Clostridium difficile Infection: Emerging Therapies and Recurrence Prevention

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Thank you for joining us for *Clostridium difficile Infection: Emerging Therapies and Recurrence Prevention*, a continuing education activity.

We also thank our esteemed speakers for sharing their time and expertise. Through this activity, they will describe the role of gastrointestinal flora in health and the mechanisms of recurrent *Clostridium difficile* infection (CDI); identify patients at risk for recurrence and poor outcomes; summarize recent evolutions in CDI treatment options; use appropriate CDI diagnostic testing; and choose appropriate infection control methods and therapies to improve patient outcomes.

This workbook includes the presenters’ slides and will help guide you through the activity. If you would like to receive 2.0 AMA PRA Category 1 Credits™, 2.0 ACPE contact hours, or 1.9 ANCC contact hours, please complete the activity evaluation as instructed on this activity’s website.

We hope that you will find this activity rewarding and informative.
AGENDA

Activity Overview
Dale N. Gerding, MD, FACP, FIDSA

Diagnostic Challenges and Controversies: Becoming Less Difficile
Stephen M. Brecher, PhD

Clostridium difficile: Pathophysiology, Risk Factors, and Recurrence
Kathleen Mullane, DO, PharmD

Emerging CDI Treatment Options and Infection Control
Stuart Johnson, MD, DTM&H

Question-and-Answer Session
Target Audience
This activity has been designed to meet the educational needs of physicians, pharmacists, and nurses involved in the care of patients with *Clostridium difficile* infection (CDI).

Statement of Need
Rates of CDI incidence, hospitalizations, and deaths have been increasing in recent years, suggesting that current management of this condition may be suboptimal.\(^1\) Although much has been discovered regarding the role of gastrointestinal flora in the pathogenesis of CDI, the mechanisms of recurrent disease and poor outcomes remain elusive. Surveys of practice patterns suggest that healthcare professionals are unaware of or fail to utilize optimal methods for managing patients with CDI.\(^2,3\) Given the recent updated guidelines for CDI, combined with several new agents emerging for this disease, it is important that healthcare professionals be aware of the most current research and recommendations for the management of CDI.

Educational Objectives
After participating in this educational activity, participants should be able to:

- Describe the role of gastrointestinal flora in health and the mechanisms of recurrent *Clostridium difficile* infection (CDI)
- Identify patients at risk for recurrence and poor outcomes
- Summarize recent evolutions in CDI treatment options
- Use appropriate CDI diagnostic testing
- Choose appropriate infection control methods and therapies to improve patient outcomes

Statement of Support
This activity is jointly sponsored by RMEI, LLC and Postgraduate Institute for Medicine. RMEI gratefully acknowledges an educational grant from Optimer in support of this CE activity.

\(^3\) Association for Professionals in Infection Control (APIC) Pace of Progress poll. May 2010.
Dale N. Gerding, MD, FIDSA, is Professor of Medicine at Loyola University Chicago Stritch School of Medicine in Maywood, Illinois and Research Physician at Hines Veterans Affairs Hospital. Prior to his present position, Dr. Gerding was Associate Chief of Staff for Research and Development at the Hines Veterans Affairs Hospital, Chief of Medicine at Lakeside VA Hospital in Chicago, and Professor of Medicine at Northwestern University Feinberg School of Medicine. Dr. Gerding received his undergraduate degree in physics from St. John’s University in Collegeville, Minnesota, attended graduate school in physics at UCLA in Los Angeles, California, and received his MD from the University of Minnesota Medical School. He was a medical intern at the Peter Bent Brigham Hospital in Boston and, following two years at the National Institutes of Health, completed his medical residency and infectious diseases fellowship at the University of Minnesota and Minneapolis VA Medical Center. He is board certified in internal medicine and infectious diseases.

Dr. Gerding is an infectious diseases specialist and hospital epidemiologist, past president of the Society for Healthcare Epidemiology of America and past chair the antibiotic resistance committee of SHEA. He is a fellow of the Infectious Diseases Society of America and past chair of the National and Global Public Health Committee and the Antibiotic Resistance Subcommittee of IDSA. He served as a member of the board of directors of IDSA from 2005-2008. He is a fellow of the American College of Physicians and a member of the American Society for Microbiology.

Dr. Gerding’s research interests include the epidemiology and prevention of Clostridium difficile disease, antimicrobial resistance, and antimicrobial distribution and kinetics. He has been a Merit Review funded research investigator in the VA for over 35 years and is the author of over 300 peer-reviewed journal publications, book chapters, and review articles. He holds patents for the use of non-toxigenic C. difficile for the prevention and treatment of this disease. He is a member of the editorial boards of Clinical Infectious Diseases, Antimicrobial Agents and Chemotherapy, Gut Microbes, and Infection Control and Hospital Epidemiology, and is an ad hoc reviewer for numerous other medical journals.
Dr. Stephen M. Brecher has been the Director of Microbiology at the Boston VA Healthcare System for 28 years and holds academic appointments at the Boston University School of Medicine and at the University of Massachusetts/Dartmouth. Dr. Brecher is on the editorial board of the *Journal of Clinical Microbiology*.

Dr. Brecher has been honored as an American Society of Microbiology (ASM) Foundation Speaker and has convened and lectured at numerous symposia and workshops at the ASM annual meetings (the general and “infections meetings”). Dr. Brecher is well known and respected for his work and lectures on methicillin-resistant *S. aureus* (MRSA), *C. difficile* infections (CDI), and multi-drug resistant bacteria. He has lectured from Boston to Beijing and, as an accomplished and highly acclaimed speaker, Dr. Brecher is appreciated for his ability to make you laugh while he is telling you that bacteria are the dominant species on earth and that your days are numbered. CD infections are particularly important to him because of the poor outcomes, treatment difficulties, diagnostic dilemmas, and unexplained community cases.
Kathleen M. Mullane, DO, PharmD, is Associate Professor of Medicine at the University of Chicago in Chicago, Illinois. Following graduation from the Chicago College of Osteopathic Medicine at Midwestern University, Dr. Mullane completed her residency in internal medicine at Rush-Presbyterian-St. Luke's Medical Center and her fellowship in infectious diseases at the University of Illinois/University of Chicago Combined Program.

Dr. Mullane's clinical interest is in infectious diseases and antimicrobials. She has co-authored numerous original articles and abstracts on investigational treatments for infectious diseases including human immunodeficiency virus (HIV) and hepatitis C, as well treatment of skin, soft tissue, and fungal infections. Dr. Mullane has also participated in numerous lectures and grand rounds on topics such as HIV, West Nile virus, tuberculosis, fungal infections, and sexually transmitted diseases.

Dr. Mullane currently holds positions on the *American Journal of Transplantation* and *Transplant Infectious Diseases* journal review panels. She is the Director of Infectious Diseases Clinical Trials, Chairman of the Antibiotic Subcommittee, and a member of various BSD committees at the University of Chicago. In 2004, she was the recipient of the Inspirational Attending of the Year at Loyola University Medical Center.
Stuart Johnson, MD, DTM&H, is a professor of medicine at Loyola University Stritch School of Medicine at Loyola University Medical Center in Maywood, Illinois and the Deputy ACOS for Research at the Hines VA Hospital. Dr. Johnson received his MD from the University of Minnesota Medical School and completed his internal medicine residency and infectious disease fellowship training at the University of Minnesota Hospital and the Minneapolis VA Medical Center. He received a diploma in Tropical Medicine and Hygiene at Mahidol University in Bangkok, Thailand and a Career Development Award from the Department of Veterans Affairs. He is the past president of the Anaerobe Society of the Americas.

His main research interest and focus has involved the epidemiology and pathogenesis of Clostridium difficile infections. He is actively studying variant strains of C. difficile and the role of the various toxins in the pathogenesis of C. difficile disease. He also has been involved in clinical research on the parasite, Angiostrongylus cantonensis, responsible for most cases of eosinophilic meningitis, world-wide.
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Live ACPE Release Date: October 22, 2011

Type of Activity: Knowledge

Pharmacy Educational Objective
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• Provide accurate and appropriate counsel as part of the treatment team

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After completing this activity, the participant should be able to:
• Provide appropriate care and counsel for patients and their families

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Media
Internet

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- Dale Gerding, MD, FACP, FIDSA, has affiliations with ViroPharma (Patent); ViroPharma, Merck, Pfizer, Optimer, Cubist, TehraDoc, Medicines Co., Astellas, and Actelion (Advisory Board); and Merck, Optimer, GOJO, Sanofi Pasteur, ViroPharma, Actelion, and Eurofins Medinet (Research).
- Stephen M. Brecher, PhD, has no affiliations with commercial interests to disclose.
- Kathleen Mullane, DO, PharmD, has affiliations with Actelion Pharmaceuticals Ltd, Cubist, Sanofi Pasteur SA, and ViroPharma Incorporated (Research); and Merck & Co., Inc., Novartis AG, and Optimer Pharmaceuticals, Inc. (Research and Consultant).

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- Sherri Kramer, MD, has no affiliations with commercial interests to disclose.
- Nora Duffy has no affiliations with commercial interests to disclose.

Postgraduate Institute for Medicine
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- Julia Kimball, RN, BSN, has no affiliations with commercial interests to disclose.
- Samantha Mattiucci, PharmD, has no affiliations with commercial interests to disclose.
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The opinions expressed in this presentation are those of the presenter and do not necessarily represent the views of the Veterans Affairs Health-Care System.

Overview

- Recent guidelines for testing
- Overview of testing
- RIP for EIA
- Molecular tests
- Repeat testing
- Mural dyslexia
The Most Accurate Method to Diagnose *C. difficile* is

1. EIA
2. GDH
3. EIA/GDH combined
4. PCR

Specimens for *C. difficile* Should Be

1. Frozen before testing to release toxin
2. Heated to select for spores
3. Stored at room temperature
4. Fresh and loose
What Do You Want for CDI Testing?

1. An assay with low sensitivity and high specificity (false negatives)
2. An assay with high sensitivity and low specificity (false positives)
3. An assay that is inexpensive, easy, and quick to perform
4. I want to get it right even if it is very expensive

Clinical Practice Guidelines 2010 SHEA and IDSA

• Test only unformed stool (exception: ileus)
• Do not perform a test of cure
• Stool cultures sensitive but not practical except for epidemiological studies
• EIA is rapid, not very sensitive and is sub-optimal
• 2 step GDH and EIA is an interim recommendation
• More data needed on PCR before they can recommend
• Repeat testing discouraged

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Clostridium difficile Infection: Emerging Therapies and Recurrence Prevention
A Practical Guidance Document for the Laboratory Detection of Toxigenic *Clostridium difficile*

**ASM September 21, 2010 (ASM online)**

- Utilizing toxin A/B EIA for *C. difficile* diagnosis is insensitive and no longer recommended as a stand-alone test
- GDH antigen assays have been found to be good screening tests for CDI in many studies (high sensitivity and NPV)
- +GDH must be confirmed (need + A/B EIA or + cytotoxin or + nucleic acid amplification test (NAAT))
- NAAT can be used as a stand alone test
- Do not perform a test of cure

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*C. difficile* Testing 1984 – 2010

Ducks in a Row?
**Laboratory Diagnosis of CDI**

- Glutamate Dehydrogenase (GDH)
- Enzyme Immunoassay (EIA)
- Cell Culture Neutralization Assay (CCNA)
- Toxigenic Culture (Culture and CCNA)
- Stool Culture
- Molecular Based (PCR or LAMP)

**Specimen and Testing Guidelines**

- Use the “Brecher” guidelines
  - Only test loose or liquid stool
    - “If it ain’t loose, it’s of no use”
  - Stick test for stool consistency
    - “If the stick stands, the tests are banned
    - If the stick falls, test them all”
- Limit testing to 1 test/patient/week (if using PCR)
- Do not perform a test for cure
- Do not perform tests on asymptomatic patients
CDI Testing Issues

- What is the gold standard?
- Is it time to abandon EIA?
- What about 2-3 step algorithms (difficile dancing)?
- Is PCR/molecular ready for prime time?

The Gold Standard is Tarnished*

- All *C. difficile* test assay studies are flawed
- There is no reliable gold standard¹
- Patients can carry toxigenic strains
- Suggested gold standard has to include a very reliable assay as well as the clinical status of the patient

*"Rate Sin With Gold and it Goes Untarnished" W. Shakespeare

CDI Testing Issues

- What is the gold standard?
- Is it time to abandon EIA?
- What about 2-3 step algorithms (difficile dancing)?
- Is PCR/molecular ready for prime time?

Conflicting Results with EIA

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>32 – 98.7%</td>
</tr>
<tr>
<td>Specificity</td>
<td>92 – 100%</td>
</tr>
<tr>
<td>PPV</td>
<td>76.4 – 96%</td>
</tr>
<tr>
<td>NPV</td>
<td>88 – 100%</td>
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</tbody>
</table>

Recently Published EIA Papers(1-6)

- With an average sensitivity of 60-70%, do not perform as a stand-alone test
**CDI Testing Issues**

- What is the gold standard?
- Is it time to abandon EIA?
- What about 2-3 step algorithms (difficile dancing)?
- Is PCR/molecular ready for prime time?

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**C. Diff Quik Chek Complete**

- Lateral flow GDH and EIA on one test card
- 2 recent studies
  - Quinn et al. reported that if
    - Both + = +
    - Both - = -
    - 13.2% discrepant, re-test. Use PCR
  - Sharp et al. reported that 88% of specimens were both positive or both negative
    - Used random access PCR to resolve remaining 12%

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Possible Explanation for EIA and GDH Tests Failure

- Tenover et al\(^1\) reported that EIA testing of certain ribotypes (002, 027, and 016) had very poor sensitivity compared to PCR
  - EIA test failures may be associated with geographical ribotype differences
- GDH had lower sensitivity for non-027 ribotypes
- GDH has equal sensitivity (to PCR) for 027 ribotypes

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CDI Testing Issues

- What is the gold standard?
- Is it time to abandon EIA?
- What about 2-3 step algorithms (*difficile dancing*)?
- Is PCR/molecular ready for prime time?

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### Commercially Available Molecular Assays

<table>
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<th>Assay</th>
<th>Target</th>
<th>Instrument</th>
<th>TAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>BD GeneOhm&lt;sup&gt;TM&lt;/sup&gt; C.diff Assay</td>
<td>Toxin B</td>
<td>SmartCycler Amplication</td>
<td>75-120 min</td>
</tr>
<tr>
<td>Prodesse proGASTRO&lt;sup&gt;TM&lt;/sup&gt;</td>
<td>Toxin B</td>
<td>easyMag extraction SmartCycler Amplication</td>
<td>~ 3 hrs</td>
</tr>
<tr>
<td>Cepheid Xpert&lt;sup&gt;TM&lt;/sup&gt; C. difficile</td>
<td>Toxin B, tcdC deletion</td>
<td>GeneXpert</td>
<td>45 min</td>
</tr>
<tr>
<td>Meridian Illumigene</td>
<td>conserved 5' sequence of the tcdA gene</td>
<td>Illumigene Incubator/reader</td>
<td>45-60 min</td>
</tr>
</tbody>
</table>

Slide provided by Dr. Susan Novak-Weekley, modified by Dr. S. Brachter

### BD GeneOhm<sup>TM</sup> C. diff Assay Procedure Overview

Results in <2 Hours

Slide courtesy BD GeneOhm
Clostridium difficile Infection: Emerging Therapies and Recurrence Prevention

**Illumigene Assay Protocol**

- **Illumigene-10** provides walk-away amplification and detection.
- No precision pipetting (3 x 50µl pipetting steps)
- Amplicons contained in sealed & locked Illumigene-device
- Total assay:
  - < 2 min hands-on time
  - < 60 minutes to result
  - No centrifugation or precision pipetting required

**Summary of C. difficile PCR Published Data (2010-2011)**

<table>
<thead>
<tr>
<th>Publication</th>
<th>PCR Assay</th>
<th>Sens/Spec</th>
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</thead>
<tbody>
<tr>
<td>Chapin, 2011</td>
<td>Compared 3 molecular methods</td>
<td>88.5-96.2%/91.6-100% (range)</td>
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<tr>
<td>Noren, 2011</td>
<td>Illumigene (LAMP)</td>
<td>98%/98.6%</td>
</tr>
<tr>
<td>Kvach, 2010</td>
<td>BD GeneOhm</td>
<td>91.4%/100%</td>
</tr>
<tr>
<td>Novak-Weekley, 2010</td>
<td>Cepheid Xpert</td>
<td>94.4%/96.3%</td>
</tr>
<tr>
<td>Swindells, 2010</td>
<td>Cepheid Xpert</td>
<td>100%/99.2%</td>
</tr>
<tr>
<td></td>
<td>BD GeneOhm</td>
<td>94.4%/99.2%</td>
</tr>
</tbody>
</table>

Diagnostic Accuracy of Real-time Polymerase Chain Reaction in Detection of Clostridium difficile in the Stool Samples of Patients With Suspected Clostridium difficile Infection: A Meta-Analysis

- 19 studies, 7382 samples, 15 years (1995-2010)
- Mean sensitivity was 90%
- Mean specificity was 96%
- As prevalence increased, accuracy increased


Camp Clin Micro

- 40 Microbiologists met in Houston last February
- Consensus opinion on C. difficile testing¹
  - EIA for Toxins A&B should not be used
  - 2 step tests (GDH and Toxin A&B) with confirmation of discrepant results acceptable
  - Used appropriately, molecular based tests are preferred

If the First PCR is Negative Should I Order Another PCR?

- Of 406 tests from 293 patients with a prior negative PCR
  - 396 negative
  - 10 positive
    - Only 3+ in <7 days
- Exceptions
  - Severe clinical changes


Consequences of Unreliable CDI Assays

- Repeat testing (common to order x 3)
- Low sensitivity
  - False negative patients don’t get treated and spread the organism
- Low specificity
  - False positive patients get costly treatments and IC protocols

Consequences of Improved CDI Assays

- Increased sensitivity
  - True prevalence (will go up with PCR)
  - Infected patients treated and put on Infection Control (IC) protocols sooner
- Increased specificity
  - Prevent unnecessary treatment
  - Improved utilization of IC protocols
- Increased productivity
  - Eliminate duplicate/triplicate testing
  - Improves lab utilization and image

Which Molecular Test Should I Use?

- Do your homework
- Look at
  - Reagent costs
  - Equipment costs
  - TAT/Hands on time
  - Batch or on demand
  - Prevalence of CDI
  - Cost of incorrect tests
Do I Need to Test for the “Hypervirulent” Ribotype?

- The fidaxomycin treatment relapse rate was significantly lower than the vancomycin relapse rate for all strains except NAP1/B1/027.
- The Cepheid PCR assay can detect the gene deletion associated with this strain (tcdC).
- Recommend treating patients based on symptoms and severity of disease, not the strain.
  - Need more data.


Mural Dyslexia

- We don’t see the big picture because we have become bean counters.
  - “we can’t afford to do PCR”
- We can save money by spending money.
- With an accurate method and strict specimen requirements, test volume will decrease.
  - Boston VA HCS: Test volume decreased by 50% with PCR.
- With the correct diagnosis:
  - Appropriate treatment gets patients home faster and that’s the way to save money (LOS).
  - IC dollars spent on the right patients.
Recommendations

- Test by a molecular method
- Test only unformed stool in symptomatic at-risk patients
- Test only 1 stool/patient/week
- Do not perform a test of cure
- Remember no lab test is perfect so correlate test results with patient data/clinical observations
- There is light at the end of the colon!!!
**Clostridium difficile: Pathophysiology, Risk Factors, and Recurrence**

Kathleen M. Mullane, D.O., Pharm. D., FIDSA
University of Chicago
Department of Medicine / Section of Infectious Diseases

**Disclosures**

- Clinical trials research in CDI (*C. difficile* infection)
  - Actelion
  - Cubist
  - Merck
  - Novartis
  - Optimer
  - Sanofi-Pasteur
  - Viropharma
- Protocol / publication committees
  - Merck
  - Novartis
  - Optimer
**CDI Pathophysiology**

- Ingestion of vegetative organisms and spores
- Overgrowth of toxigenic strains of *C. difficile*
  - Antibiotics
  - Chemotherapy
- Production of toxins
  - Toxin A (TcdA) classically: endotoxin
  - Toxin B (TcdB) classically: cytotoxin
  - *C. difficile* binary toxin (CDT) some strains
  - Isolates lacking toxins are nonpathogenic

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**CDI Pathophysiology**

- Development of a range of clinical signs
  - Mild to severe self-limiting diarrhea
  - Life-threatening pseudomembranous colitis
  - Toxic megacolon / intestinal perforation
  - Systemic inflammatory response syndrome (SIRS)
    - Intestinal tissue damage and inflammation
### Patient Characteristics as Risk Factors for Acquisition of CDI

- Aged > 65 years
- Multiple Medical Co-morbidities
  - Antibiotic therapy
    - Cefazolin, Clindamycin, Fluoroquinolones
  - Inflammatory bowel disease
  - Chemotherapy / Bone marrow transplant
  - Renal impairment
  - Human immunodeficiency virus (HIV)
  - Organ transplant
- PPI

### Predictors of Hospital-Acquired CDI

- Hospital-level predictors
  - More likely to have concurrent infections (rank)
    - *Pseudomonas*, *Staphylococcus*, *Streptococcus*, *E. coli*
  - Discharge diagnosis of infection
    - Bloodstream infections, endocarditis, osteomyelitis, pneumonia, UTI and cellulitis
  - Low nurse : patient and resident : patient ratio
  - Slow bed turnover (ie: longer LOS)
    - Cardiac intensive care services
    - Transplant services
Risk Factors for Community Acquired CDI

- Antimicrobial drug exposure ≤ 1 month
- Anti-motility agent use
- Recent hospitalization (< 6 months)
- Markers of chronic disease
  - Frequent outpatient visits
  - GERD (? Proton pump inhibitors / H2 blockers)
    - OTC use of agents may not be well accounted
  - Cardiac failure
- Contact with infants ≤ 2 years

Community Acquired CDI Risk Factors

- Foodborne: Meats and produce?
  - *C. difficile* isolated from the feces of food animals
    - Cattle/calves, pigs/piglets, horses and chickens
    - Role in causing disease in some animals is unclear, but is well documented in piglets (typhlycolitis)
  - Few small studies in various geographic regions with different sampling / culture methods
    - Colonization rates decrease from sucklings to finishers
    - Potential concern: shedding by asymptomatic animals
      - Causing contamination of food, water, and the environment
  - Etiology of colonization unknown (humans: animals)
  - PCR Ribotype 078 most common pig strain and increasingly prevalent human strain
Clostridium difficile Infection: Emerging Therapies and Recurrence Prevention

**TcdA and TcdB Multifactorial Activities**

- Clostridial Glucosylating toxin family
  - Large Clostridial Toxins (large molecular mass)
  - Direct toxin target is colonic epithelium
    - Receptor mediated endocytosis followed by pore formation and translocation into the cytosol
    - Target/modify small GTPases of the Rho/Ras family
      - Molecular switches involved in signaling processes
        - Regulation of the actin cytoskeleton dynamics (Depolymerization disrupts tight junctions breaching intestinal-epithelial barrier / increased permeability)
        - Gene transcription / expression
        - Cell cycle progression / cell proliferation
        - Apoptosis

**TcdA and TcdB Multifactorial Activities**

- Enhanced permeability leads to immune cell stimulation
  - Cytokine / pro-inflammatory cytokine release
    - Mucosal damage causes expression of leukocyte and endothelial adhesion molecules
      - Neutrophil attachment and migration into mucosa
      - Acute / intense inflammation with neutrophil infiltration and destruction of enterocytes and colonocytes
      - Edema and cell damage
  - Induction of apoptosis of intestinal epithelial cells (lamina propria and submucosa)
    - TcdA: monocytes / mitochondria and T cells
    - TcdB: direct mitochondrial apoptosis
  - Necrosis: epithelial necrotic death

**Binary Toxin**

- CDT (*C. difficile* transferase)
  - Pathophysiologic role not well understood
  - Less than 10% of *C. difficile* isolates
    - Including 100% of NAP1/027 (toxinotype III)
  - Actin-ADP-ribosylating toxin
    - Cytopathic in cell culture
      - Modifies G-actin
    - Induces formation of microtubule-based protrusion
      - Increases adherence of bacteria to intestinal epithelium

---

**Risk factors for Severe CDI**

- Age >70
- Leukocyte count >20,000 cells/ml
- Albumin <2.5 g/dl
- Creatinine >2 mg/dl
- Presence of small bowel obstruction or ileus
- Computed tomography showing colorectal bowel wall thickening, stranding, ascites

**Prediction of CDI Outcome; ATLAS Scoring System**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0 points</th>
<th>1 point</th>
<th>2 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>&lt; 60</td>
<td>60-79</td>
<td>&gt;80</td>
</tr>
<tr>
<td>Temperature (C)</td>
<td>≤ 37.5</td>
<td>37.6-38.5</td>
<td>&gt; 38.6</td>
</tr>
<tr>
<td>Leukocytes (K)</td>
<td>&lt;16K</td>
<td>16K-25K</td>
<td>&gt;25K</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>&gt;35</td>
<td>25-35</td>
<td>&lt;25</td>
</tr>
<tr>
<td>Systemic concomitant antibiotics during CDI therapy</td>
<td>No</td>
<td>---</td>
<td>Yes</td>
</tr>
</tbody>
</table>

- ATLAS scores for 516 patients with CDI were calculated at their time of diagnosis and matched against their cure rates following 10 days of study treatment.
- Patients with an ATLAS score of 0 had a 98% cure rate.
- ATLAS scores of 7 corresponded to a 55% cure rate.

**Correlation of CDI rate with Age/Albumin and with ATLAS Score**

- **Actual rate** vs **Predicted rate (regression)**
  - (R²=0.57 P<0.001)
  - (R²=0.61 P<0.001)

- Age + Albumin
- Full ATLAS Score

[46th Annual Meeting of Int'l Soc Immun, Vancouver BC 2013]
Risk factors for recurrence

- Old age
- Concomitant antibiotics
  - Especially fluoroquinolones
- Low serum albumin
- Poor performance status
- Poor immune response against Toxin A or Toxin B
- Concomitant treatment with antacids / PPIs
- Concomitant VRE colonization
- Hospital acquired disease
- History of surgery
- Fecal incontinence
- Fecal microbiome disruption

CDI Recurrence by Age Group

- Proportion without a recurrence as a function of time after initial diagnosis of C. difficile-associated diarrhea
- Survival analysis for different age groups:
  - 0-17 years
  - 18-64 years
  - > 64 years

References:
Time to Resolution of Diarrhea with and without Concomitant Antibiotics (CA) Administered during CDI Treatment

Effect of Concomitant Antibiotics taken During Treatment or Any Time (Treatment or follow up)

- CAs concurrent with CDI treatment:
  - Lower cure rates compared to no CA (84% vs 93%; P < .001)
  - Cure rates for different treatment groups:
    - Fidaxomicin, 90% vs. vancomycin, 79% (P = .04)
- CA administration at any time
  - Lower global cure rate compared to no CA (66% vs 75%; P = .005)
  - Recurrence rates for different treatment groups:
    - Fidaxomicin, 16.9% and vancomycin, 29.2%; (P = .045)
**Prolonged Hospitalization or Stay in LTCF**

- Risk related to transmission of *C. difficile* spores
  - Primary source healthcare workers
    - may carry *C. difficile* spores on their hands (not likely fecal carriers)
  - Environmental contamination secondary source
- Up to 50% of LTCF residents and 40% of hospitalized patients have been found to be colonized with *C. difficile* or its toxin

**Defective immune response to toxin A**

- Generation of an antibody response to toxin A is associated with protection against symptomatic disease and asymptomatic carriage of *C. difficile*
- Following symptomatic infection, many individuals develop anti-toxin A and B antibodies
- Inability to acquire immunity to toxin A increases risk for recurrent disease
  - Individuals with recurrent CDI mount poor anti-toxin responses
Human Fecal Microbiota and CDI

- Complex ecosystem in symbiosis with host that is altered with antibiotics
  - Epithelium: immune cells: microbiota
    - 100 trillion bacteria colonize the gut
    - 200 to 1000 distinct bacterial species
  - All 3 play a defensive role
    - Essential for immune cell development and function
    - Peyer's patches, lymph nodes, spleen, immunoglobulins
  - Gut microbes cross talk across intestinal epithelium and the immune system
  - Colonization resistance (competition for space and nutrients)
  - Products of bacterial metabolism bactericidal
    - Short chain fatty acids, reactive oxygen species
    - Bacteriocin molecules

References:

Intestinal Microbiota & Risk of CDI

- Antibiotic perturbation manifests as decreased colonization resistance of commensals
  - Short term: quantity and composition
  - May have a long-term influence on return of gut flora to pre-treatment levels
    - Alter microbial diversity (Bacteroidetes/Firmicutes)
  - Antibiotic associated diarrhea
    - C. difficile, K. oxytoca, C. perfringens, Salmonella spp., Candida spp., and S. aureus

References:
Recurrent *C. difficile* Infection

- Rates of recurrent CDI
  - 20% after first episode
  - 45% after first recurrence
  - 65% after two or more recurrences
- Not a consequence of resistance to the 2 major treatment drugs: metronidazole or vancomycin
- Several empirical approaches to management have been advocated but most have no controlled data


Strategies Currently Available for Managing Recurrent CDI

- Vancomycin in tapering/pulsed doses
- *Saccharomyces boulardii*
- Rifaximin (400 mg bid x 14d) *following* vancomycin (the so called ‘Chaser’ regimen)
- Nitazoxanide (500 mg bid x 10d)
- IVIG (300 – 500 mg/kg)
- Fecal transplantation
- ??Fidaxomicin (200 mg bid x 10d)

*Vancomycin & fidaxomicin are the only FDA-approved agents for CDI*
Vancomycin Taper/Pulse Regimen

- 125 mg QID 10–14 days
- 125 mg BID 7 days
- 125 mg daily 7 days
- 125 mg once every 2 days 8 days
- 125 mg once every 3 days 15 days

Bacteriotherapy for Recurrent CDI: Changes in Fecal Microbiome
Conclusions

- *Clostridium difficile* infection continues to cause significant morbidity and mortality
- Understanding the pathophysiology (particularly, the role of toxins & immune response) may assist in the development of specific treatment modalities - Antitoxins, vaccines, specific antibodies
- Better patient assessment may assist in determination of level of risk and appropriate treatment in individuals with CDI & recurrent CDI
- Better understanding of the enteric microbiome may lead to better modalities of biologic therapy (synthetic stool?)

Question 1

- Documented risk factors for developing CDI include all of the following except:
  1. Diagnosis of inflammatory bowel disease
  2. History of receiving chemotherapy
  3. Antimicrobial drug exposure ≤ 1 month
  4. Eating veal cutlets in Canada
Question 2

- The ATLAS bedside CDI score includes all of the following except:
  1. Age
  2. Temperature
  3. Systolic blood pressure
  4. Leukocyte count
Emerging CDI Treatment Options and Infection Control

Stuart Johnson, MD DTM&H
Loyola University Medical Center
Hines VA Hospital

Disclosures

• Consultant: Optimer, ViroPharma, Astellas, Pfizer, Cubist, and Bio-K+
• Grants: VA Research Service
• FDA approved CDI Treatment Agents: Vancomycin, Fidaxomicin
A patient sees you with frequent watery stools, tender abdomen and low grade fever, she just finished treatment for CDI seven days ago (metronidazole 500 mg tid for 14 days), her WBC is 12,000/mm³; you recommend:

1. Repeat metronidazole, same regimen
2. Repeat metronidazole, but treat for 3 weeks
3. Start vancomycin 125 mg qid for 10 days
4. Start nitazoxanide 500 mg bid for 10 days

Which of the following drugs does not have FDA approval for treatment of CDI?

1. Metronidazole
2. Vancomycin capsules
3. Vancomycin solution
4. Fidaxomicin
Overview:

- Current SHEA/IDSA treatment guidelines
- Downsides of current CDI therapies
- Newly approved CDI treatment option
- Current infection control strategies
- Potential future infection control strategies

Clinical Practice Guidelines for CDI in Adults: 2010 Update by SHEA/IDSA: Treatment Recommendations

- Metronidazole is the drug of choice for the initial episode of mild-moderate CDI (500 mg orally TID) for 10-14 days (A-I)
- Vancomycin is the drug of choice for an initial episode of severe CDI*. The dose is 125 mg orally QID for 10-14 days (B-I)
- *Severe CDI defined as:
  - WBC > 15,000/mm³ or,
  - Cr > 1.5 x baseline

Available Antibiotics for Treatment of CDI (prior to May 2011):

- Metronidazole
- Vancomycin (only FDA-approved agent for CDI prior to May 2011)
- Nitazoxanide
- Rifaximin
- Bacitracin
- Tigecycline (anecdotal experience only for CDI)
- Teicoplanin**
- Fusidic Acid**

**Not available in the U.S.

---

Metronidazole

- Widely used in the US after 1994 CDC HICPAC caution against PO vancomycin (due to concern about potential resistance in Enterococci)\(^1\)
- Decreased cure rates; slower response time compared to vancomycin\(^2\)
- Risk of neurotoxicity with prolonged use\(^3\)
- Inferior to vancomycin for treatment of severe CDI\(^4\)

---

Fecal Drug Concentrations with Metronidazole Compared to Vancomycin (asymptomatic CD carriers)

Vancomycin

- Only agent approved for CDI in US by the FDA prior to May 2011
- Highly effective, but:
  - Higher cost vs metronidazole
  - Potential for selection of vancomycin-resistant Enterococci and Staphylococci
  - Frequent dosing
  - 20% (or more) rate of recurrence

Vancomycin Temporarily Clears *C. difficile* from Feces, but Prolongs Shedding! (Attempted CD Eradication from asymptomatic carriers)

![Graph showing the effect of Vancomycin and Metronidazole on *C. difficile* shedding over time.]

**Nitazoxanide (Prospective, Randomized, Comparative Trials for CDI)**

- **Compared to metronidazole (n=174)**
  - Similar response rates, but also similar recurrence rates:
    | Antimicrobial  | Response | Recurrence |
    |----------------|----------|------------|
    | Metronidazole  | 28/34 (82.4%) | 8/27 (29.6%) |
    | 250 mg qid x 10d |   |            |
    | Nitazoxanide   | 68/76 (89.5%) | 14/65 (21.5%) |
    | 500 mg bid x 7d or 10d |   |            |

- **Compared to vancomycin (n=50)**
  - Similar response rates (94% vs 87%)
  - Study too small to confirm non-inferiority or to assess recurrence rates

Rifaximin

- Rifaximin “chaser” therapy for multiple recurrent CDI (400mg bid x 2 wks, immediately following last course of vancomycin)
  - No further recurrence: 7/8 pts
    - 1 patient responded to 2nd rifaximin course
    - Follow-up isolate was resistant to rifaximin
  - No further recurrence: 2/6 pts
    - Rifaximin resistance identified in 1 isolate
- **Resistance risk similar to other rifamycins**
  - 36.8% of 470 recovered *C. difficile* isolates at 1 center were rifampin-resistant

---

The “Ideal” CDI Treatment

- Effective without recurrence
- Efficacious against virulent strains (eg, BI/027)
- Does not facilitate resistance
  - ...to *C. difficile* and other pathogens that reside in the gut, eg, *Enterococcus*
- Does not cross-react with clinically important antibiotics used for treating systemic infections eg, vancomycin
- Decreases spore shedding and transmission in the hospital setting
- Good safety profile

---

Newly Available CDI Therapy: Fidaxomicin

- Approved by FDA on May 27, 2011
- Indication and dosing¹
  - Treatment of *Clostridium difficile*-associated diarrhea (aka, CDI) in adults (≥18 years of age)
  - Recommended dose 200 mg orally bid for 10 d
- Advantageous characteristics¹,²
  - Minimal systemic absorption
  - Bactericidal agent unrelated to agents used for treatment of systemic infections
  - Narrow spectrum (less collateral damage to host flora)

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Fidaxomicin

- Rate of clinical cure with fidaxomicin non-inferior to that of vancomycin (phase 3 trial results)
- Fidaxomicin associated with significantly lower rate of CDI recurrence & similar adverse event profile
- Results of first phase 3 trial (nearly identical results from 2nd phase 3 trial):

![Graph showing clinical cure rates](image.png)
**Bacteroides Group Counts in Feces Before and After 10 Days of Treatment with Fidaxomicin* or Vancomycin**

*Fidaxomicin (200 mg twice daily), vancomycin (125 mg four times daily)

**Cure Rates for Fidaxomicin & Vancomycin in CDI Patients infected with BI- and non-BI Strains**

![Graph showing cure rates](image)
Fidaxomicin, Challenges

- Fidaxomicin challenges include:
  - Which patients should receive fidaxomicin treatment?
  - How will fidaxomicin fit in with the SHEA/IDSA guidelines for treatment based on severity?
  - Hospital formulary inclusion
  - Post approval monitoring for unanticipated side effects, evidence for resistance
- Additional potential antimicrobial agents in pipeline:
  - Ramoplanin, CB-183,315, etc. other

Which of the following infection control interventions for CDI is not based on clinical evidence?

1. Glove use when caring for patients with CDI
2. Hand washing with soap & water after gloving when caring for patients with CDI
3. Terminal cleaning of CDI patient rooms with bleach
4. Antimicrobial use restriction
Current Infection Control Strategies: Methods to Prevent Horizontal Transmission of *C. difficile*

- **Barrier Precautions:**
  - Gloves
  - Handwashing
  - Gowns
  - Patient Cohorting
- **Cleaning, Disinfection, Disposables**
  - Patient Rooms
  - Endoscopes
  - Rectal Thermometers

**Clinical Efficacy**
- Proven
- Probable
- Untested
- Probable

Randomized Study of Gloves for CD Intervention

- Four wards randomized
- Intervention
  - Education: gloves when handling body substances (stool, blood, urine)
  - Gloves placed at bedside
- Significant reduction in CDI rate on glove wards

Hand Hygiene for CDI Intervention

- Appropriate hand hygiene – area of controversy
  - In routine settings, alcohol-based hand hygiene *in conjunction with isolation precautions using gloves* may be acceptable
  - In setting of outbreak or increased rates, consider washing hands with soap and water after caring for patients with *C. difficile*


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Time Series Study of Environment Disinfection with Bleach

![Graph showing time series study of environment disinfection with bleach]

- Pre
- Post

- HR = 0.37
- HR = 0.93
- HR = 1.11

- HSCT unit
- Neuro ICU
- Medicine

- Intervention Unit

### Current Infection Control Strategies: Methods to Reduce the Risk of *C. difficile* Diarrhea if Exposed to the Organism

<table>
<thead>
<tr>
<th>Method Used</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Antimicrobial use restriction</td>
<td>Proven</td>
</tr>
<tr>
<td>(clindamycin, 3rd gen cephalosporins, fluoroquinolones)</td>
<td></td>
</tr>
<tr>
<td>- Prophylactic treatment of patients receiving antimicrobials probiotics</td>
<td>Possible</td>
</tr>
</tbody>
</table>

### Potential Future Strategies for Prevention

- **Primary Prevention**
  - Active Vaccination
  - ‘Effective Probiotics/Biotherapeutics’
- **Secondary Prevention**
  - Adjunctive Monoclonal Antibodies
  - Luminal Toxin Binders *(tolevamer: No current plans for development)*
### C. difficile Toxoid Vaccine in 3 Patients with Chronic Recurrent CDI

![Graphs showing the effectiveness of toxoid vaccine against C. difficile over time.](image)


### Provocative Probiotic Primary Prevention Studies for Antibiotic-associated Diarrhea (ADD) and C. difficile infection (CDI)

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Placebo</th>
<th>Probiotic</th>
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</thead>
<tbody>
<tr>
<td>Probiotic Drink*</td>
<td>AAD: 34% CDI: 17%</td>
<td>AAD: 12% CDI: 0%</td>
</tr>
<tr>
<td>Probiotic Capsule†</td>
<td>AAD: 44% CDI: 24%</td>
<td>AAD: 28% CDI: 9%</td>
</tr>
</tbody>
</table>

*Lactobacillus casei, L. rhamnosus, Bifidobacterium longum
†Lactobacillus plantarum 299v, L. rhamnosus GG 100,000

Multiple criticisms of these studies: exclusion criteria, study blinding, & unexplained high rate of CDI in controls
Conclusions:

- Currently available antimicrobial agents for treatment of CDI have several limitations; eg, recurrence after initially successful treatment
- Fidaxomicin, a newly-approved antimicrobial that appears to be a more narrow spectrum agent shows promise as an improved treatment for CDI
- Proven infection control interventions include gloving, antimicrobial restriction, and replacing rectal thermometers with disposable units; Hand hygiene & environmental decontamination with sporocidal agents are likely important, but may not be needed universally
- Future prevention strategies include immunotherapy & more effective probiotics
REFERENCES

Stephen M. Brecher, PhD


REFERENCES

Kathleen Mullane, DO, PharmD


REFERENCES

Stuart Johnson, MD, DTM&H


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