C. difficile Associated Diarrhea

Dr. Andreas Widmer, University Hospital, Basel, Switzerland

Sponsored by WHO First Global Patient Safety Challenge, Clean Care is Safer Care

Outline

- Background
- Diseases associated with C. difficile
- Diagnostic issues
- New Strains NAP1/027 078 Binary toxin
- Therapy
- Infection control

History

- 1893 – first case of pseudomembranous colitis reported as *diphtheritic colitis*, discovered in 1935 by Hall & O’Toole.
- 1935 – “Bacillus difficile” isolated.
- 1970s – antibiotic-associated colitis identified.
- 1978 – *C. difficile* toxins identified in humans.
- 1979 – therapy with vancomycin or metronidazole
- 2000 – increased incidence and virulence
- 2010 – New treatment options, new diagnostic tools

Reservoirs for Toxigenic C. difficile

- 15% to 70% of healthy neonates (to age 1 y)
- <3% of healthy adults (up to 15% of inpatients)
- 10% to 20% of hospitalized patients, especially on antibiotics
- Most disease-causing strains are exogenously acquired
- Spores survive in the environment for at least 6 months
  - Hospital environment
  - HCW hands
    - Water
      - River (98%)
      - Lake (47%)
      - Sea (47%)
    - Swimming pool
      - Mains tap (30%)
      - Mains tap 1/18 (6%)
    - Soil
      - (21%)
    - Raw vegetables
      - (2%)
    - Private residences
      - (2%)
    - Dogs
      - (10%)
    - Cats
      - (2%)
    - 4 hospital environments
      - (20%)

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**C. difficile: Basics (-2000)**

<table>
<thead>
<tr>
<th>Toxin A (enterotoxin)</th>
<th>Toxin B (cytotoxin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight, kD</td>
<td>308</td>
</tr>
<tr>
<td>Chemical properties</td>
<td>Inactivated by proteases</td>
</tr>
<tr>
<td></td>
<td>Heat- and acid-labile</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Causes mucosal damage,</td>
</tr>
<tr>
<td></td>
<td>Chemo-attraction for neutrophils,</td>
</tr>
<tr>
<td></td>
<td>Activator of macrophages/mast cells</td>
</tr>
<tr>
<td>Effects on animals</td>
<td>Hemorrhagic enterocolitis</td>
</tr>
<tr>
<td></td>
<td>Increased intestinal fluid secretion</td>
</tr>
<tr>
<td></td>
<td>Increased vascular permeability</td>
</tr>
</tbody>
</table>

*~25% of C. difficile isolates are toxin A-/B- (Fekety, JAMA 1993)*

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**Typical Incubation times for Pathogens causing Nosocomial Diarrhea**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Incubation time (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Salmonella B. cereus</em></td>
<td>4</td>
</tr>
<tr>
<td><em>EHEC</em> / <em>ETEC</em></td>
<td>6</td>
</tr>
<tr>
<td><em>Clostridium perfringens</em></td>
<td>12</td>
</tr>
<tr>
<td><em>Vibrio cholerae</em></td>
<td>24</td>
</tr>
<tr>
<td><em>Salmonella</em></td>
<td>36</td>
</tr>
<tr>
<td><em>Vibrio cholerae</em></td>
<td>48</td>
</tr>
<tr>
<td><em>Shigella</em></td>
<td>72</td>
</tr>
<tr>
<td><em>Norwalk</em></td>
<td>5</td>
</tr>
<tr>
<td><em>Campylobacter</em></td>
<td>14</td>
</tr>
<tr>
<td><em>Cryptosporidium</em></td>
<td>18</td>
</tr>
<tr>
<td><em>Giardia lamblia</em></td>
<td>10</td>
</tr>
<tr>
<td><em>Listeria</em> / <em>Typhus</em></td>
<td>20</td>
</tr>
<tr>
<td><em>E. histolytica</em> / <em>Aeromonas</em></td>
<td>21</td>
</tr>
</tbody>
</table>

---

**Clinical Pictures of CDAD**

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>Diarrhea</th>
<th>Other symptoms</th>
<th>Clinical exam</th>
<th>endoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic colonization</td>
<td>No</td>
<td>No</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>CDAD without colitis</td>
<td>Some diarrhea</td>
<td>Abdominal cramps</td>
<td>Some abdominal tenderness</td>
<td>normal</td>
</tr>
<tr>
<td>CDAD with colitis</td>
<td>Profuse diarrhea, fecal leukocytes, hemocult plus</td>
<td>Loss of appetite, anorexia, fever, vomiting, dehydration;</td>
<td>Serious abdominal tenderness</td>
<td>Localized colitis</td>
</tr>
<tr>
<td>Pseudomembranous colitis</td>
<td>Profuse diarrhea, fecal leukocytes, hemocult plus</td>
<td>Loss of appetite, anorexia, fever, vomiting, abdominal pain, dehydration;</td>
<td>Tenderness, local peritonitis</td>
<td>Adherent, yellow plaque 2-70mm, Pseudomembrane (colitis)</td>
</tr>
<tr>
<td>Fulminant colitis</td>
<td>Profuse diarrhea, fecal leukocytes, hemocult plus development of paralytic ileus</td>
<td>Fever, abdominal pain, peritonitis, septic syndrome, paralytic ileus</td>
<td>Peritonitis; Sepsis to septic shock</td>
<td>Contaminated, CT-scan</td>
</tr>
</tbody>
</table>

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**Outline**

- **Background**
- **Diseases associated with *C. difficile***
- **Diagnostic issues**
- **New Strains NAP1/027 078 Binary toxin**
- **Therapy**
- **Infection control**

---

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Excretion of C. difficile by healthy volunteers treated for 10 days with placebo or antibiotics

Pooled Odds Ratio for each Antibiotic in Relation to CDAD

Risk of Contributing to CDAD

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Risk factors for CDAD
- Age >65y
- Malignant Disease
  - Leukemia
  - While under chemotherapy
- Multiple Antibiotics
- Proton pump inhibitors
- Long hospital stay

Risk factors for Dissemination of C. difficile
- Strain’s epidemicity and virulence
  (Wilcox et al., J Hosp Infect 1997;37:331-343)
- Susceptibility of the patient
  (Barbut Bull Soc Fr Microbiol 2002;17:25)
- Antibiotic pressures operating on the ward or hospital
  (Wilcox et al., J Hosp Infect Lett. to the Editor 1997, ECCMID Glasgow 2003)
- Level of patient’s hygiene and clinical status
  (Monrey M.A., JAC 1998;41,supp C:53-68)
- Quality of environmental cleaning (floors, furniture and equipment) and the choice of the cleaning product
  (Jones et al., Lancet;352:505-6/Wilcox and Fawley, Lancet 2000;356:1324)
- Compliance with standard and contact precautions: hand hygiene, gloves use, symptomatic patient’s isolation

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Laboratory Testing for Clostridium difficile Infection

Abstract
It is critical that C. difficile diagnosis be accurate so ongoing epidemiology, disease prevention, and treatment remain satisfactory. We tested 10 diagnostic assays, including 1 commercial mid-time polymerase chain reaction (qPCR) test for the laboratory detection of toxigenic C. difficile on 1,000 stool samples. Sensitive culture for toxigenic C difficile using 2 types of media with broth enrichment defined the reference standard.

For the study, 1,000 tests were performed on samples from 919 patients. Of the samples, 146 contained evidence for toxigenic C difficile and represented the true-positive results. Only the US FDA qPCR assay and 1 glutamate dehydrogenase test were not statistically inferior to culture in sensitivity. The common enzyme immunoassay tests all had sensitivity values less than 50%. Clinical laboratory professionals need to seriously consider their diagnostic testing and use the assays that perform best for the detection of CDI.

Table 1
<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Positive predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2%</td>
<td>67.7</td>
</tr>
<tr>
<td>4%</td>
<td>61.7</td>
</tr>
<tr>
<td>6%</td>
<td>55.3</td>
</tr>
<tr>
<td>8%</td>
<td>49.5</td>
</tr>
<tr>
<td>10%</td>
<td>46.4</td>
</tr>
</tbody>
</table>

Chand MA. J Hosp Infect 2011;79:8-12

Rapid Reliable Testing of C. difficile

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Algorithm to diagnose CDI
European Society of Clinical Microbiology and Infectious Diseases (ESCMID):

Guideline 2010
American Society for Microbiology

GeneXpert MTB/RIF

PCR Xpert™ C. difficile*
• Resultate in <1 Std.
• Detection of Toxin B, binary Toxin und tcdC-Deletion → NAP1 / PCR Ribotyp 027

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Annual Incidence (per 100,000 Population) of C. difficile Infection in Sherbrooke, Quebec, 1991-2003

Impact of Quinolones on the Incidence of CDI

National estimates of US short-stay hospital discharges with Clostridium difficile listed as primary or as any diagnosis

Rates of US short-stay hospital discharges with Clostridium difficile listed as any diagnosis, by age
Because of low rates and the resulting uncertainty of yearly rate estimates, data for patients <15 years of age are not included.

Clostridium difficile in Discharged Inpatients

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C. difficile Ribotype 027 Distribution in Europe

Distribution of The C. difficile NAP1/Ribotype 027 cases among 20 hospitals that submitted stool specimens (Chicago and Cook County Departments).

Major Genes in the Pathogenicity Locus (PaLoc) of Clostridium difficile NAP1/027 and Relation to the Genes for Binary Toxin

Comparison of Molecular Characteristics of 2 C. difficile Isolates with Historical Standard-Type Strains and a Recently Recognized Epidemic Strain, by Selected Characteristics, OH and PA, 2005

Increased Toxin B production in vitro

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States with the North American Pulsed Field Type 1 strain of C. difficile confirmed by CDC as of May 15, 2006 (N=17)

Spread of PCR ribotype 027 across The Netherlands.

A: Spread of PCR ribotype 027
B: Spread of PCR ribotype 078


Patient survival with C. difficile infection by infection group
Binary Toxin vs Ribotype 027

Bacci S Emerg Infect Dis 2011;6:976


Hubert B et al, Clin Inf Dis 2007;44:238-244

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Association of CDI Treatment-Concurrent PPI Exposure With Recurrent CDI Within 90 Days

<table>
<thead>
<tr>
<th>Model</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>1.42 (1.11-1.82)</td>
<td>.006</td>
</tr>
<tr>
<td>Adjusted, antibiotics, if possible</td>
<td>1.42 (1.10-1.83)</td>
<td>.006</td>
</tr>
<tr>
<td>Age stratified, y&lt;60 (n=189)</td>
<td>1.19 (0.56-2.55)</td>
<td>.65</td>
</tr>
<tr>
<td>60-80 (n=593)</td>
<td>1.32 (0.94-1.85)</td>
<td>.11</td>
</tr>
<tr>
<td>&gt;80 (n=384)</td>
<td>1.86 (1.15-3.01)</td>
<td>.01</td>
</tr>
<tr>
<td>Non-CDI antibiotic exposure stratified, Antibiotic exposure (n=468)</td>
<td>1.71 (1.11-2.64)</td>
<td>.01</td>
</tr>
<tr>
<td>No additional antibiotic exposure (n=740)</td>
<td>1.30 (0.94-1.79)</td>
<td>.12</td>
</tr>
</tbody>
</table>

*Mantel for age, incident CDI treatment, additional antibiotic exposure, length of hospital stay, chronic obstructive pulmonary disease, liver disease, diabetes, renal disease, and symptoms of septicemia.


Suggested Approaches to Therapy

Step 1: stop antibiotics, if possible

**Step 2:**

Suggested Approaches to Therapy

<table>
<thead>
<tr>
<th>Initial episode</th>
<th>Severe infection or severe disease</th>
<th>Re-infection</th>
<th>Severe disease</th>
<th>Re-infection</th>
<th>Severe disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin, if possible</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Oral metronidazole</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Mullane KM. Clinical Infectious Diseases 2011;53(5):440-447


Response Rates to Vancomycin and Metronidazole Therapy, According to the Severity of C. difficile Infection

<table>
<thead>
<tr>
<th>Vancomycin</th>
<th>Metronidazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>58%</td>
<td>90%</td>
</tr>
<tr>
<td>60%</td>
<td>97%</td>
</tr>
</tbody>
</table>

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### Treatment guidance document for CDAD

**European Society of Clinical Microbiology and Infectious Diseases (ESCMID):**

- **ORAL**
  - non-severe: metronidazole 500 mg tid orally for 10 days (A-I)
  - severe: vancomycin 125 mg qid* orally for 10 days (A-I)
  - *Oral vancomycin may be replaced by teicoplanin 100 mg bid, if available.
- **IV**
  - non-severe: metronidazole 500 mg tid intravenously for 10 days (A-III)
  - severe: metronidazole 500 mg tid intravenously for 10 days (A-III)
  - + intracolonic vancomycin 500 mg in 100 mL of normal saline every 4–12 h (C-III) and/or vancomycin 500 mg qid by nasogastric tube (C-III)

---

### Suggested management cascade for C. difficile infection

**UK**

- Severe disease: one or more of:
  - white blood cell count >15x10⁹/l,
  - acutely rising serum creatinine (≥50% baseline),
  - temperature >38.5°C,
  - clinical or radiological evidence of severe infection.

**Diarrhea Department chart, L. or B. and positive C. difficile toxin A or B or diarrheal C. difficile infection is strongly suspected:**

- Mild disease
  - Metronidazole 500 mg orally 3 hourly (for 10–14 days)
- Severe disease
  - Vancomycin 125 mg orally 6 hourly (for 10–14 days)

**Diarrhea should be reassessed by 48 hours and resolved by 48–72 h of treatment. Stop antibiotics after 10 days.**

---

### Recovery kinetics of C. difficile LC3 following a 1-h exposure to fidaxomicin (OPT-80) and vancomycin (VANC)

- **PAE Values:**
  - VANC: 1.5 - 2 hr
  - FDX: >12.5 hr

- **Postantibiotic effect**

---

### Results: Rates of Primary and Secondary End Points

**Fidaxomicin vs Vancomycin**

- N=629 patients

---

### Time to Recurrence of C. difficile Infection: Monoclonal antibody vs placebo: RCT

- In this randomized trial involving patients with Clostridium difficile infection, treatment with monoclonal antibodies against C. difficile toxins A and B, in addition to metronidazole or vancomycin, reduced the rate of recurrence of infection, as compared with placebo (7% vs. 25%).

---

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Outline

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**Clostridium difficile** infection

- HICPAC Contact Isolation for *Clostridium difficile* infection
  - Colonization with multidrug-resistant bacteria
  - Risk of MR bacteria: transfer from healthcare facility where MRB are prevalent
  - Major abscess, cellulitis or decubiti
  - Acute diarrhea in an incontinent or diapered patient
  - RSV infection, croup or bronchiolitis in young infants

**SHEA / IDSA**

16. Accommodate patients with CDI in a private room with contact precautions (B-III).

**Clostridium difficile-associated disease**

Frequency of *Clostridium difficile* contamination of skin sites of 27 patients with *C. difficile*-associated disease (CDAD) (A) and frequency of acquisition on sterile gloves after contact with skin sites of a subset of 10 patients (B). Typical illustration of acquisition of *C. difficile* on sterile gloves after contact with a CDAD-affected patient's groin. The larger yellow colonies outlining the fingers are *C. difficile*. Of note, the patient had showered 1 h before collection of the culture specimen.


**Glove use**

- Prevent heavy hand's contamination
  - 3 CFU/min wearing gloves
  - 16 CFU/min not wearing gloves
  (Fittet et al, Arch Intern Med 1999;159:821-6)
- Decrease incidence of CDAD and asymptomatic carriers
  - 7.7 cases/1000 pt discharges before to
  - 1.5 cases/1000 pt discharges during intervention
  - p=.015

**Does the environment need to be disinfected?**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Reduction of initial contamination or incidence of CDAD</th>
</tr>
</thead>
</table>

*No gluoprotamin. No Quats. No Amines*  

**Cases with C. difficile:**

Disinfection with an active disinfectant against spores necessary

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Oxygen-releasing Agents
e.g. Magnesium monoperoxypthalate hexahydrate (MMPP) 80.0 g

Directions for use
- Surfaces 0.5 % - 1 hrs.
- Surfaces during epidemics (NLV) 4.0 % - 1 hrs.
- HBV 0.5 % - 5 min.
- HIV 0.25 % - 5 min.
- BVDV* (Surrogate virus for Hep-C) 0.5 % - 1 min.
- Rotavirus 0.25 % - 1 min.
- Poliovirus 1.0 % - 1 hrs.
- Adeno-, Vaccinia-, Papovaviruses 0.25 % - 5 min.
- Bacterial spores 1.0 % - 4 hrs.
- M. tuberculosis 0.5 % - 1 hrs.

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Hosted by Dr. Kate Ellingson, CDC, Atlanta
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Laboratory-Acquired *C. difficile* Ribotype 027: A New Risk for Laboratory Workers?

- Clostridium difficile is not recognized as a pathogen that presents a risk of acquisition in the laboratory, and no particular safety precautions are commended for working with this microorganism.
- We report 2 cases of laboratory acquisition of *C. difficile* infection.
- After these laboratory-acquired infections occurred, we decided that technicians and researchers should work with *C. difficile* ribotype 027 only in class II biosafety cabinets. We also recommend the use of disposable gloves and gowns, disinfection of hands with water and soap, and decontamination of materials and instruments with chlorine-containing disinfectants.


CONCLUSIONS

- The incidence of CDAD has significantly increased over the last 5 years worldwide.
- Epidemics are common today.
  - NAP1/027 / 078 and Binary Toxin
  - Age >65y
  - Worldwide:
    - Canada, USA, France, Belgium, Germany, Switzerland, the Netherlands and more

- Identification of outbreaks and control of CDAD requires:
  - Epidemiological surveillance AND
  - State of the art microbiology and molecular microbiology
  - And state of the art infection control

WHO Patient Safety Challenge … Clean Care is Safer Care 2011 Teleclass Series

- February 1 – Quality Improvement in Infection Prevention and Control
- April 8 – Hand Hygiene Education and Monitoring: Returning to the WHO “My Five Moments” Concept
- May 5 – The Importance of Worldwide Hand Hygiene Events and Activities
- June 21 – Establishing an Infection Control Program for Acute Respiratory Infections and Ensuring Pandemic Preparation
- August 31 – Latest Update on *Clostridium difficile* Control
- September 7 – Highlights From May 5, 2011 Initiatives Around the World
- October 4 – MRSA – Is Search & Destroy the Way To Go?
- December 7 – Best Practice for Cleaning, Disinfection and Sterilization in Healthcare

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