruitment (anti-CD18 mAb) prevents toxin-mediated intestinal injury in animals
- Toxins activate phagocytes
  - PMN & Macrophage activation
  - NF-κB & MAP kinase signal induction
  - Cytokine release (IL-8, IL-1β)
- IL-8 promoter SNP assoc with symptomatic CDAD
- Role for corticosteroid [or other immunosuppressive Rx] in severe CDAD?
CDAD: Adaptive immune response

- ~60% of humans have serum IgG and colonic IgA anti-toxin antibody
- Animals protected by anti-toxin immunization

Hypothesis:

The host immune response plays a pivotal role in determining the clinical outcome of infection with toxigenic Clostridium difficile
Nosocomial *C. difficile* associated diarrhea and asymptomatic carriage are common

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  - 311 eligible
  - Hospital patients (Acute medical ward)
  - LOS > 2 days
  - Receiving antibiotic

- **271 enrolled**

**Colonized by *C. difficile***
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**Carriers**
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**Colonized on admission**
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**CDAD rate: (Jan to Jun)**
- 7 per 1,000 admissions

Serum IgG anti-toxin A levels are high in asymptomatic carriers of *C. difficile*.
High serum IgG anti-toxin A levels are associated with a lower risk for recurrent *C. difficile* diarrhea

For a level < 1.29
Odds ratio = 48
(95% CI, 3.5 - 663)

Kyne et al, Lancet 2001
Treatment approaches for *C. difficile* associated diarrhea

- Antibiotic therapy
  - *C. difficile* colonization
  - Toxin production
  - Diarrhea
  - Recurrent diarrhea
  - Primary immune response
  - Memory immune response

- Active Immunization: Toxoid vaccine

- Passive: Immune globulin mAbs
  - Anti-toxin immune response
  - Protection

- Probiotics
- Antibiotics
- Toxin binder

- mAbs: Monoclonal antibodies