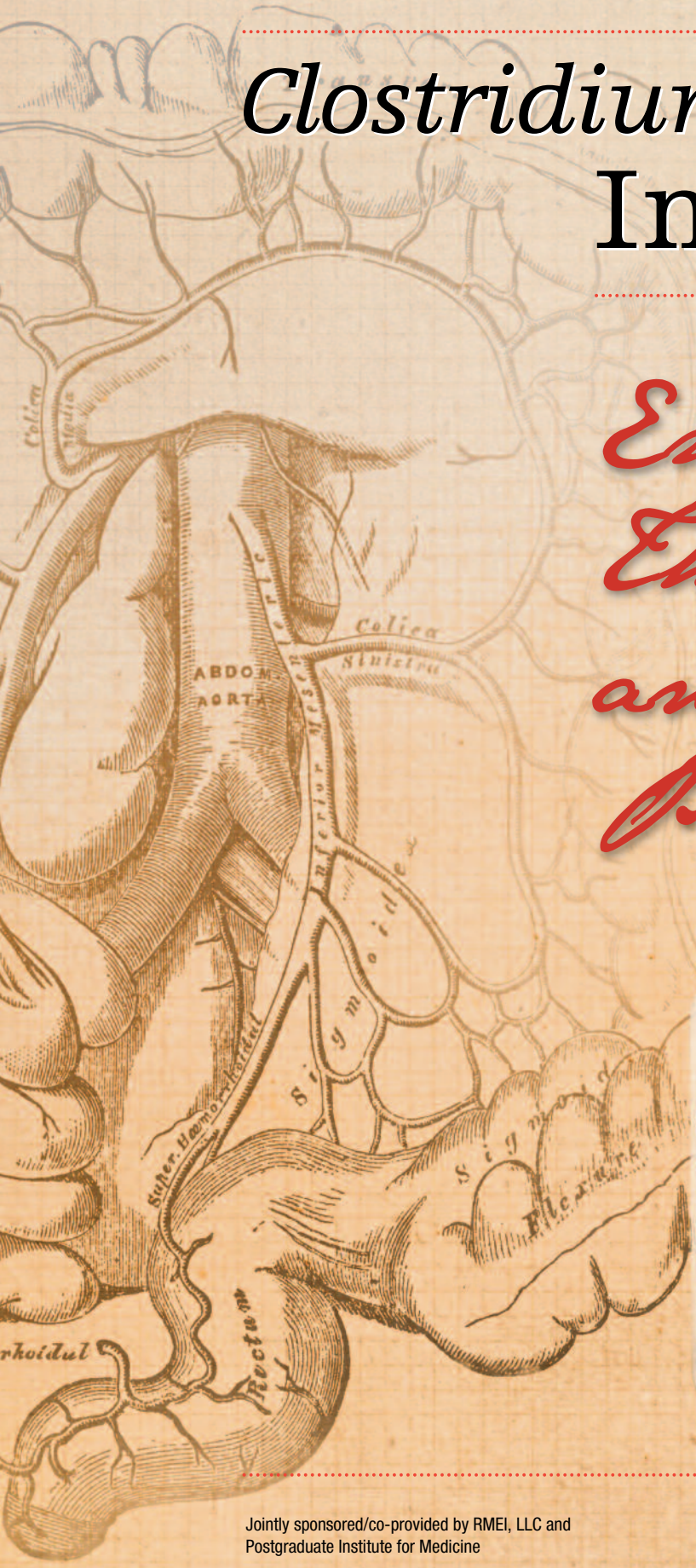
WORKBOOK

Clostridium difficile Infection:

Emerging Therapies and Recurrence Prevention



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October 22, 2011

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December 20, 2012

Estimated time to complete this activity: 2 hours

Jointly sponsored/co-provided by RMEI, LLC and Postgraduate Institute for Medicine

RMEI MEDICAL EDUCATION FOR BETTER OUTCOMES

PIM Postgraduate Institute for Medicine

RMEI gratefully acknowledges an educational grant from Optimer in support of this CE activity

OPTIMER

CONTENTS

WELCOME

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

OVERVIEW

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.

1 Zilberberg MD, et al. *Emerg Infect Dis*. 2008;14:929-931.

2 Byker GL, et al. *Infect Control Hosp Epidemiol*. 2009;30:397-399.

3 Association for Professionals in Infection Control (APIC) Pace of Progress poll. May 2010.

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

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FACULTY BIOGRAPHIES

Dale N. Gerding,
MD, FACP, FIDSA (Moderator)

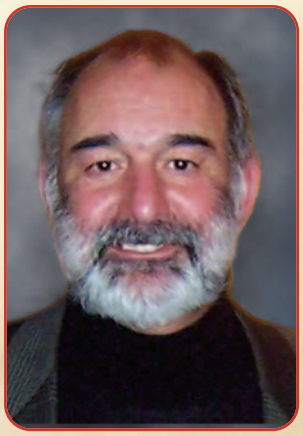
Professor of Medicine
Loyola University Chicago
Stritch School of Medicine
Maywood, IL
Research Physician
Hines Veterans Affairs Hospital
Hines, IL

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.

FACULTY BIOGRAPHIES



Stephen M. Brecher, PhD

Director of Microbiology
VA Boston Healthcare System
West Roxbury, MA

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.

FACULTY BIOGRAPHIES

Kathleen Mullane,
DO, PharmD

Associate Professor of Medicine
University of Chicago
Chicago, IL

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.

FACULTY BIOGRAPHIES

Stuart Johnson,

MD, DTM&H

Professor of Medicine
Loyola University Medical Center
Stritch School of Medicine
Maywood, IL
Staff Physician
Hines VA Hospital
Hines, IL

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.

ACCREDITATION & CREDIT

Physician Continuing Education

Accreditation Statement

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Postgraduate Institute for Medicine and RMEI, LLC. Postgraduate Institute for Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation

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Live ACPE Release Date: October 22, 2011

Type of Activity: Knowledge

Pharmacy Educational Objective

After completing this activity, the participant should be able to:

- Provide accurate and appropriate counsel as part of the treatment team

A statement of credit will be issued only upon receipt of a completed activity evaluation form and will be mailed to you within 3 weeks.

Nursing Continuing Education

Credit Designation

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California Board of Registered Nursing

Provider approved by the California Board of Registered Nursing, Provider Number 13485, for 1.9 contact hours.

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Nursing Educational Objective

After completing this activity, the participant should be able to:

- Provide appropriate care and counsel for patients and their families

Method of Participation and Request for Credit

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PIM supports Green CME by offering your Request for Credit online. If you wish to receive acknowledgment for completing this activity, please complete the post-test and evaluation on www.cmeuniversity.com. On the navigation menu, click on "Find Post-test/Evaluation by Course" and search by course ID 8232. Upon registering and successfully completing the post-test with a score of 70% or better and the activity evaluation, your certificate will be made available immediately. Processing credit requests online will reduce the amount of paper used by nearly 100,000 sheets per year.

Media

Internet

Fee Information

There is no fee for this educational activity.

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The ***faculty*** reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

- **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)*.
- **Stuart Johnson, MD, DTM&H,** has affiliations with Optimer Pharmaceuticals, Inc., ViroPharma Incorporated, Astellas Pharma US, Inc., Pfizer, Cubist Pharmaceuticals, and Bio-K+ *(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.

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- **Jan Hixon, RN, BSN, MA,** has no affiliations with commercial interests to disclose.
- **Trace Hutchison, PharmD,** has no affiliations with commercial interests to disclose.
- **Julia Kimball, RN, BSN,** has no affiliations with commercial interests to disclose.
- **Samantha Mattiucci, PharmD,** has no affiliations with commercial interests to disclose.
- **Jan Schultz, RN, MSN, CCMEP,** has no affiliations with commercial interests to disclose.
- **Patricia Staples, MSN, NP-C, CCRN,** has no affiliations with commercial interests to disclose.

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Disclaimer

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Clostridium difficile
Infection:
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and Recurrence Prevention
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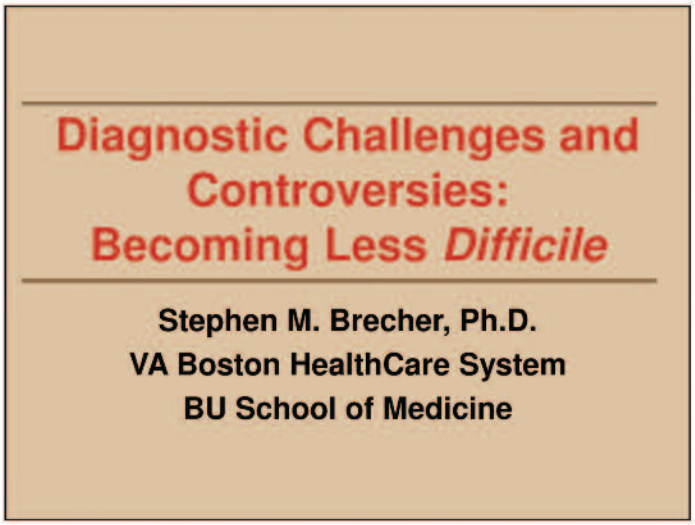
Diagnostic Challenges and
Controversies:
Becoming Less Difficile
Stephen M. Brecher, Ph.D.
VA Boston HealthCare System
BU School of Medicine

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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

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Overview

- Recent guidelines for testing
- Overview of testing
- RIP for EIA
- Molecular tests
- Repeat testing
- Mural dyslexia

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The Most Accurate Method to Diagnose *C. difficile* is

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

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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

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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

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Clinical Practice Guidelines 2010 SHEA and IDSA[1] Summary

- 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

Cohen SH, et al. *Infection Control and Hospital Epidemiology*. 2010;31:431-455.

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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?

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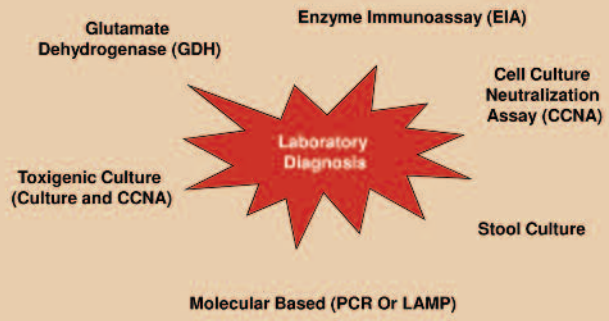
Laboratory Diagnosis of CDI



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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

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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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The Gold Standard is Tarnished*

- All *C. difficile* test assay studies are flawed
- There is no reliable gold standard[1]
- Patients can carry toxigenic strains
- Suggested gold standard has to include a very reliable assay as well as the clinical status of the patient

"Plate Sin With Gold and it Goes Untarnished" W. Shakespeare

1. Wilcox MH, et al. *J Clin Microbiol.* 2010;48(12):4347-4353.

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CDI Testing Issues

- What is the gold standard?
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Conflicting Results with EIA

Recently Published EIA Papers[1-6]	
Parameter	Range
Sensitivity	32 – 98.7%
Specificity	92 – 100%
PPV	76.4 – 96%
NPV	88 – 100%

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

1. Stamper PD, et al. *J Clin Microbiol.* 2009;47:373-378.
2. Musher DM, et al. *J Clin Microbiol.* 2007;45:2737-2739.
3. Sloan LM, et al. *J Clin Microbiol.* 2008;46:1996-2001.
4. Gilligan PH. *J Clin Microbiol.* 2008;46:1523-1525.
5. Ticehurst JR. *J Clin Microbiol.* 2006;44:1145-1149.
6. Planche T, et al. *Lancet Infect Dis.* 2008;8(12):777-784.

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CDI Testing Issues

- What is the gold standard?
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C. Diff Quik Chek Complete

- Lateral flow GDH and EIA on one test card
- 2 recent studies
  - Quinn et al[1] reported that if
    - Both + = +
    - Both - = -
    - 13.2% discrepant, re-test. Use PCR
  - Sharp et al[2] reported that 88% of specimens were both positive or both negative
    - Used random access PCR to resolve remaining 12%

1. Quinn CD, et al. *J Clin Microbiol.* 2010;48:603-605.
2. Sharp SE, et al. *J Clin Microbiol.* 2010;48:2082-2086.

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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 106) 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

1. Tenover FC, et al. *J Clin Microbiol*. 2010;48:3719-3724.

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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

Assay	Target	Instrument	TAT
BD GeneOhm™ Cdiff Assay	ToxinB	SmartCycler Amplification	75-120 min
Prodesse proGASTRO™	Toxin B	easyMag extraction SmartCycler Amplification	~ 3 hrs
Cepheid Xpert™ *C. difficile*	Toxin B+/- *tcdC* deletion	GeneXpert	45 min
Meridian Illumigene	conserved 5' sequence of the *tcdA* gene	illumigene Incubator/reader	45-60 min

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

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BD GeneOhm™ *C. diff* Assay Procedure Overview

Slide courtesy BD GeneOhm

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proGASTRO™ Cd Workflow
Specimens
Clarified Stool
Add buffer, Vortex & spin
Dilute Internal Control. Combine 20 µl clarified stool and 10 µl Internal Control
Run Lysis, Add Beads
Perform extraction and elute in 110 µl
110 µl of nucleic acid for analysis
Slide courtesy Gen-Probe

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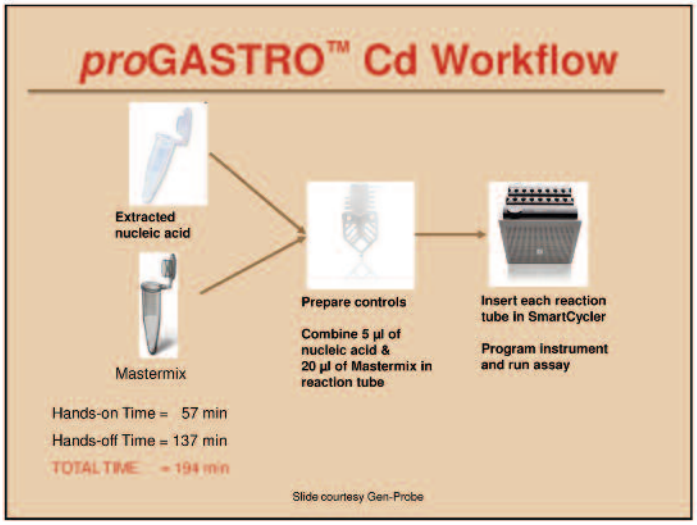
proGASTRO™ Cd Workflow
Extracted nucleic acid
Mastermix
Prepare controls
Combine 5 µl of nucleic acid & 20 µl of Mastermix in reaction tube
Insert each reaction tube in SmartCycler
Program instrument and run assay
Hands-on Time = 57 min
Hands-off Time = 137 min
TOTAL TIME = 194 min
Slide courtesy Gen-Probe

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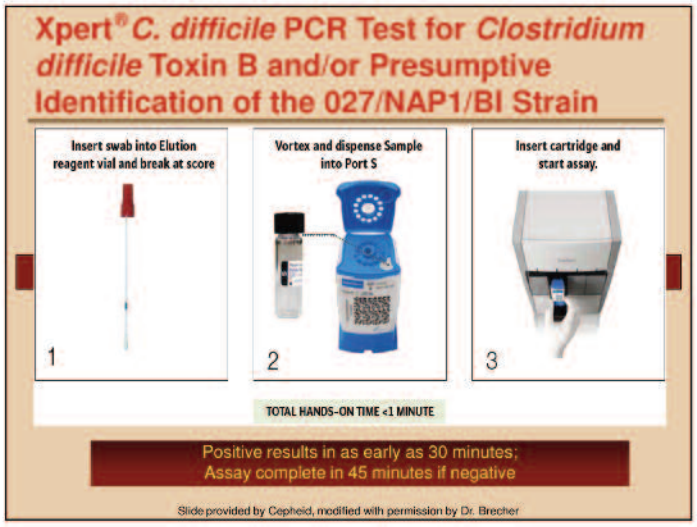
Xpert® C. difficile PCR Test for Clostridium difficile Toxin B and/or Presumptive Identification of the 027/NAP1/BI Strain
Insert swab into Elution reagent vial and break at score
1
Vortex and dispense Sample into Port S
2
Insert cartridge and start assay.
3
TOTAL HANDS-ON TIME <1 MINUTE
Positive results in as early as 30 minutes; Assay complete in 45 minutes if negative
Slide provided by Cepheid, modified with permission by Dr. Brecher

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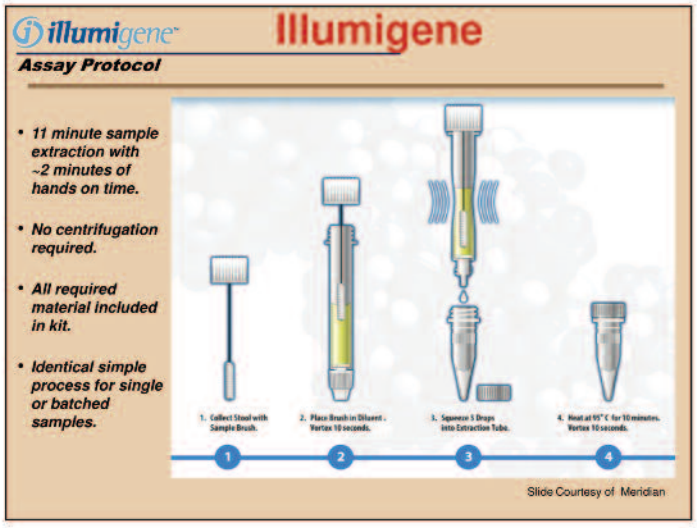
illumigene
Illumigene
Assay Protocol
• 11 minute sample extraction with ~2 minutes of hands on time.
• No centrifugation required.
• All required material included in kit.
• Identical simple process for single or batched samples.
1
2
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Slide Courtesy of Meridian

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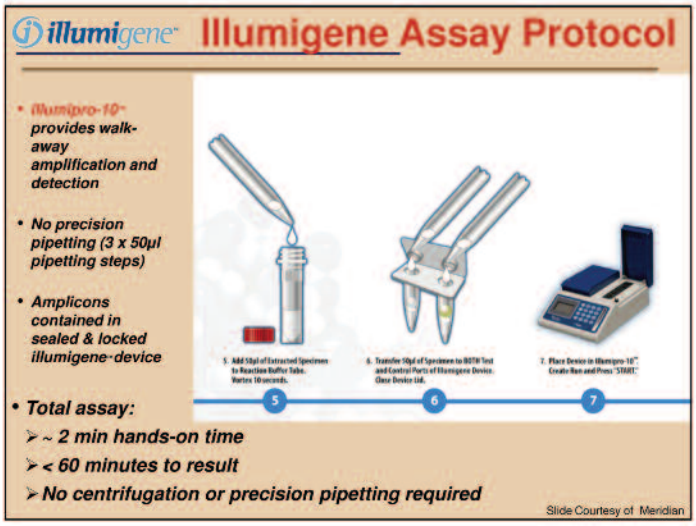
illumigene
Illumigene Assay Protocol
• Illumipro-10™ provides walk-away amplification and detection
• No precision pipetting (3 x 50µl pipetting steps)
• Amplicons contained in sealed & locked illumigene-device
• Total assay:
➢ ~ 2 min hands-on time
➢ < 60 minutes to result
➢ No centrifugation or precision pipetting required
5
6
7
Slide Courtesy of Meridian

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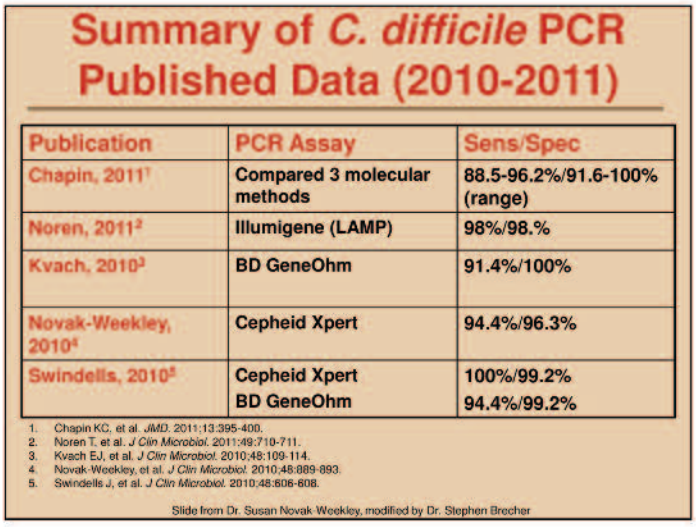
Summary of C. difficile PCR Published Data (2010-2011)
Publication
PCR Assay
Sens/Spec
Chapin, 2011[1]
Compared 3 molecular methods
88.5-96.2%/91.6-100% (range)
Noren, 2011[2]
Illumigene (LAMP)
98%/98.%
Kvach, 2010[3]
BD GeneOhm
91.4%/100%
Novak-Weekley, 2010[4]
Cepheid Xpert
94.4%/96.3%
Swindells, 2010[5]
Cepheid Xpert
BD GeneOhm
100%/99.2%
94.4%/99.2%
1. Chapin KC, et al. JMD. 2011;13:395-400.
2. Noren T, et al. J Clin Microbiol. 2011;49:710-711.
3. Kvach EJ, et al. J Clin Microbiol. 2010;48:109-114.
4. Novak-Weekley, et al. J Clin Microbiol. 2010;48:889-893.
5. Swindells J, et al. J Clin Microbiol. 2010;48:606-608.
Slide from Dr. Susan Novak-Weekley, modified by Dr. Stephen Brecher

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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, 7392 samples, 15 years (1995-2010)
- Mean sensitivity was 90%
- Mean specificity was 96%
- As prevalence increased, accuracy increased

Deshpande A. et al. *Clin Infect Discord.* 2011;53:e81-e90. October, 2011.

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Camp Clin Micro

- 40 Microbiologists met in Houston last February
- Consensus opinion on *C. difficile* testing[1]
  - EIA for Toxins A&B should not be used
  - 2 step tests (GDH and Toxins A&B) with confirmation of discrepant results acceptable
  - Used appropriately, molecular based tests are preferred

1. Carroll KC, et al. *J Clin Microbiol.* 2011;49:S49-S52.

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

- Of 406 tests from 293 patients with a prior negative PCR[1]
  - 396 negative
  - 10 positive
    - Only 3+ in <7 days
- Exceptions
  - Severe clinical changes

1. Luo RF, Banaei N. *J Clin Microbiol.* 2010;48:3738-3742.

31

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[1]
- Low specificity
  - False positive patients get costly treatments and IC protocols

1. Guerrero DM, et al. *Clin Infect Dis.* 2011;53:287-290.

32

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

33

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

34

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[1]
- 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

1. Louie TJ, et al. *N Eng J Med.* 2011;364:422-431.

35

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

36

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!!!

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C. difficile Testing 2011 Heading in the Right Direction

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Clostridium difficile: Pathophysiology, Risk Factors, and Recurrence

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Department of Medicine / Section of Infectious Diseases

1

Disclosures

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

2

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

3

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

4

Patient Characteristics as Risk Factors for Acquisition of CDI

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

2008 Nationwide Inpatient Sample, 2009 Medicare Provider Analysis and Review file, Florida fiscal year 2006-2007 Medicaid claims and 2007-2008 Medicare 5% Standard Analytical Files. Dubberke, et. al. SHEA April 2, 2011; Dallas, Tx

5

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

Ricciardi R. *Epidemiol Infect*. 2008;136(7):913-921.

6

Risk Factors for Community Acquired CDI

7

- 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

Wilcox MH, et al. *J Antimicrob Chemother.* 2008;62:388–396.
Wilcox MH, et al. *Arch Int Med.* 2010;170(9):785-790.
Kutty PK, et al. *Emerg Infect Dis.* 2010;16(2):197-204.

Community Acquired CDI Risk Factors

8

- 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 (typhylocolitis)
  - Few small studies in various geographic regions with different sampling / culture methods
    - Colonizaton 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

Eur Soc Clin Micro Inf Dis 2009; 16: 3-10.
Gould LH, Limbago B. *Clin Infect Dis.* 2010;51(5):577–582.
Keessen EC, et al. *Vet Microbiol.* 2011 Mar 26. [Epub ahead of print].

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

Sun X , et al. *Toxins*. 2010;2(7):1848-1880.
Giesemann T, et al. *J Med Microbiol*. 2008;57(Pt 6):690-696.

9

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

Sun X , et al. *Toxins*. 2010;2(7):1848-1880.

10

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

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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

Henrich TJ, et al. *Emerg Infect Dis*. 2009;15(3):415-422.

12

Prediction of CDI Outcome; ATLAS Scoring System

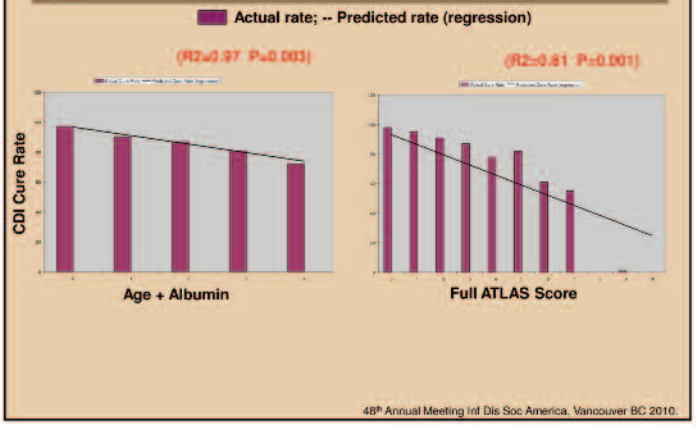
Parameter	0 points	1 point	2 points
Age (yrs)	< 60	60-79	>80
Temperature (C)	≤ 37.5	37.6-38.5	≥ 38.6
Leukocytosis	<16K	16K-25K	>25K
Albumin (g/L)	>35	26-35	<25
Systemic concomitant antibiotics during CDI therapy	No	---	Yes

- 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

48th Annual Meeting Inf Dis Soc America, Vancouver BC 2010.

13

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



48th Annual Meeting Inf Dis Soc America, Vancouver BC 2010.

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Risk factors for recurrence

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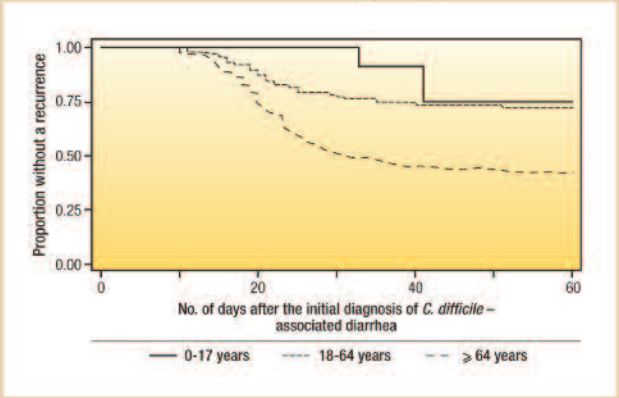
- Old age
- Concomitant antibiotics
  - Especially fluoroquinolones
- Low serum albumin
- Poor performance status
- Poor immune response against Toxin A or Toxin B
- Concomitant treatment with antacids / PPIs
- Concomitant VRE colonization
- Hospital acquired disease
- History of surgery
- Fecal incontinence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

Mullane KM, et al. *Clin Infect Dis*. 2011;53(5):440-447.
Pepin J, et al. *Clin Infect Dis*. 2005;40(11):1591-1597.
Garey KW, et al. *J Hosp Infect*. 2008;70(4):298-304.
Cadena J, et al. *Am J Med Sci*. 2010;339(4):350-355.
Kim JW, et al. *World J Gastroenterol*. 2010;16(28):3573-3577.
Leav BA, et al. *Vaccine*. 2010;28(4):965-969.
Jung KS, et al. *Gut Liver*. 2010;4(3):332-337.

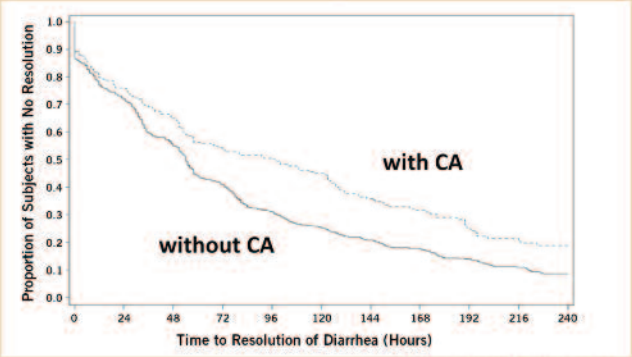
CDI Recurrence by Age Group

16



Pépin J, et al. *Clin Infect Dis*. 2005;40:1591-1597.

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



Mullane KM, et al. *Clin Infect Dis.* 2011;53:440-447.

17

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 = .048)

Mullane KM, et al. *Clin Infect Dis.* 2011;53:440-447.

18

Prolonged Hospitalization or Stay in LTCF

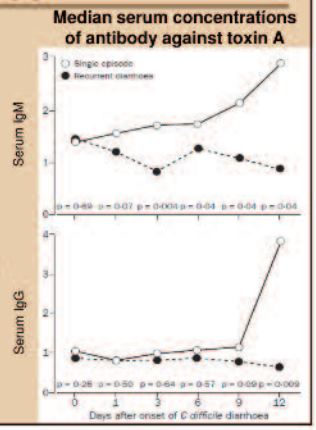
- Risk related to transmission of *C. difficile* spores
  - Primary source healthcare workers
    - may carry *C. difficile* spores on their hands (not likely fecal carriers)
  - Environmental contamination secondary source
- Up to 50% of LTCF residents and 40% of hospitalized patients have been found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

McFarland LV, et al. *N Engl J Med.* 1989;320:204-210.
Bartlett JG, Gerding DN. *Clin Infect Dis.* 2008;46(Suppl 1):S12-S18.
Simor AE, et al. *Infect Control Hosp Epidemiol.* 2002;23:696-703.
Hookman P, Barkin JS. *World J Gastroenterol.* 2009;15:1554-1580.

19

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



Giannasca PJ, Warny M. *Vaccine.* 2004;22:848-856.
Kyne L, et al. *Lancet.* 2001;357:189-193; with permission.

20

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
      - Bacteriocidin molecules

Chang JY, et al. *J Infect Dis.* 2008;197(3):435-438.
Jernberg C, et al. 2010;156(Pt 11):3216-3223.
Wardwell LH, et al. *Curr Infect Dis Rep.* 2011;13(1):28-34.

21

Intestinal Microbiota & Risk of CDI

- Antibiotic pertubation 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*

Wardwell LH, et al. *Curr Infect Dis Rep.* 2011;13(1):28-34.

22

Recurrent *C. difficile* Infection

- Rates of recurrent CDI
  - 20% after first episode[1]
  - 45% after first recurrence[2]
  - 65% after two or more recurrences[3]
- 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

1. Aslam S, et al. *Lancet Infect Dis*. 2005;5:549-557.
2. McFarland LV, et al. *Am J Gastroenterol*. 2002;97:1769-1775.
3. McFarland LV, et al. *JAMA*. 1994;271:1913-1918.

23

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

Johnson S. *J Infect*. 2009;58:403-410.

24

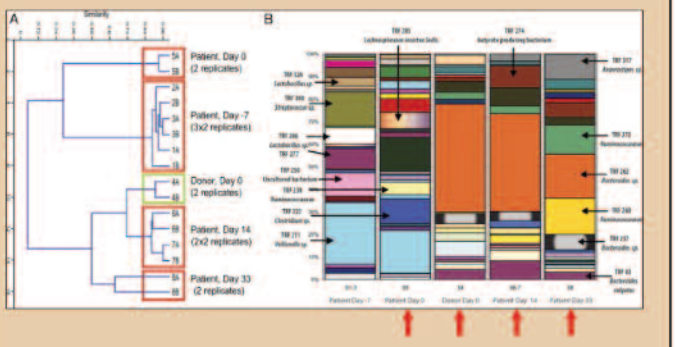
Vancomycin Taper/Pulse Regimen

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

Kyne L, Kelly CP. *Gut*. 2001;49:152.
Tedesco FJ, et al. *Am J Gastroenterol*. 1985;80:867-868.

25

Bacteriotherapy for Recurrent CDI: Changes in Fecal Microbiome



Khoruts A, et al. *J Clin Gastroenterol*. 2010;44:354–360.

26

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?)

27

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

28

Question 2

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

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Emerging CDI Treatment Options and Infection Control

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Hines VA Hospital

1

Disclosures

- Consultant: Optimer, ViroPharma, Astellas, Pfizer, Cubist, and Bio-K+
- Grants: VA Research Service
- FDA approved CDI Treatment Agents: Vancomycin, Fidaxomicin

2

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/mm^3; 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

3

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

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

4

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

5

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/mm^3 or,
  - Cr > 1.5 x baseline

Cohen SH, et al. *Infection Control Hospital Epidemiology.* 2010;31:431-455.

6

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 *(anectodal experience only for CDI)*
- Teicoplanin**
- Fusidic Acid**

**Not available in the U.S.

7

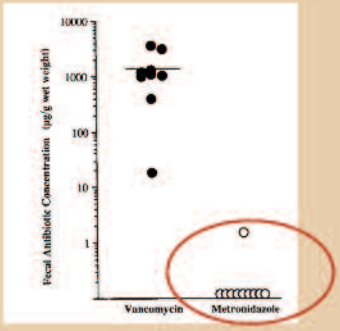
Metronidazole

- 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]

1. Hospital Infection Control Practices Advisory Committee. *MMWR Recomm Rep.* 1995;44(RR-12):1-13.
2. Wilcox MH, et al. *J Antimicrob Chemother.* 1995;36(4):673-679.
3. Cohen SA, et al. *Infection Control and Hospital Epidemiology.* 2010;31:431–455.
4. Zar FA, et al. *Clin Infect Dis* 2007;45:302-307.

8

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



Johnson S, et al. *Ann Intern Med.* 1992;117(4):297-302.

9

Vancomycin

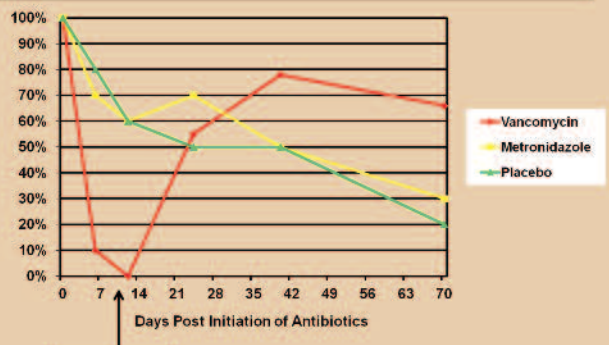
- Only agent approved for CDI in US by the FDA prior to May 2011
- Highly effective, but:
  - Higher cost vs metronidazole
  - Potential for selection of vancomycin-resistant *Enterococci* and *Staphylococci*
  - Frequent dosing
  - 20% (or more) rate of recurrence

1. Bauer, et al. *Clin Microbiol Infect.* 2009;15:1067–1079.
2. Kelly, LaMont. *N Engl J Med.* 2008;359:1932–1940.

10

Vancomycin Temporarily Clears *C. difficile* from Feces, but Prolongs Shedding!

(Attempted CD Eradication from asymptomatic carriers)



Johnson S, et al. *Ann Intern Med.* 1992;117(4):297-302.

11

Nitazoxanide (Prospective, Randomized, Comparative Trials for CDI)

- **Compared to metronidazole (n=174)[1]**
  - Similar response rates, but also similar recurrence rates:

Antimicrobial	Response	Recurrence
Metronidazole 250 mg qid x 10d	28/34 (82.4%)	8/27 (29.6%)
Nitazoxanide 500 mg bid x 7d or 10d	68/76 (89.5%)	14/65 (21.5%)

- **Compared to vancomycin (n=50)[2]**
  - Similar response rates (94% vs 87%)
  - Study too small to confirm non-inferiority or to assess recurrence rates

1. Musher DM, et al. *Clin Infect Dis.* 2006;43:421–427.
2. Musher DM, et al. *Clin Infect Dis.* 2009;48(4):e41–46.

12

Rifaximin

13

- 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

1. Johnson S. et al. *Clin Infect Dis.* 2007;44:846–848.
2. Johnson S. et al. *Anaerobe.* 2009;15:290–291.
3. Curry SR, et al. *Clin Infect Dis.* 2009;48:425–429.

The "Ideal" CDI Treatment

14

- 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

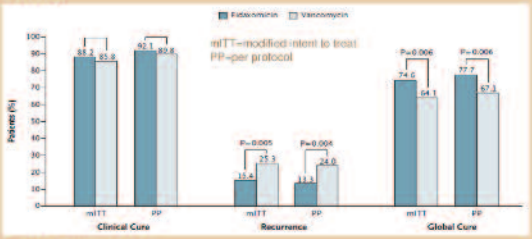
- Approved by FDA on May 27, 2011
- Indication and dosing[1]
  - Treatment of *Clostridium difficile*-associated diarrhea (aka, CDI) in adults (≥18 years of age)
  - Recommended dose 200 mg orally bid for 10 d
- Advantageous characteristics[1,2]
  - Minimal systemic absorption
  - Bactericidal agent unrelated to agents used for treatment of systemic infections
  - Narrow spectrum (less collateral damage to host flora)

1. Dificid [package insert]. San Diego, CA: Optimer Pharmaceuticals; 2011.
2. Tannock GW, et al. *Microbiology*. 2010;156(Pt11):3354-3359.

15

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):



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

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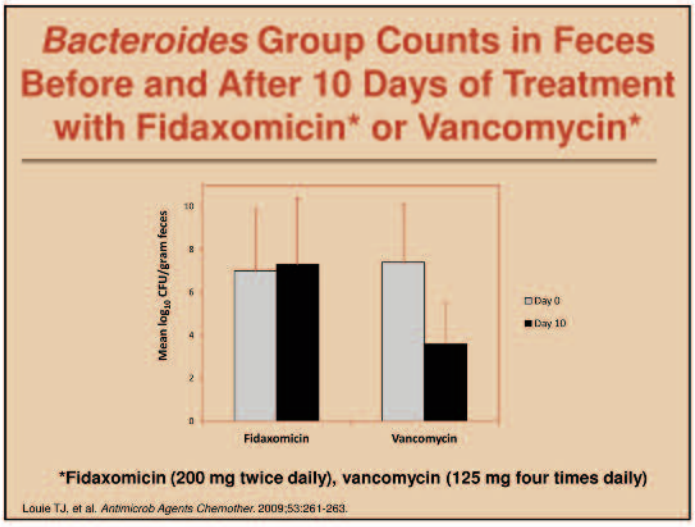
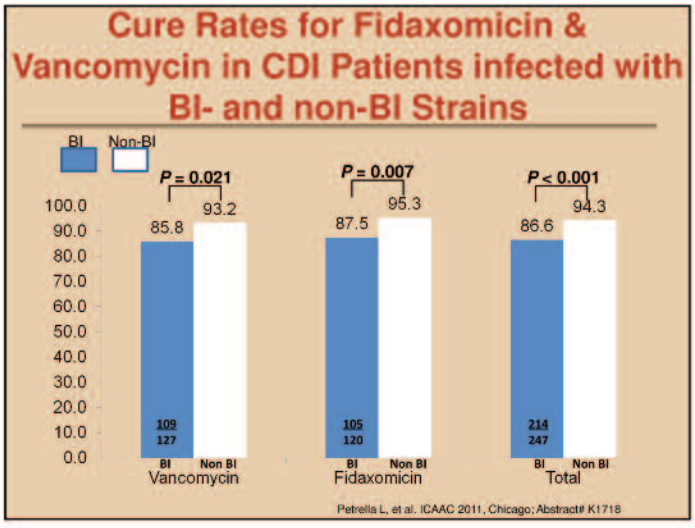

Bacteroides Group Counts in Feces Before and After 10 Days of Treatment with Fidaxomicin* or Vancomycin*
Mean log_{10} CFU/gram feces
Day 0
Day 10
Fidaxomicin
Vancomycin
*Fidaxomicin (200 mg twice daily), vancomycin (125 mg four times daily)
Louie TJ, et al. *Antimicrob Agents Chemother.* 2009;53:261-263.

17


Cure Rates for Fidaxomicin & Vancomycin in CDI Patients infected with BI- and non-BI Strains
BI
Non-BI
P = 0.021
P = 0.007
P < 0.001
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
85.8
93.2
87.5
95.3
86.6
94.3
109
127
105
120
214
247
BI
Non BI
Vancomycin
Fidaxomicin
Total
Petrella L, et al. ICAAC 2011, Chicago; Abstract# K1718

18

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,... other

Dificid [package insert]. San Diego, CA: Optimer Pharmaceuticals; 2011.
Tannock GW, et al. *Microbiology*. 2010;156(Pt11):3354-3359.

19

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

20

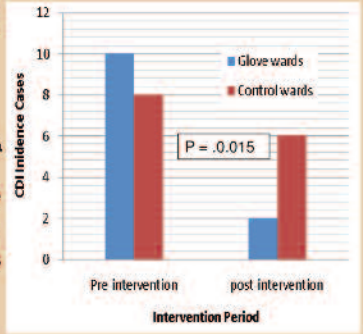
Current Infection Control Strategies: Methods to Prevent Horizontal Transmission of *C. difficile*

	Clinical Efficacy
• Barrier Precautions:	
– Gloves	**Proven**
– Handwashing	Probable
– Gowns	Untested
– Patient Cohorting	Probable
• Cleaning, Disinfection, Disposables	
– Patient Rooms	Probable
– Endoscopes	Probable
– Rectal Thermometers	**Proven**

21

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**



Johnson S, et al. *Am J Med.* 1990;88:137-140.

22

Hand Hygiene for CDI Intervention

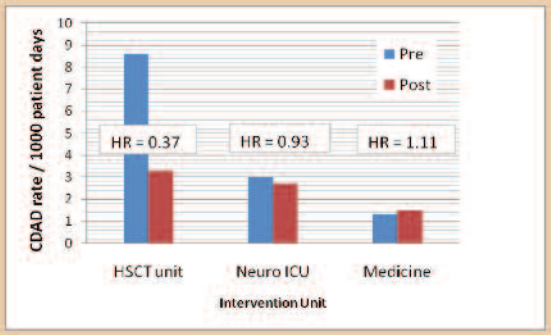
23

- 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*

1. Cohen SH, et al. *Infect Control Hosp Epidemiol.* 2010;31:431-455.
2. Dubberke ER, et al. *Infect Control Hosp Epidemiol.* 2008;29:S81-S92.
3. APIC *Guide to the Elimination of Clostridium difficile in Healthcare Settings*, Association for Professionals in Infection Control and Epidemiology, Inc. November 2008.

Time Series Study of Environment Disinfection with Bleach

24



Mayfield JL, et al. *Clin Infect Dis.* 2000;31:995-1000.

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

Method Used	Efficacy
- Antimicrobial use restriction (clindamycin, 3rd gen cephalosporins, ?fluoroquinolones)	Proven
- Prophylactic treatment of patients receiving antimicrobials probiotics	Possible

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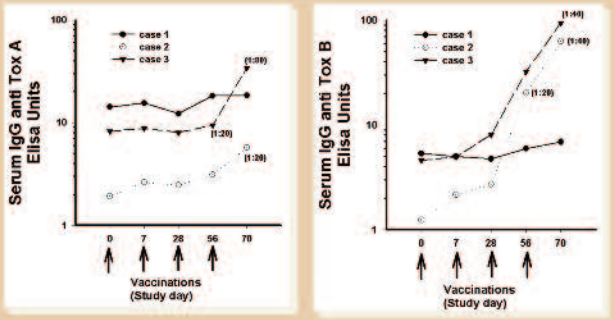
Potential Future Strategies for Prevention

- Primary Prevention
  - Active Vaccination
  - 'Effective Probiotics/Biotherapeutics'
- Secondary Prevention
  - Adjunctive Monoclonal Antibodies
  - Luminal Toxin Binders (tolevamer: No current plans for development)

26

C. difficile Toxoid Vaccine in 3 Patients with Chronic Recurrent CDI



Sougioultzis S, et al. *Gastroenterology* 2005;128:764-770.

27

Provocative Probiotic Primary Prevention Studies for

Antibiotic-assoc Diarrhea (ADD) and *C. difficile* infection (CDI)

- **Probiotic Drink* Study**

	Placebo	Probiotic
AAD	34%	12%
CDI	17%	0%

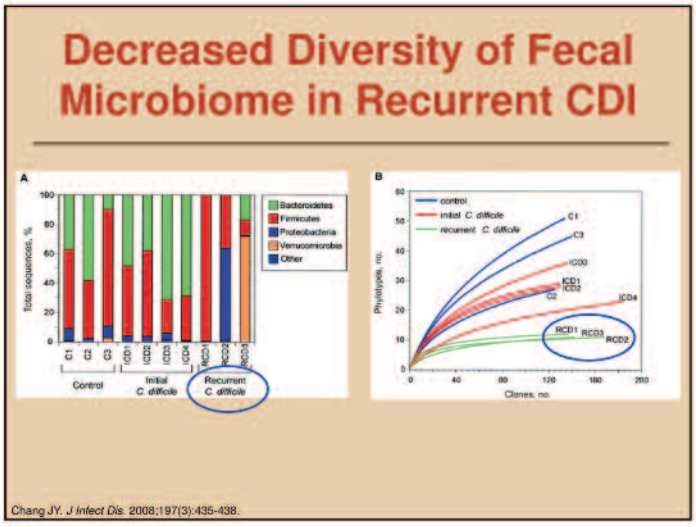
- **Probiotic Capsule† Dose-ranging Study**

	Placebo	Probiotic-1	Probiotic-2
AAD	44%	28%	16%
CDI	24%	9%	1%

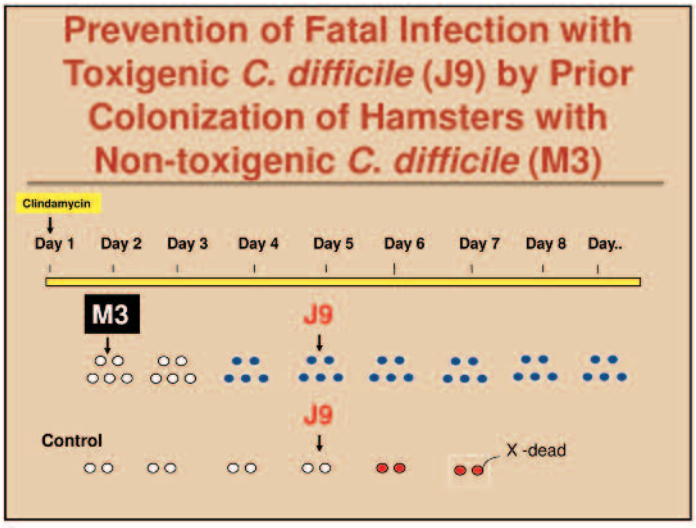
- **Multiple criticisms of these studies; exclusion criteria, study blinding, & unexplained high rate of CDI in controls**

*Lactobacillus casei, L bulgaricus, Streptococcus thermophilus
†Lactobacillus acidophilus CL1285, Lactobacillus casei LBC80R

28

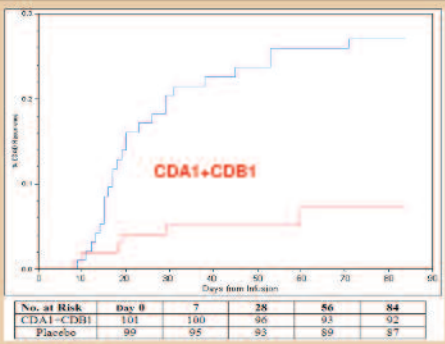

Decreased Diversity of Fecal Microbiome in Recurrent CDI
A
B
Bacteroidetes
Firmicutes
Proteobacteria
Verrucomicrobia
Other
Control
Initial C. difficile
Recurrent C. difficile
control
initial C. difficile
recurrent C. difficile
Clones, no.
Chang JY. J Infect Dis. 2008;197(3):435-438.

29


Prevention of Fatal Infection with Toxigenic C. difficile (J9) by Prior Colonization of Hamsters with Non-toxigenic C. difficile (M3)
Clindamycin
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7
Day 8
Day..
M3
J9
J9
Control
X -dead

30

Time to CDI Recurrence in Patients Receiving Mabs (CDA1 + CDB1) vs Placebo in Addition to Standard Therapy



No. at Risk	Day 0	7	28	56	84
CDA1+CDB1	101	100	96	93	92
Placebo	99	95	93	89	87

Lowy, et al. *N Eng J Med.* 2010;362:197-205.

31

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

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