Clostridium difficile
Colitis

John G. Bartlett, MD
Emeritus, Johns Hopkins University School of Medicine
Clostridium difficile: History

1935: Hall & O’Toole: C. difficile—stool from newborn infants; 1 ml produced 100,000 MLD, but ? significance

1970-1980: “Anaerobic bandwagon.” Clindamycin introduced and became preferred agent, but pseudo membraneous colitis (PMC) or “clindamycin colitis”

1976: Hamster model; antibiotic challenge ➡ wet tail ➡ lethal colitis; PO vancomycin protection, but relapse

1977: Two toxins: cytotoxin (A) and enterotoxin (B)

1978: 1st patient: lethal with cytotoxin titer 1:1,000,000
Clostridium difficile Infection (CDI)

Data from hamster model (1977-1978):

- Cause — Abx
- Pathogen — *C. difficile*
- Mechanism — toxins A (enterotoxin) & B
- Test — B (cytotoxin)
- Treatment — vanco
- Relapse rate — 100%
CDI: 1978-2015

**Principal inducing agents**: “Clindamycin colitis” & 2nd gen ceph.; 2005—fluoroquinolones (NAP-1 strain resistant)


**Treatment**: PO vanco-1978, metro-1980, fidaxomicin-2012

**Relapse**: Oral vancomycin, pulse/taper & stool transplant -1978; fecal caps- 2010

**Epidemiology**: Epidemics: Europe and N. America with NAP-1 strain (FQ use/abuse) 2001-05; UK restricted use-rate ↓ 70%!

**Risk**: Age, antibiotics, exposure to the healthcare system

**Priority**: CDC, CMS, HCR, Pres. Obama (2014)

CMS target: ↓ 50%
New epidemic strain: NAP1-(ribotype 027)
• Resistant FQ
• Ribotype-? predicts virulence/relapse
• Epidemics-national & local
• New data: – Epidemiology, stool transplant treatment
Health Care–Associated Infections: A meta-analysis of costs...


<table>
<thead>
<tr>
<th>Infection</th>
<th>Incidence /procedure, Pt-d</th>
<th>Cost (mean 2012 $)</th>
<th>Total cost/yr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central-line bacteremia</td>
<td>1.3/100 proc</td>
<td>$45,814</td>
<td>$1.9B</td>
</tr>
<tr>
<td>VAP</td>
<td>1.3/100 proc</td>
<td>$40,144</td>
<td>$3.1B</td>
</tr>
<tr>
<td>Surgical site infection</td>
<td>3.0/100 proc</td>
<td>$20,875</td>
<td>$3.3B</td>
</tr>
<tr>
<td><strong>C. difficile infection</strong></td>
<td><strong>3.9/1000 Pt-d</strong></td>
<td><strong>$11,285</strong></td>
<td><strong>$1.5B</strong></td>
</tr>
<tr>
<td>Cath-associated UTI</td>
<td>1.9/1000 Pt-d</td>
<td>$896</td>
<td>$27K</td>
</tr>
</tbody>
</table>
**Patient risks**: Big 3: Age, abx, healthcare system

**New Pop.**: Outpatients, peds, pregnancy

**Pathophysiology**: Population control in the colonic microbiome

**Expression**: Watery diarrhea, cramps, + fever and unique odor (P-cresol-?)

**Prog**: WBC, creatinine, albumin, lactate

**Treatment**: PO Vanco, +/- IV metro, PO fidaxomicin
CDI in Patients with HIV
(Haines CF, et al. AIDS. 2013;27:2799)

Source: Moore Clinic database Dec 2003-Jan 2011

Incidence: 154 cases or 8.3/1000 pt yrs (2X usual rate)

Risk: CD4 <50/mL (OR 20.7); hospital onset (OR 26.7)
    Clind (OR 27.6); FQ (OR 4.5); macrolides (OR 6.3);
    gastric acid suppression (OR 3.1); CD4 <50 (OR 6.1)

Conclusion: Risk factors include CD4 <50), but CMI
defects not common risk for CDI. More abx?
Severe *C. difficile* Infection
(Lamontagne F. Ann Surg. 2007;245:267)

**Method:**
Retrospective analysis of 165 patients admitted to ICU for *C. difficile* infection

**Results:**
Mortality (30 day): 87/165 (53%)

**Risks:**
- WBC >50K: 18
- Age >75 yrs: 7
- Immunosuppression: 9
- Lactate >5: 12
PCR: Molecular test to detect the B toxin gene
- Use: 51% of 711 hospital labs in US; cost (JHH) $50/test
- Advantage: Sensitivity approaches 100%
- Disadvantage: Specificity & cost; Hosp rev - 542 patients: 2.8% CDI; 7.4% carriers (Loo V. NEJM. 2011;365:1697)
- Conclusion: Must have clinical correlations
- Recommendations: Test only diarrheal stools, >1 wk between tests, “there is no test of cure” (but ? PCR)

EIA: Detects B toxin: Used in 33% of US hospital labs;
  Problem- sensitivity (correlates with titer)
C. difficile produces unique odor of P-cresol; dog’s olfactory sense- 300x that of humans (Bomers MK. BMJ. 2012;345:e7396)

<table>
<thead>
<tr>
<th></th>
<th>Stools</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>stools</td>
<td>30/30 (100%)</td>
<td>270/270 (100%)</td>
</tr>
<tr>
<td>Ward</td>
<td>25/30 (83%)</td>
<td>265/270 (98%)</td>
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</tbody>
</table>
## Testing for *C. difficile* (CDI)

Planche P. Infect Dis N Amer. 2015;29:63

<table>
<thead>
<tr>
<th>Test</th>
<th>Detect</th>
<th>Sens*</th>
<th>Spec*</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCTA</td>
<td>Cytotoxin</td>
<td>4</td>
<td>4</td>
<td>$5-15</td>
</tr>
<tr>
<td>GDH</td>
<td><em>C. difficile</em>*</td>
<td>4</td>
<td>2</td>
<td>$5-15</td>
</tr>
<tr>
<td>EIA</td>
<td>Toxin</td>
<td>3</td>
<td>3</td>
<td>$5-15</td>
</tr>
<tr>
<td>PCR</td>
<td>Toxin Gene</td>
<td>4</td>
<td>2</td>
<td>$30-50</td>
</tr>
<tr>
<td>Dog</td>
<td>P-cresol</td>
<td>4</td>
<td>4</td>
<td>$2</td>
</tr>
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*Score 1-4; **Requires second test*
50-year-old man - dental infection → clindamycin → diarrhea → PCR+

Vancomycin 125 mg po qid x 10 d or Metronidazole 500 mg po tid x 10 d

Relapse #1 → Repeat prior rx or fidaxomicin ($140/pill)

Relapse #2 → Vancomycin 125 qid 10 d → 125 bid 7 d → 125 qd 7 d → 125 qod 4 wks
or fidaxomicin 200 mg bid 7 d (cost issue)
or vancomycin x 10 d, then rifaximin x 10 d
or stool transplant (guidelines 3+ relapses)
CDC Study: Source of *C. difficile*  
(MMWR. 2012;61:157)

**Analysis:**
10,342 cases CDI: 111 hospital + 310 nursing homes

**Results:**
94% “healthcare-related”; 75% acquired *C. difficile* before hospitalization
Vancomycin vs Fidaxomicin for Second CDI Relapse – 36% vs 20% (Cornely Ol. CID. 2012;55 Suppl 2:S154)
Fecal Microbiota Transplantation for Recurrent C. difficile Infection
(Brandt L. J Clin Gastro. 2011;45:Suppl 3:S159)

**Issue**: How successful is stool transplant for C. difficile infection?

**Experience**: Literature review 1958-2010

**Method**:
- Enema . . . . . .  99
- NG Tube . . . . .  75
- Colonscopy . .  87

**Location**: Hospital, clinic, home

**Results**: No more relapses- 246/275 (89%). It doesn’t matter how (enema, endoscope, NG tube) or where (hospital, OPD, home) you put it in, but cost difference is big
Stool Transplant:  
**INDICATIONS:** Relapsing CDI X 3 or more  
Acute CDI: Limited but favorable reports  
**SITE:** Hospital, clinic, or home  
**METHOD:** Endoscopy, enema, NG tube, caps  
**DONOR:** Who selects? Patient or “universal”  
Other sources: Stool constructs, open. biome ($250)  
**SCREENING TESTS:** >$600 and not covered  
**DONOR ISSUES:** Metabolic syn, obesity, IBD, CVD, etc.  
**FDA (3/14):** Stool is drug  
1) Need consent  
2) Patient/MD must know donor  
3) Donor screen  
4) Need long-term follow-up studies
# New Developments in CDI

<table>
<thead>
<tr>
<th>Development</th>
<th>Implications</th>
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<tr>
<td>US/ European guidelines 2013</td>
<td>Relapse: vanco taper-pulse or fidaxomicin or stool transplant</td>
</tr>
<tr>
<td>Surgery for acute CDI</td>
<td>Loop ileostomy to save the colon and reduce mortality</td>
</tr>
<tr>
<td>Fecal caps- relapses</td>
<td>First trial (Louie T 2010); cheap &amp; effective</td>
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<tr>
<td>Epidemiology</td>
<td>75% of CDI patients are colonized at admission; changes infect control</td>
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<tr>
<td>Fidaxomicin</td>
<td>Reduces relapses, but $140/pill</td>
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<tr>
<td>Fecal transplant</td>
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<tr>
<td>Infection Control</td>
<td>1st controlled trial after 58 yrs; stool by enema, scope, NG tube, pills</td>
</tr>
<tr>
<td></td>
<td>Molecular sequencing?</td>
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Stool Transplant:
IDSA/FDA recommendations (2013-2014)

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Stool - Any human source, insert any method
Oral Stool Caps for Relapsing CDI

**Patients**: 20 patients aged 11-89 yrs. with >2 CDI relapses (2 severe)

**Stool source**: Healthy adults w/BMI 18-25 → Screened
→ Stored and retested at 4 weeks → Double-capsules
→ Frozen at – 80C

**Procedure**: 15 caps delivered on 2 consecutive days

**Results**: Resolution w/1-day treatment: 14/20 and 4/6 requiring second-day dosing.

**Conclusion**: 18/20 (90%) responded. ADR: None

**Author (2/16/15)**: Donor screen for BMI based on microbiome-assoc obesity with case report; FDA-IND obtained; N 2/15 = 45
CDI: What’s Important for Clinical Management

• **RISKS**: Age, abx (FQ >cephalosporins), healthcare system

• **TEST**: Know what test; PCR: false positives; EIA: false negatives

• **PROGNOSIS**: WBC> Renal function> albumin

• **EPIDEMIOLOGY**: “Healthcare associated,” most CDI patients have *C. difficile* colonization on admission; IC - important, but must change

• **TREATMENT**: PO vanco, metronidazole and fidaxomicin - equally good for initial infection; po vancomycin +IV metro best for serious disease; fidaxomicin best for relapsing disease ($$$)

• **STOOL TRANSPLANT**: Best for multiple relapses; know local and commercial resources, patient preference and new FDA regs