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 1933 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 (89%)
  - lake (47%)
  - sea (30%)
  - swimming pool (8%)
- Soil (21%)
- Raw vegetables (2%)
- Private residences (13%)
- Dogs (10%)
- Cats (2%)
- 4 hospital environments (20%)
C. difficile: Basics (-2000)

| Toxin       | Molecular weight, kD | Chemical properties | Mechanism | Effects on animals | Toxicity |
|-------------|----------------------|---------------------|-----------|-------------------|---------|
| Toxin A (enterotoxin) | 308                  | Heat- and acid-labile | Causes mucosal damage, chemo-attraction for neutrophils, activator of macrophages/mast cells | Hemorrhagic enterocolitis, increased intestinal fluid secretion, increased vascular permeability |  
| Toxin B (cytotoxin)  | 270                  | Heat- and acid-labile | Inhibits adenylate cyclase, disrupts actin filaments, activates macrophages/mast cells | Ten times more potent than toxin A, lethal in high doses |  

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

Typical Incubation times for Pathogens causing Nosocomial Diarrhea

| Pathogen | 4 hrs | 6 hrs | 12 hrs | 24 hrs | 36 hrs | 48 hrs | 72 hrs | 5 days | 1 week | 2 weeks | 3 weeks |
|----------|-------|-------|--------|--------|--------|--------|--------|--------|--------|---------|---------|
| Staphylococcus aureus | B. cereus | EHEC | ETEC | Clostridium perfringens | Vibrio cholerae | Shigella | Rotavirus | Norwalk | Campylobacter | | |

Clinical Pictures of CDAD

| Type of infection | Diarrhea                      | Other symptoms               | Clinical exam | endoscopy |
|-------------------|--------------------------------|-----------------------------|---------------|-----------|
| Asymptomatic colonization | No                            | No                          | normal        | normal    |
| CDAD without colitis | Some diarrhea                  | Abdominal cramps            | Some abdominal tenderness | normal    |
| CDAD with colitis | Profuse diarrhea, fecal leukocytes, hemocult pos | Loss of appetite, anorexia, fever, vomiting, dehydration | Serious abdominal tenderness | Localized colitis |
| Pseudomembranous colitis | Profuse diarrhea, fecal leukocytes, hemocult pos | Loss of appetite, anorexia, fever, vomiting, abdominal pain, dehydration, Tenderness, bowel peritonitis | Adherent, yellow plaques 2-7mm, Pseudomembranes (colitis/mucositis) | |
| Fulminant colitis | Profuse diarrhea, fecal leukocytes, hemocult pos, development of paralytic ileus | Fever, abdominal pain, peritonitis, septic syndrome, paralytic ileus | Peritonitis, Septic shock | Contraindicated, CT-scan |

In vitro cytotoxicity of C.difficile

- a, b. Comparisons of the parental strain A+B and the three mutants A−B+, A+B− and A−B− were made in cell culture assays to measure cytotoxicity. HT29 cells (a) and Vero cells (b) were cultured or flat monolayers before adding C. difficile supernatants in serial dilutions. Data represent the mean ± standard deviation.

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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
- Susceptibility of the patient
- Antibiotic pressures operating on the ward or hospital
- Level of patient’s hygiene and clinical status
- Quality of environmental cleaning (floors, furniture and equipment) and the choice of the cleaning product
- 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 CDI diagnosis be accurate so ongoing epidemiology, disease prevention, and treatment remain satisfactory.

We tested 10 diagnostic assays, including 1 commercial real-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.

Rapid Reliable Testing of C. difficile

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**Algorithm to diagnose CDI**

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

[Diagram]

Crobach MAT et al (A. Widmer) Clin Microbiol Infect 2008;15:1053-66

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**Guideline 2010**

American Society for Microbiology

- GDH assay
  - positive
  - negative = Negative for toxigenic C. difficile
- Toxin A/B assay or Cytotoxin Neutralization
  - positive
  - Positive for Toxigenic C. difficile
  - negative
- NAAT assay or Toxigenic Culture
  - positive
  - Positive for Toxigenic C. difficile
  - negative
  - Negative for Toxigenic C. difficile

GDH = glutamate dehydrogenase antigen NAAT = nucleic acid amplification test

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**GeneXpert MTB/RIF**

- Sample automatically dried and prepared
- DNA isolated
- Sample enters into test cartridge
- Signal detection
- Result in <1 Std.
- Detection of Toxin B, binary Toxin und tcdC-Deletion → NAP1 / PCR Ribotyp 027

N Engl J Med 2010;363:1005-15

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**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

University of Basel Cluster von CDAD by C. difficile Ribotype 027

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

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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

Annual Clostridium difficile–associated disease rates for hospitals with 1500 beds, by ICU surveillance component (National Nosocomial Infections Surveillance System, 1997–2001)

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

| Model                  | HR (95% CI) | P Value |
|------------------------|-------------|---------|
| Unadjusted             |             |         |
| Adjusted*              |             |         |
| Age stratified, y<60   | 1.19 (0.56-2.55) | 0.55   |
| >60 (n=593)            | 1.32 (0.94-1.85) | 0.11   |
| Non-CDI antibiotic exposure stratified* | 1.46 | 0.01   |
| Antibiotic exposure (n=466) | 1.71 (1.11-2.64) | 0.01   |

*Adjusted for age, incident CDI, treatment, additional antibiotic exposure at time of hospitalization, episode-related antibiotic exposure, pre-existing gastrointestinal disease, past or future antibiotic exposure, and administration of probiotics.

Linsky, A. et al. Arch Intern Med 2010;170:772-778.

Step 1: stop antibiotics, if possible

| Group                  | No. CDI | n No. CDI | Difference % (95% CI) | P |
|------------------------|---------|-----------|------------------------|---|
| Initial episode        | 4/10    | 5/10      | -2.00 (-3.30 to -0.70) | 0.005 |
| Repeat episode         | 3/10    | 4/10      | -1.00 (-4.30 to 2.30)  | 0.80 |

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

Suggested Approaches to Therapy

| Initial episode         | Stop antibiotics, if possible |
|------------------------|------------------------------|
| Severe infection or unresponsiveness to or intolerance of vancomycin or metronidazole | |
| Vancomycin at a dose of 125 mg orally 4 times daily for 10-14 days |

Kelly C, LaMont J. N Engl J Med 2008;359(5):440-447

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

| Severity               | Vancomycin | Metronidazole |
|------------------------|------------|---------------|
| Mild                    | 90%        | 70%           |
| Severe                  | 97%        | 76%           |

Kelly C, LaMont J. N Engl J Med 2008;359(5):440-447

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Suggested management cascade for C. difficile infection

- Severe disease: one or more
  - White blood cell count >15x10^9/l
  - Acute rise in serum creatinine (>50% baseline)
  - Temperature >38.5{degrees}C
  - Clinical or radiological evidence of severe disease

UK

Diarrhea

Shannon-Lowe, J et al. BMJ 2010;340:c1296

• Severe disease:
  - WBC count >15x10^9/l
  - Acutely rising serum creatinine (>50% baseline)
  - Temperature >38.5{degrees}C
  - Clinical or radiological evidence of severe disease

Treatment guidance document for CDAD

- 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)
  - Oral vancomycin (500 mg qid by nasogastric tube)

UK

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Clin Microbiol Infect 2009; 15:1067–1079

Fidaxomicin versus Vancomycin for C. difficile Infection

A randomized controlled clinical trial

Louie TJ et al. N Engl J Med 2011;364:422-431

Results: Rates of Primary and Secondary End Points

Fidaxomicin vs Vancomycin

N=629 patients

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

P. A. R. Values:

- VANC: 7 S - 5 hr
- FDX: >12.5 hr

P. I. T. Values:

- VANC: 12 S - 4 hr
- FDX: >12.5 hr

Postantibiotic effect

Babakhani, F. et al. 2011. Antimicrob. Agents Chemother. 55(9):4427-4429

Recovery 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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### Clostridium difficile infection

- HICPAC Contact Isolation for *Clostridium difficile* infection
  - Colonization with multi-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 CDC Guidelines July 2007  
  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*-resistant spores after contact with a *C. difficile*-infected 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
  - Pittet 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
  - Johnson et al, Am J Med 1990;88:137-40

### Does the environment need to be disinfected?

- No glutoprotamin. No Quats. No Amines

### Kaplan-Meier Estimation of Time from resolution of diarrheas to negative culture results

- Kaplan-Meier estimation of time from resolution of diarrheas to negative culture results of abdominal skin specimens of abdomen and or distal site of patients with *Clostridium difficile*-associated disease.

### References

- Widmer AF & Frei R.. Infect Control Hosp Epidemiol Nov 2003
- Widmer AF & Frei R. Disinfection. Manual of Clinical Microbiology, ASM 2007 /2011
- Widmer AF & Frei R. Infect Control Hosp Epidemiol Nov 2003

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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.
Poliomyelitis 1.0 % - 1 hrs.
Adeno-, Vaccinia-, Papovaviruses 0.25 % - 5 min.
Bacterial spores 1.0 % - 4 hrs.
M. tuberculosis 0.5 % - 1 hrs.

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

Sterilisation EN 554
Disinfectant level
sterilant (high level disinfectant with prolonged exposure time)
high level
intermediate level
low level

Increasing Order of Resistance of Microorganisms to Disinfectants

Widmer AF & Frei R. in: Manual of Clinical Microbiology. American Society of Microbiology 2011

Policlinico degli orrori
Ospedale Universita Umberto I, Roma, 5 Jan 2007

Wash or Disinfect Hands after care of C. difficile diseased patients?

• Pro and contra wash
  – + Physically removes bacteria and spores
  – + effective based on good studies
  – - Less effective against vegetative bacteria
  – - Poor compliance / time consuming

• Pro and contra Alcohol
  – - No activity against spores
    (alcohol used in the lab to select spores from cultures)
  – + Enhanced compliance
  – + No evidence that washing stops epidemics faster

Wash hands if soiled e.g. after taking care of a patient with diarrhea

Lack of Association Between the Increased Incidence of C. difficile–Associated Disease and the Increasing Use of Alcohol-Based Hand Rubs

Use of alcohol hand rub by healthcare workers, in thousands 1,000 patient-days, per quarter, 2006-2005.

Number of patients with 1 or more tests positive for C. difficile toxin A per 1,000 patient-days, 2006-2005.

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www.webbertraining.com
Laboratory-Acquired *Clostridium 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 recommended 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.

- Bouza E & Ed J. Kuijper. Clinical Infectious Diseases 2008; 47:1493–4 (Dec)

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
  - Bouza E & Ed J. Kuijper. Clinical Infectious Diseases 2008; 47:1493–4 (Dec)
- 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

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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 Preparedness

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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