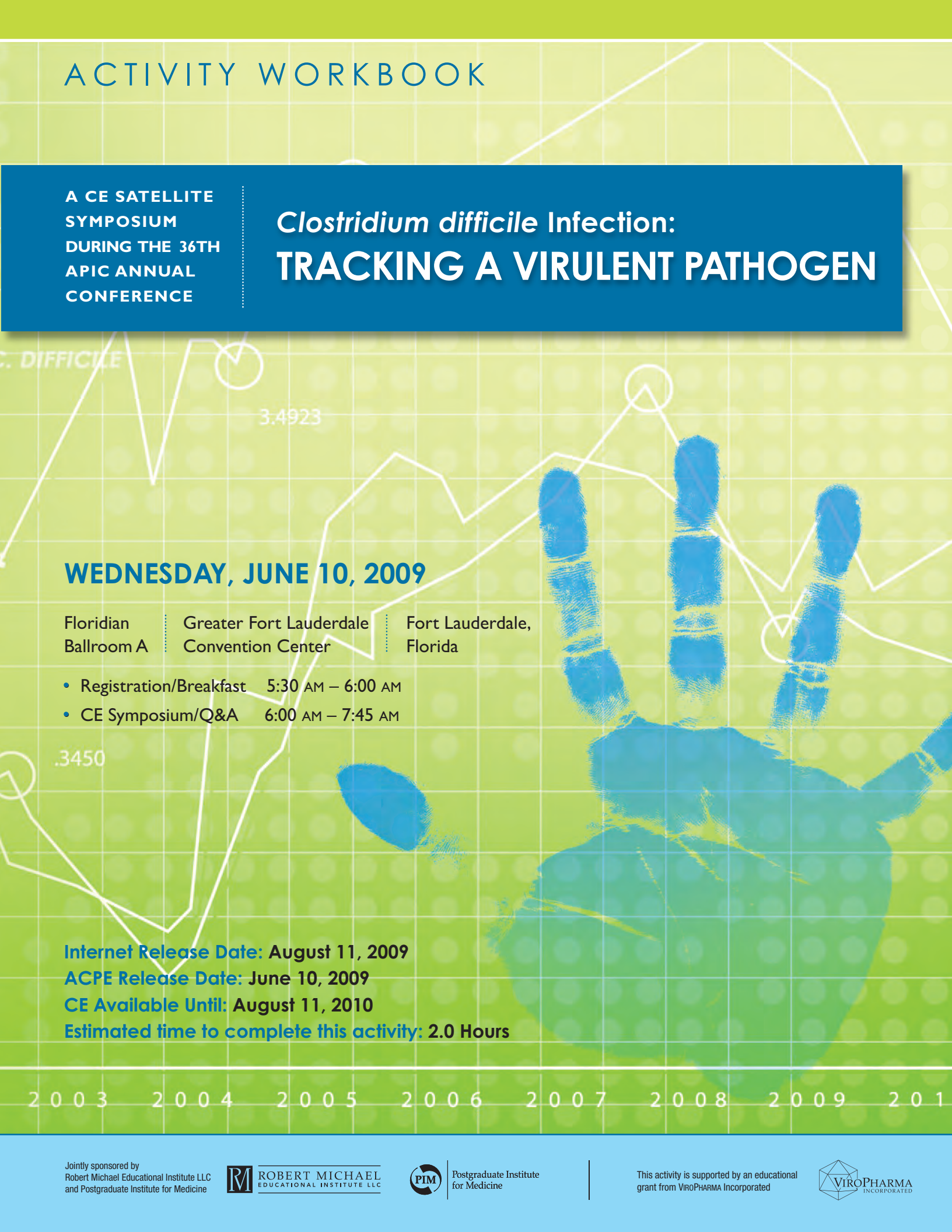
ACTIVITY WORKBOOK

A CE SATELLITE SYMPOSIUM DURING THE 36TH APIC ANNUAL CONFERENCE

Clostridium difficile Infection: TRACKING A VIRULENT PATHOGEN



WEDNESDAY, JUNE 10, 2009

Floridian Ballroom A | Greater Fort Lauderdale Convention Center | Fort Lauderdale, Florida

- Registration/Breakfast 5:30 AM – 6:00 AM
- CE Symposium/Q&A 6:00 AM – 7:45 AM

Internet Release Date: August 11, 2009
ACPE Release Date: June 10, 2009
CE Available Until: August 11, 2010
Estimated time to complete this activity: 2.0 Hours

Jointly sponsored by
Robert Michael Educational Institute LLC
and Postgraduate Institute for Medicine

ROBERT MICHAEL EDUCATIONAL INSTITUTE LLC

PIM Postgraduate Institute for Medicine

This activity is supported by an educational grant from ViroPharma Incorporated

ViroPharma Incorporated

Contents

Activity Overview

Thank you for joining us for ***Clostridium difficile*: Tracking a Virulent Pathogen**, a continuing education symposium originally presented during the 36th APIC Annual Conference.

We also thank our esteemed speakers for sharing their time and expertise. Through this activity, they will review the changing epidemiology of *C. difficile*, outline advantages and disadvantages of current diagnostic methods for *C. difficile*, cite evidence-based strategies for the treatment of *C. difficile* infection (CDI), and identify methods for the prevention and control of CDI.

This workbook includes the presenters' slides to help guide you through the activity.

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

Agenda

Program Overview
Stuart Johnson, MD, DTM&H

Clostridium difficile: ***Changing Epidemiology***
Stuart Johnson, MD, DTM&H

CDI Testing: What Are the Current Shortcomings and How Can We Improve Testing?
Dale N. Gerding, MD, FACP, FIDSA

Clostridium difficile ***Infection (CDI): Treatment Strategies***
Ciarán P. Kelly, MD

Clostridium difficile: ***Prevention and Infection Control***
Keith S. Kaye, MD, MPH

Panel Question-and-Answer Session

Overview

TARGET AUDIENCE

This activity has been designed to meet the educational needs of physicians, pharmacists, and registered nurses involved in the care of patients with *Clostridium difficile* infection.

ACTIVITY PURPOSE

This activity is intended to provide healthcare professionals with clinical information that will contribute to improving competence in the management of patients with *Clostridium difficile* infection.

STATEMENT OF NEED

In recent years, the rates and severity of *Clostridium difficile* infection (CDI) have been increasing.[1] This trend may be the result of changes in the epidemiology of *C. difficile* that may reflect changes in antimicrobial use, other drug-prescribing practices, or infection control practices.[2] The increasing rates of CDI may also be the result of a new strain of *C. difficile*, one that appears to produce greater quantities of toxins A and B, is more resistant to fluoroquinolones, and is associated with higher rates of morbidity and mortality.[3,4] Healthcare professionals should be aware of the changing epidemiology of this increasingly virulent pathogen and apply evidence-based principles for the prevention, diagnosis, and treatment of CDI.

[1] McDonald LC, et al. *Emerg Infect Dis*. 2006;12:409-415.
[2] Centers for Disease Control and Prevention. Fact Sheet, July 2005.
[3] Warny M, et al. *Lancet*. 2005;366:1079-1084.
[4] McDonald LC, et al. *N Engl J Med*. 2005;353:2433-2441.

EDUCATIONAL OBJECTIVES

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

- Review the changing epidemiology of *C. difficile*
- Outline advantages and disadvantages of current diagnostic methods for *C. difficile*
- Cite evidence-based strategies for the treatment of *C. difficile* infection (CDI)
- Identify methods for the prevention and control of CDI

STATEMENT OF SUPPORT

This activity is jointly sponsored by Robert Michael Educational Institute LLC and Postgraduate Institute for Medicine, and is supported by an educational grant from ViroPharma Incorporated.

MEDIUM

Internet

Faculty Biographies

Stuart Johnson, MD, DTM&H

Associate Professor of Medicine
Loyola University Medical Center
Stritch School of Medicine
Maywood, Illinois

Staff Physician
Hines Veterans Affairs Hospital
Hines, Illinois

Stuart Johnson, MD, DTM&H, is associate professor of medicine at Loyola University Medical Center Stritch School of Medicine in Maywood, Illinois, and a staff physician at the Hines Veterans Affairs Hospital in Hines, Illinois. He also is president of the Anaerobe Society of the Americas and past-president of the Chicago Area Infectious Diseases Society.

Dr. Johnson received a medical degree from the University of Minnesota Medical School and completed a residency in internal medicine and a fellowship in infectious diseases at the University of Minnesota Hospital and Minneapolis Veteran Affairs Medical Center. He also received a diploma in tropical medicine and hygiene from Mahidol University in Bangkok, Thailand, and a Career Development Award from the Department of Veterans Affairs.

Dr. Johnson's main research interests lie in the epidemiology and pathogenesis of *Clostridium difficile* infection. He is actively studying variant strains of *C. difficile* and the role of the various toxins in the pathogenesis of *C. difficile* disease. He has been involved in clinical research of the parasite *Angiostrongylus cantonensis*, which is responsible for most cases of eosinophilic meningitis worldwide. Dr. Johnson also is the author of more than 60 peer-reviewed journal articles, reviews, and book chapters.

Faculty Biographies

Dale N. Gerding, MD, FACP, FIDSA

Professor of Medicine
Loyola University Chicago
Stritch School of Medicine
Maywood, Illinois

Associate Chief of Staff for Research and Development
Hines Veterans Affairs Hospital
Hines, Illinois

Dale N. Gerding, MD, FACP, FIDSA, is professor of medicine at Loyola University Chicago Stritch School of Medicine in Maywood, Illinois, and associate chief of staff for research and development at Hines Veterans Affairs (VA) Hospital in Hines, Illinois. Prior to his present positions, he was chief of medicine at VA Chicago Health Care System, Lakeside Division; professor of medicine at Northwestern University Feinberg School of Medicine in Chicago; chief of infectious diseases at the Minneapolis VA Medical Center; and professor of medicine at the University of Minnesota Medical School.

After receiving an undergraduate degree in physics from St. John's University in Collegeville, Minnesota, Dr. Gerding attended the University of California, Los Angeles, on a Hughes Fellowship while working for Hughes Aircraft on the Surveyor lunar lander. He received a medical degree from the University of Minnesota Medical School. Dr. Gerding completed an internship at the Peter Bent Brigham Hospital in Boston and, following 2 years at the National Institutes of Health, completed a 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 became a member of the Infectious Diseases Society of America (IDSA) in 1979, and a Fellow in 1982. He served as Councilor, North Central Chapter in 1990 and was Secretary from 1991 to 1992. He has served on numerous IDSA committees and was the IDSA representative to the Centers for Disease Control and Prevention ABCs Steering Committee, 2000 to 2004. Dr. Gerding was a writer of the IDSA and The Society for Healthcare Epidemiology of America (SHEA) joint position paper on antibiotic resistance in hospitals, 1996–1997; drafted the IDSA response to the federal government document on antibiotic resistance, 2000; and drafted the IDSA public position statement on strategies to limit the impact of antibiotic resistance, 2001.

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 nearly 30 years and is the author of more than 250 peer-reviewed journal articles, book chapters, and reviews. He holds patents for the use of nontoxigenic *C. difficile* for the prevention and treatment of *C. difficile*–associated disease.

In addition, Dr. Gerding is a member of the editorial boards of *Clinical Infectious Diseases*, *Antimicrobial Agents and Chemotherapy*, and *Infection Control and Hospital Epidemiology*, and is an ad hoc reviewer for numerous other medical journals. He also is a fellow of the American College of Physicians, a member of the American Society for Microbiology, past-president of SHEA, and past-chair of the Antibiotic Resistance Committee of SHEA.

Faculty Biographies

Ciarán P. Kelly, MD

Associate Professor of Medicine
Harvard Medical School
Director, Gastroenterology Fellowship Training
Beth Israel Deaconess Medical Center
Chief, Herrman L. Blumgart Internal Medicine
Boston, Massachusetts

Ciarán P. Kelly, MD, is associate professor of medicine at Harvard Medical School, chief of the Herrman L. Blumgart Internal Medicine Firm, Medical director of the Celiac Center, and director of gastroenterology fellowship training at Beth Israel Deaconess Medical Center in Boston, Massachusetts. He has been involved in patient care and research in the area of *Clostridium difficile*–associated diseases for 20 years and has a special interest in the immune response to *C. difficile* toxins.

Dr. Kelly earned a medical degree from Trinity College in Dublin, Ireland, where he was a Foundation Scholar and recipient of numerous academic awards. He has also received postgraduate clinical and research awards from the Crohn's & Colitis Foundation of America, the American Gastroenterological Association, and the National Institutes of Health (NIH). He is a current fellow of the American College of Gastroenterology and a past-fellow of the Royal College of Physicians of Ireland.

Dr. Kelly has longstanding clinical and research interests in intestinal infection and inflammation. He has served as a committee member of the NIH Center for Scientific Review and leads NIH-funded research programs on *C. difficile* colitis and inflammatory bowel disease.

Dr. Kelly is the author of numerous clinical and basic research book chapters, invited reviews, and more than 70 peer-reviewed publications appearing in such journals as *Infection and Immunity*, *American Journal of Physiology*, *Gastroenterology*, *Journal of Biological Chemistry*, *The Journal of Clinical Investigation*, *The New England Journal of Medicine*, and *The Lancet*.

Faculty Biographies

Keith S. Kaye, MD, MPH

Professor of Medicine
Wayne State University
Corporate Director
Infection Prevention, Epidemiology, and Antimicrobial Stewardship
Detroit Medical Center
Detroit, Michigan

Keith S. Kaye, MD, MPH, is professor of medicine at Wayne State University and corporate director of infection prevention, epidemiology, and antimicrobial stewardship for Detroit Medical Center in Detroit, Michigan. Dr. Kaye is board-certified in internal medicine and infectious diseases.

After receiving a medical degree in 1994 from the University of Pennsylvania School of Medicine, Philadelphia, Dr. Kaye completed a master's degree program in 2000 at the Harvard School of Public Health in Boston, Massachusetts. He also completed a residency in internal medicine at Beth Israel Hospital in Boston.

Dr. Kaye is involved in many mentorship and preceptorship programs, including a mentorship program in clinical infectious diseases. He is a fellow of the Infectious Diseases Society of America, a founding member of the Infectious Diseases and Aging Special Interest Group of that society, and a member of the American Society for Microbiology and Society of Healthcare Epidemiology of America.

Dr. Kaye has reported his work in numerous national presentations, peer-reviewed articles, abstracts, and books.

Accreditation & Credit

METHOD OF PARTICIPATION

There are no fees for participating and receiving continuing education (CE) credit for this activity. During the period of August 11, 2009, through August 11, 2010, participants must 1) read the learning objectives and faculty disclosures; 2) study the educational activity; 3) complete the Learning Assessment by recording the best answer to each question in the "Learning Assessment Answers" box on the Evaluation form; 4) complete the Evaluation form; and 5) mail or fax the Evaluation form with the Learning Assessment answers to Postgraduate Institute for Medicine. You may also complete the Learning Assessment online at www.cmeuniversity.com.

Click on "Find Post-Test/Evaluation by Course" on the navigation menu, and search by project ID 6528. Upon successfully completing the Learning Assessment and Evaluation form, your certificate will be made available immediately.

Participants must receive a score of at least 70% on the Learning Assessment and must complete and submit the Evaluation form to successfully complete this activity. Participants who successfully complete this activity will be issued a statement of credit via US mail in 4 to 6 weeks.

Additional educational activities offered by Robert Michael Educational Institute LLC can be found at www.RMEI.com or by calling toll-free to 866-770-RMEI.

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 (ACCME) through the joint sponsorship of Postgraduate Institute for Medicine (PIM) and Robert Michael Educational Institute (RMEI). PIM is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation

PIM designates this educational activity for a maximum of 2.0 *AMA PRA Category 1 Credits*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

PHARMACIST CONTINUING EDUCATION

Accreditation Statement

Postgraduate Institute for Medicine (PIM) is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Credit Designation

PIM designates this continuing education activity for 2.0 contact hours (0.2 CEUs) of the Accreditation Council for Pharmacy Education. (Universal Activity Number – 809-999-09-098-H01-P)

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.

If you have received credit for UAN 809-999-09-072-L01-P, you are not eligible for this activity.

NURSING CONTINUING EDUCATION

Credit Designation

This educational activity for 2.0 contact hours is provided by Postgraduate Institute for Medicine (PIM).

Accreditation Statement

PIM is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

California Board of Registered Nursing

PIM is approved by the California Board of Registered Nursing, Provider Number 13485 for 2.4 contact hours.

FEE INFORMATION

There is no fee for this educational activity.

Disclosures & Disclaimer

DISCLOSURE OF CONFLICTS OF INTEREST

Postgraduate Institute for Medicine (PIM) assesses conflict of interest with its instructors, planners, managers, and other individuals who are in a position to control the content of continuing education (CE) activities. All relevant conflicts of interest that are identified are thoroughly vetted by PIM for fair balance, scientific objectivity of studies utilized in this activity, and patient care recommendations. PIM is committed to providing its learners with high-quality CE activities and related materials that promote improvements or quality in healthcare and not a specific proprietary business interest of a commercial interest.

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 CE activity:

- **Dr. Stuart Johnson** has affiliations with Genzyme Corporation; ViroPharma Incorporated; Salix Pharmaceuticals, Inc.; Acambis; Replidyne, Inc.; Optimer Pharmaceuticals, Inc.; and BD Diagnostics GeneOhm *(Consultant)*.
- **Dr. Dale N. Gerding** has affiliations with ViroPharma Incorporated *(Patents)*; Cepheid; BD Diagnostics GeneOhm; Massachusetts Biologics Laboratories; Merck & Co., Inc.; GOJO Industries, Inc.; Optimer Pharmaceuticals, Inc.; Salix Pharmaceuticals, Inc.; Schering-Plough; and ViroPharma Incorporated *(Research Grants* and *Consultant)*.
- **Dr. Ciarán P. Kelly** has affiliations with Actelion Pharmaceuticals *(Consultant* and *Research Grants)*; Salix Pharmaceuticals, Inc.; Cubist Pharmaceuticals, Inc.; and ViroPharma Incorporated *(Consultant)*.
- **Dr. Keith S. Kaye** has affiliations with Cubist; Merck & Co., Inc.; Pfizer Inc.; Schering-Plough *(Speakers' Bureau)*; Forest Laboratories, Inc.; Ortho-McNeil Pharmaceutical, Inc.; Schering-Plough; TheraDoc Inc.; Wyeth Pharmaceuticals *(Consultant)*; Merck & Co., Inc. and Pfizer Inc. *(Research)*.

The following planners and managers have the following to disclose:

Robert Michael Educational Institute LLC

- **Sherri Kramer, MD,** has no affiliations with commercial interests to disclose.
- **Elise Paxson** has no affiliations with commercial interests to disclose.
- **Laura Altobelli, MS,** has no affiliations with commercial interests to disclose.

Postgraduate Institute for Medicine

- **Jan Hixon, RN, BSN, MA,** has no affiliations with commercial interests to disclose.
- **Linda Graham, RN, BSN,** has no affiliations with commercial interests to disclose.
- **Trace Hutchison, PharmD,** has no affiliations with commercial interests to disclose.
- **Julia Kirkwood, RN, BSN,** has no affiliations with commercial interests to disclose.
- **Jan Schultz, RN, MSN, CCMEP,** has no affiliations with commercial interests to disclose.

DISCLOSURE OF UNLABELED USE

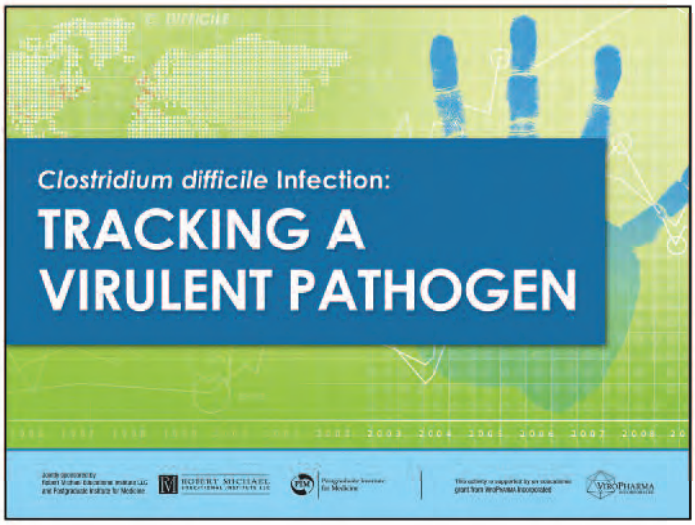
This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. PIM, Robert Michael Educational Institute LLC (RMEI) and ViroPharma Incorporated do not recommend the use of any agent outside of the labeled indications.

The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of PIM, RMEI, or ViroPharma Incorporated. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings.

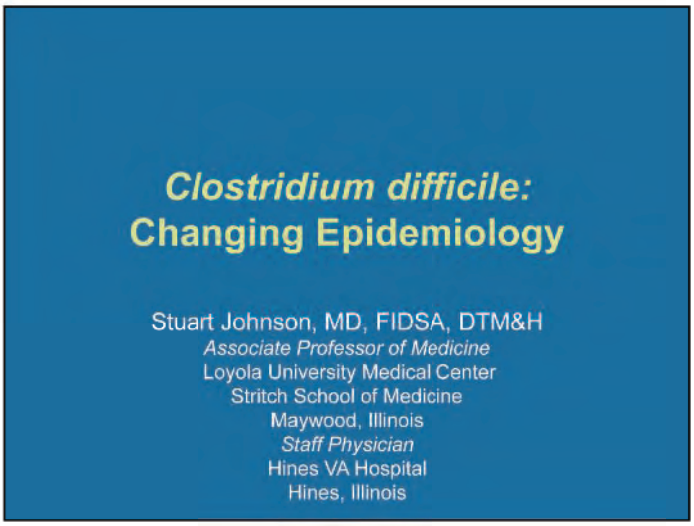
DISCLAIMER

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information and comparison with recommendations of other authorities.

Presentations



1



2

Disclosure of Conflicts of Interest

Stuart Johnson, MD, FIDSA, DTM&H

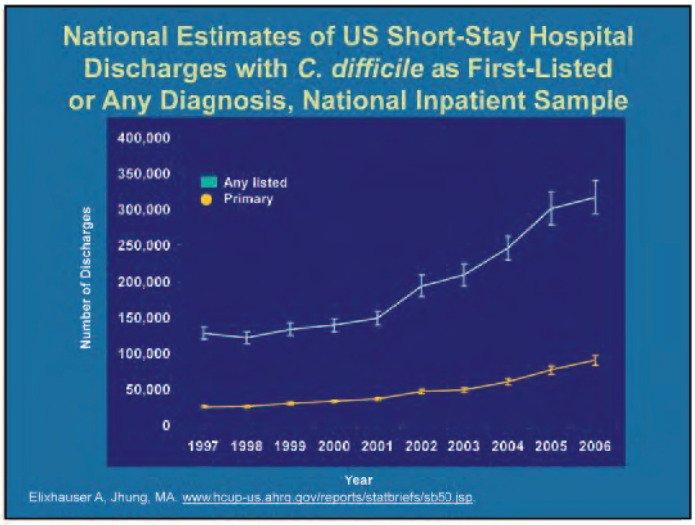
Dr. Stuart Johnson has an affiliation with Genzyme Corporation; ViroPharma Incorporated; Salix Pharmaceuticals, Inc.; Acambis; Replidyne, Inc.; Optimer Pharmaceuticals, Inc.; and BD Diagnostics GeneOhm *(Consultant)*.

3

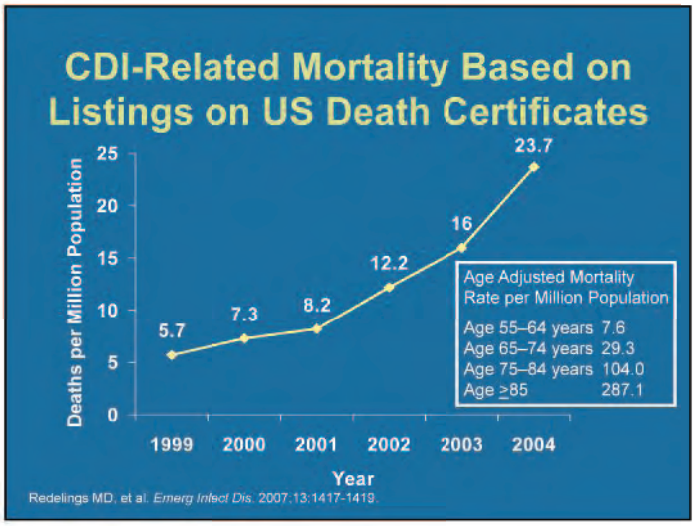
Overview

- Is the incidence of hospital-acquired *Clostridium difficile* infection (CDI) still increasing?
- What is the current status of the BI/NAP1/027 epidemic?
- Is there a community-acquired CDI epidemic?
- Are there other clinically important strains that have emerged?
- Are there new risk groups?
- Are there new reservoirs/sources of infection?

4


National Estimates of US Short-Stay Hospital Discharges with C. difficile as First-Listed or Any Diagnosis, National Inpatient Sample
400,000
350,000
300,000
250,000
200,000
150,000
100,000
50,000
0
Number of Discharges
Any listed
Primary
1997 1998 1999 2000 2001 2002 2003 2004 2005 2006
Year
Elixhauser A, Jhung, MA. www.hcup-us.ahrq.gov/reports/statbriefs/sb50.jsp.

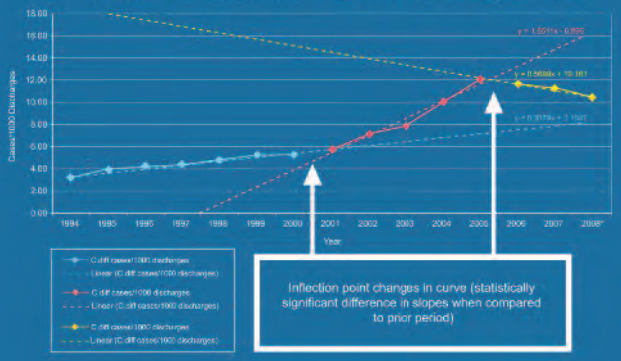
5


CDI-Related Mortality Based on Listings on US Death Certificates
25
20
15
10
5
0
Deaths per Million Population
5.7
7.3
8.2
12.2
16
23.7
1999 2000 2001 2002 2003 2004
Year
Age Adjusted Mortality Rate per Million Population
Age 55–64 years 7.6
Age 65–74 years 29.3
Age 75–84 years 104.0
Age ≥85 287.1
Redelings MD, et al. Emerg Infect Dis. 2007;13:1417-1419.

6

Presentations

National Estimates of VA Hospital Discharges With *C. difficile* Listed as a Diagnosis



Kralovic S, et al. Presented at the 19th Annual Scientific Meeting of the Society for Healthcare Epidemiology of America. March 19-22, 2009, San Diego, CA.

7

CDI Rates and Mortality Increase in Parallel With Patient Age

Age (Years)	CDI Rate per 1000 Admissions	Attributable 30-Day Mortality Rate (%)
<40	3.5	2.6
41–50	11.2	1.2
51–60	20.0	3.2
61–70	24.4	5.1
71–80	38.3	6.2
81–90	54.5	10.2
>90	74.4	14.0

Loo VG, et al. *N Engl J Med*. 2005;353:2442-2449.

8

Emergence of the Epidemic BI/NAP1/027 Strain of *C. difficile* in North America

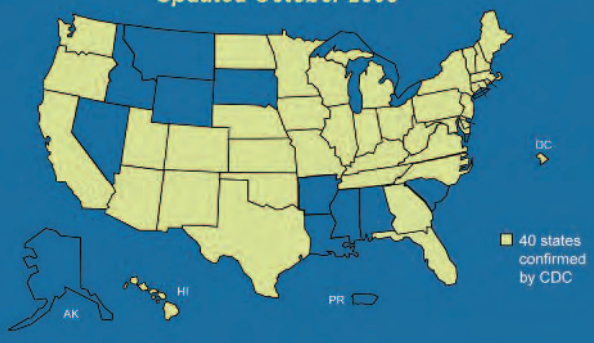
- Predominant strain in 8 US hospital CDI outbreaks in 7 states (2000–2003); strain identified as toxinotype III, had binary toxin genes, and an 18-bp deletion in *tcdC*[1]
- Multi-hospital (12+) regional outbreak in Montreal, Quebec (2003–2004); increased rates and severity of CDI (*estimated 2000 deaths directly attributable to CDI*); Montreal-area task force formed; public reporting mandatory for CDI; same predominant strain as in US outbreaks[2-4]

1. McDonald LC, et al. *N Engl J Med*. 2005;353:2433-2441.
2. Eggertson L. *CMAJ*. 2004;171:19-21.
3. Valiquette L, et al. *CMAJ*. 2004;171:27-29.
4. Loo VG, et al. *N Engl J Med*. 2005;353:2442-2449.

9

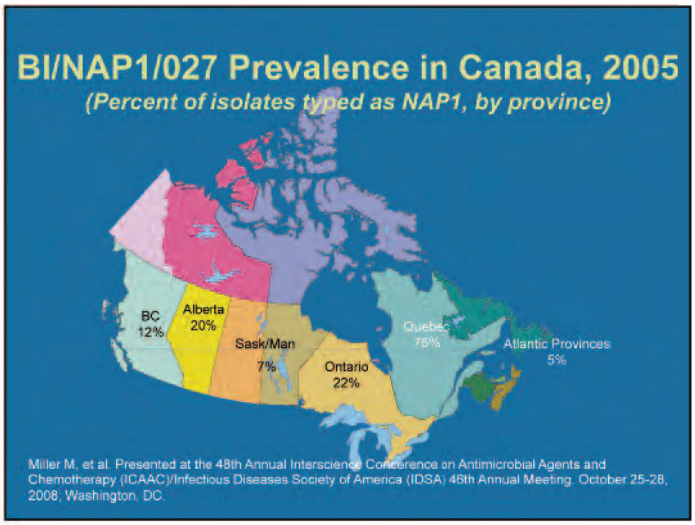
States With the Epidemic BI/NAP1/027 Strain of *C. difficile* Confirmed by CDC (*N*=40)

Updated October 2008

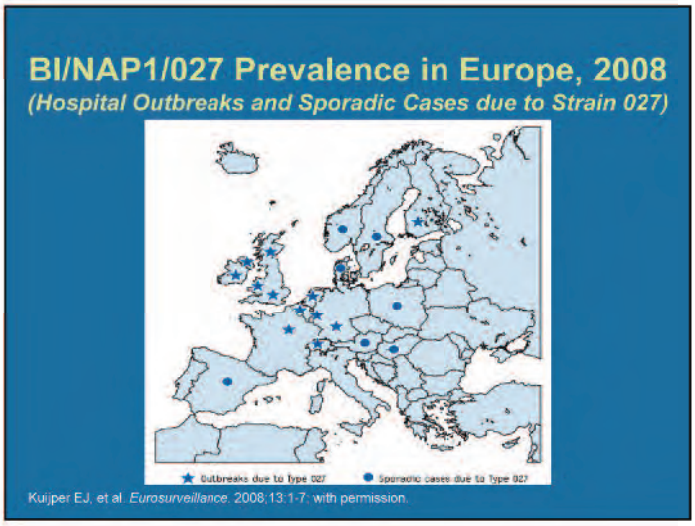


10

Presentations



11



12

Current Surveys of Clinical *C. difficile* Isolates in North America

(Microbiology Reference Laboratory, Hines VA Hospital)

- *C. difficile* isolates from a phase III, multi-center study (2005–2007)
  - North American, European, and Australian treatment comparison of the toxin-binding polymer tolevamer vs vancomycin vs metronidazole for CDI

	North America	Europe	Australia
BI	36% (160)	8% (25)	0%
J	11% (50)	19% (59)	4% (1)
Y	9% (40)	16% (49)	25% (6)
BK	2% (9)	6% (18)	4% (1)
	(*n*=443)	(*n*=308)	(*n*=24)

Cheknis A, et al. Presented at the 48th Annual Interscience Conference of Antimicrobial Agents and Chemotherapy (ICAAC)/Infectious Diseases Society of America (IDSA) 46th Annual Meeting. October 25-28, 2008; Washington, DC.
Cheknis A, et al. Presented at the 9th Biennial Congress of the Anaerobe Society of the Americas. June 24-27, 2008; Long Beach, CA.

13

Epidemiologic Risk Factors

"Classic" Risk Factors	Proposed Mechanism	"New"(?) Risk Factors
Antibiotic exposure	Susceptibility	No antibiotics
Hospitalization	Exposure	Community onset
Advanced age	Waning immunity	Peripartum women

14

Community-Onset CDI: VA Center, North Carolina

Predisposing Factors

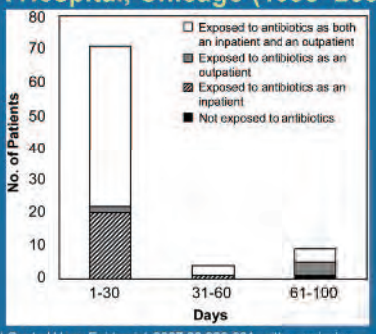
	Cases (*n*=50) *n* (%)	Controls (*n*=100) *n* (%)	*P* value
Antimicrobials	25 (50)	7 (7)	<0.001
Proton pump inhibitors	18 (36)	20 (20)	0.3
Inflammatory bowel disease	6 (12)	1 (1)	0.02
Outpatient visits	43 (86)	58 (58)	0.001

Kutty PK, et al. Presented at the 44th Annual Meeting of Infectious Disease Society of America. October 12-15, 2006. Toronto, Ontario [Abstract LB-28].

15

Time From Hospital Discharge to Positive Stool *C. difficile* Toxin Assay

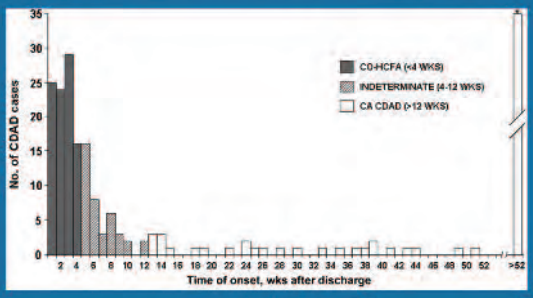
VA Hospital, Chicago (1998–2005)



Chang HT, et al. *Infect Control Hosp Epidemiol.* 2007;28:926-931; with permission.

16

Timing of Community-Onset CDI
Six hospitals (North Carolina, 2005)



Kutty PK, et al. *Infect Control Hosp Epidemiol.* 2008;29:197-202; with permission.

17

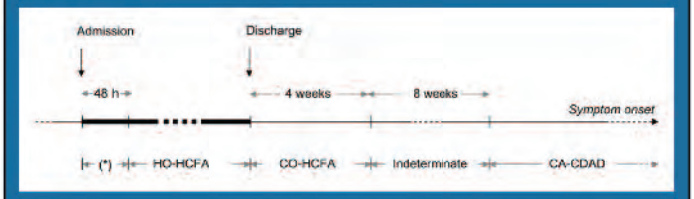
C. difficile in the Environment*

- River water: 87.5%
- Swimming pools: 50%
- Lake water: 47%
- Sea water samples (beaches): 44%
- Soil samples: 21%
- Tap water: 6%
- Dog feces: 10%
- Cat feces: 2%
- Home environments: 2.2%
- Raw vegetables: 2.4%
- Farm animal feces: 1%
- Fish guts: 0%

*7.1% of 2580 environmental cultures from Cardiff area of Wales were positive for *C. difficile*.
al Saif N, Brazier JS. *J Med Microbiol.* 1996;45:133-137.

18

Timeline for Definitions of CDI Exposure



McDonald LC, et al. *Infect Control Hosp Epidemiol*. 2007;28:140-145; with permission.

19

Severe CDI in Peripartum Women

- 20-year-old, 22 weeks' gestation with preterm labor; 2 wks watery diarrhea (up to 10 BM/d); no recent antibiotics or hospitalization
  - Temperature 103.1°F, WBC 15,800, *C. difficile* toxin +
  - **Spontaneous abortion** day 4, **colectomy day 6**
  - **Survived**
- 31-year-old, 14 weeks' gestation with twins; 3 wks watery diarrhea (black stools, 4–5 BM/d); trimethoprim-sulfamethoxazole 3 mo ago
  - Admitted to ICU 5 d later, *C. difficile* toxin A/B +, dilated colon
  - Poor response to metronidazole and vancomycin; readmitted in shock 3 d later
  - **Spontaneously aborted twins** day 2, then **patient died day 4**
- **Peripartum CDI is not common**
  - 24 cases reported
  - Most (91%) associated with prophylactic antibiotic use at delivery

Rouphael NG, et al. *Am J Obstet Gynecol*. 2008;198:635.e1-e6.
Garey KW, et al. *Am J Obstet Gynecol*. 2008;199:332-337

20

Potential New Source of *C. difficile* Transmission: Food-Producing Animals

- Previous studies have suggested that *C. difficile* isolates from humans and animals were of different lineage
- *C. difficile* increasingly recognized as a pathogen and/or commensual in food animals[1-3]
- *C. difficile* strains responsible for human disease (including BI/NAP1/027) have been found to contaminate retail meats[4]

1. Rodriguez-Palacio A, et al. *Emerg Infect Dis*. 2006;12:1730-1736.
2. Songer JG. *Anim Health Res Rev*. 2004;5:321-326.
3. Songer JG, Anderson MA. *Anaerobe*. 2006;12:1-4.
4. Rodriguez-Palacio A, et al. *Emerg Infect Dis*. 2007;13:485-487.

21

C. difficile Toxinotype V Strains in Humans and Animals

- 15 human & 33 animal (pig/bovine) isolates compared
- All isolates belonged to REA Group BK and NAP7/NAP8
- 50% of human isolates came from community-associated cases (would expect 20% or less from most surveys)
- Possible increase in toxinotype V isolates (0.02% in our Hines VA historical *C. difficile* collection; ~1.5% in CDC collection since 2001)

Jhung MA, et al. *Emerg Infect Dis*. 2008;14:1039-1045.

22

C. difficile PCR Toxinotype V (Ribotype 078) Infection in the Netherlands*

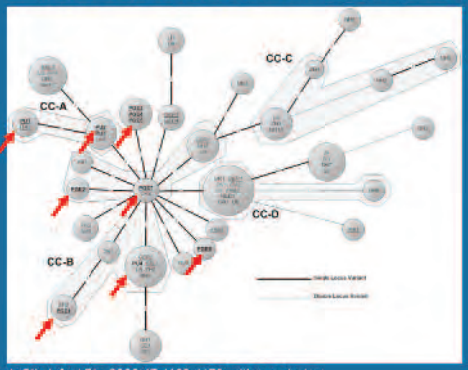
	Toxinotype III	Toxinotype V
PCR ribotype	027	078
Frequency	17%	9%
(Trend, 2005–2008)	(27%–1%)	(3%–13%)
Healthcare facility outbreaks	14	1
Age (years)	73.5	67.4
Community-associated	6.7%	17.5%

*1687 human isolates from 2005 to 2008 analyzed by polymerase chain reaction (PCR) ribotype; human 078 isolates were highly similar to pig 078 isolates by multilocus variable-number tandem repeat analysis

Goorhuis A, et al. *Clin Infect Dis.* 2008;47:1162-1170.

23

Minimum Spanning Tree Analysis of Human and Porcine 078 *C. difficile* Isolates



Goorhuis A, et al. *Clin Infect Dis.* 2008;47:1162-1170; with permission.

24

Conclusions

- Is hospital-acquired CDI still increasing? *Yes, but maybe slowing*
- What is the current status of the BI/NAP1/027 epidemic? *Remains the most prevalent strain the United States*
- Is there a community-acquired CDI epidemic? *No, but community cases will likely continue*
- Are there other clinically important strains that have emerged? *Yes (e.g., toxinotype V)*
- Are there new risk groups? *Maybe (e.g., peripartum women)*
- Are there new reservoirs/sources of infection? *Likely, but food-borne transmission is still not documented*

25

CDI Testing: What Are the Current Shortcomings and How Can We Improve Testing?

Dale N. Gerding, MD, FACP, FIDSA
Professor of Medicine
Loyola University Chicago
Stritch School of Medicine
Maywood, Illinois

Associate Chief of Staff for Research and Development
Hines Veterans Affairs Hospital
Hines, Illinois

26

Disclosures

Dale N. Gerding, MD, FACP, FIDSA

Dr. Dale N. Gerding has an affiliation with ViroPharma Incorporated (*Patents*) and Cepheid; BD GeneOhm; Massachusetts Biologic Laboratories; Merck & Co., Inc.; GOJO Industries, Inc.; Optimer Pharmaceuticals, Inc.; Salix Pharmaceuticals, Inc.; Schering-Plough; and ViroPharma Incorporated (*Research Grants* and *Consultant*).

Views expressed are those of the presenter and do not necessarily reflect the views of the US Department of Veterans Affairs, the major funding source for this research.

Unapproved Use: metronidazole, rifaximin, and nitazoxanide for treatment of *Clostridium difficile* infection have US Food and Drug Administration approval.

27

Four Major *Clostridium difficile* Infection (CDI) Clinical Problems

1. Inability to prevent CDI in high-risk settings, such as the hospital.
2. Lack of a sensitive and rapid diagnostic test for CDI.
3. Absence of a treatment that will prevent recurrence of CDI.
4. Inability to effectively treat fulminant CDI.

28

Key Points To Be Covered

- History of CDI testing
- Standard reference tests: cell cytotoxicity and toxigenic culture
- Test sensitivity, specificity, and turnaround time
- Two-step glutamate dehydrogenase (GDH): is it the answer?
- Can you beat poor sensitivity by sending more specimens?
- What is the role of real-time polymerase chain reaction (PCR) in CDI diagnosis?

29

Before We Begin CDI Testing

- Be certain that the population being tested has symptoms consistent with CDI. The stool should be watery or unformed (and should be rejected by the microbiology laboratory for testing if it is not), and the patient should meet minimum clinical criteria for diarrhea (≥3 loose or unformed stools in 24 hours or less).

30

History of CDI Diagnosis

- Cell cytotoxicity assay
  - Chang TW, et al. *Infect Immun.*1978;20:526-529.
- *C. difficile* selective media containing cefoxitin and cycloserine (culture)
  - George WL, et al. *J Clin Microbiol.* 1979;9:214-219.
- Enzyme immunoassay (EIA) for toxin A developed
  - Lyerly DM, et al. *J Clin Microbiol.* 1983;17:72-78.
- Latex test detects GDH
  - Lyerly DM, et al. *J Clin Microbiol.* 1991;29:2639-2642.

31

History of CDI Diagnosis

- Use of PCR for diagnosis
  - Kato H, et al. *J Infect Dis.*1993;167:455-458.
- Clinical outbreaks of *C. difficile* A−/B+ signaled the demise of toxin A EIA
  - Alfa MJ, et al. *J Clin Microbiol.* 2000;38:2706-2714.
- Insensitivity of EIA assays
  - O'Connor D, et al. *J Clin Microbiol.* 2001;39:2846-2849.
- Superior sensitivity of toxigenic culture vs cell cytotoxin assay
  - Delmee M, et al. *J Med Microbiol.* 2005;54:187-191.

32

Reference Test Standards: Toxigenic Culture vs Cell Cytotoxin Assay

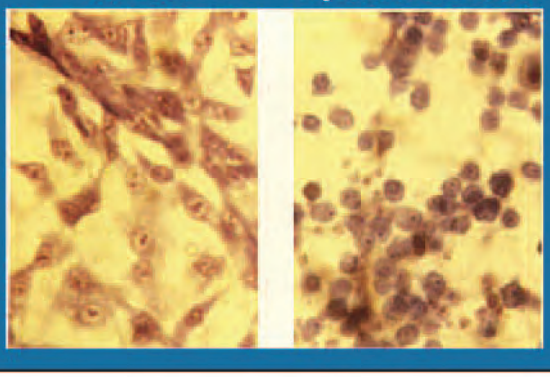
- 1058 liquid/unformed stools culture-positive for *C. difficile* using CCFA media
- 815 (77%) stools grew toxigenic *C. difficile*
- 243 (23%) stools grew nontoxigenic *C. difficile*
- Cell cytotoxin assay was positive on 460 stools
  - Sensitivity: 460/815=56% vs toxigenic culture
- Only 5 stools had a positive cell cytotoxin assay and did not grow *C. difficile* on culture
  - Sensitivity: 460/465=99% vs cell cytotoxin assay

CCFA=cycloserine-cefoxitin-fructose agar
Delmée M, et al. *J Med Microbiol*. 2005;54:187-191.

33

Cell Cytotoxicity Assay Interpretation

Normal | Cytotoxic Effect



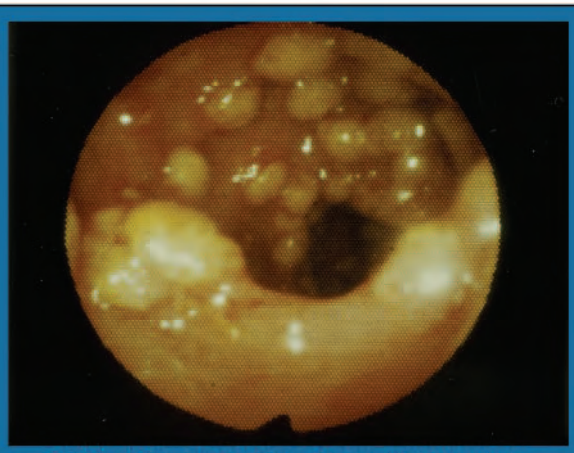
34

Presentations

An 86-Year-Old Man With Pneumonia

- An 86-year-old man is admitted to the hospital for treatment of community-acquired pneumonia and receives IV ceftriaxone followed by oral moxifloxacin. By day 4 his temperature is normal, and he is preparing for discharge when he develops loose stools with some abdominal cramping. He is having 6–8 watery bowel movements a day. There is no blood in the stool. **Three stool specimens submitted to the laboratory are negative by EIA for toxin A.**

35



Endoscopic visualization of pseudomembranes: specificity 100%, sensitivity 51%

36

The Patient Has Pseudomembranous Colitis (PMC)

Why was the stool EIA for toxin A negative?

1. The test is only ~50%–70% sensitive.
2. Some strains of *C. difficile* that cause CDI do not make toxin A.
3. It is not the best test, but laboratories like it because it is more rapid and less labor-intensive than other tests.
4. All of the above.

37

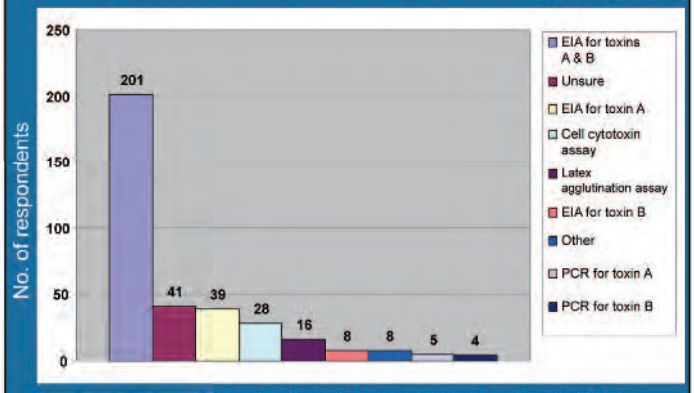
Four Toxin EIA Tests vs Cell Cytotoxin

	Sensitivity	Specificity	PPV	NPV
Cell Cytotoxin Assay	98	99	96	99
ImmunoCard Toxin A	54	99	94	84
Oxoid Toxin A	50	98	91	83
TechLab Toxin A/B	79	98	94	92
Premier Toxin A&B	80	98	94	93

NPV=negative predictive value; PPV=positive predictive value.
O'Connor D, et al. *J Clin Microbiol*. 2001;39:2846-2849.

38

Method of Laboratory CDI Diagnosis



Gerone S, et al. 16th Annual Meeting of The Society for Healthcare Epidemiology of America (SHEA). March 18-21, 2006; Chicago, IL. Late breaker abstract.

39

Clostridium difficile Diagnostic Tests[1-3]

Test	Sensitivity	Specificity
Endoscopy	~50%	~100%
Culture	~90%–100%	~77%–100%
Cell Cytotoxin	~56%–100%	~90%–100%
EIA Toxin A	~50%–90%	~75%–100%
EIA Toxin A/B	~79%–80%	~98%
GDH* Latex	~58%–92%	~50%–96%
GDH* EIA	~85%–100%	~50%–98%

*Also known as common antigen.

1. O'Connor D, et al. *J Clin Microbiol*. 2001;2846-2849.
2. Snell H, et al. *J Clin Microbiol*. 2004;42:4863-4865.
3. Ticehurst JR, et al. *J Clin Microbiol*. 2006;44:1145-1149.

40

Two-Step Testing Using GDH-EIA

- GDH-EIA (common antigen) is used as the first step to identify negative stools (80%–90% of specimens in most laboratories) that are reported as negative for *C. difficile*.
- The remaining stools are tested with the cell cytotoxicity assay and reported as positive for *C. difficile* toxin if positive, but not if negative.
- GDH-EIA negative assays are ≥99% predictive of cell cytoxicity negativity.
- This protocol saves workload and cost to labs but is **slow**.

Ticehurst JR, et al. *J Clin Microbiol*. 2006;44:1145-1149.
Reller ME, et al. *J Clin Microbiol*. 2007;45:3601-3605.

41

Sensitivity of GDH vs Toxigenic Culture

	Sensitivity	Specificity	PPV	NPV
ImmunoCard	84	90	49	98
C. DIFF® *Quik Chek*	87	87	42	98
Triage *C. difficile* panel	87	90	48	98
Cell cytototoxin	87	100	100	98

Is 84%–87% sensitivity good enough for a screening test?
A recent study found the Triage GDH only 76% sensitive.

Ribes J, et al. ICAAC-IDSA 2008; Washington DC. Abstract D-2277.
Sloan LM, et al. *J Clin Microbiol*. 2008;46:1996-2001.

42

Can Low Test Sensitivity be Overcome by Repeated Testing?

It depends on the specificity.

1000 Tests with 10% CDI Prevalence in Population

Sensitivity= 73.3% ↓ Specificity = 97.6% ↓

	Number Tested	True-Positive	False-Positive	Undetected True-Positive	Remaining Negative Patients
First Test	1000	73 (PPV = 0.75)	24	27	903
Second Test	903	18 (PPV = 0.45)	22	9	863

For typical EIA sensitivity and specificity, false-positives exceed true-positives with repeated testing.

Peterson LR. ICAAC-IDSA 2008, Washington, DC (unpublished).

43

Comparison of Real-Time PCR in Patients With ≥3 Loose Stools/Day

	Sensitivity	Specificity	PPV	NPV
Culture + toxin test*	100	99	96	99
Real-time PCR*	93	97	76	99
Toxin A/B EIA	73	98	73	98
Cell culture cytotoxin	77	97	70	98

*P<0.01 to 0.05 vs EIA.
Peterson LR, et al. *Clin Infect Dis*. 2007;45:1152-1160.

44

Real-Time PCR vs Toxigenic Culture*

Study	Sensitivity	Specificity	PPV	NPV
Barbut	93.9%	97.7%	83.8%	99.2%
Loo	92%	98.1%	82.1%	99.2%

*Using BD GeneOhm™ Cdiff real-time PCR assay.

Barbut F, et al. ICAAC-IDSA 2008, Washington, DC. Abstract D-2279.
Loo V, et al. ICAAC-IDSA 2008, Washington, DC. Abstract D-2281.

45

Real-Time PCR vs Toxigenic Culture

- Real-time PCR can be used to detect the toxin genes of *C. difficile*, usually targeting the toxin B gene to avoid missing toxin A−/B+ strains.
- Real-time PCR can also be used to detect specific genetic markers such as the *tcdC* deletion or binary toxin of BI/NAP1/027 epidemic strains that could provide useful epidemiologic data for infection control purposes

46

Unresolved CDI Diagnosis Issues

- Low sensitivity of most current tests in use
- Slow turnaround of the most sensitive current tests (cell cytotoxicity, culture)
- Use of a two-step GDH-EIA still results in slow turnaround for positive test results and may not be sufficiently sensitive
- Is the sensitivity of real-time PCR sufficiently high to displace EIA for toxin and GDH?
- Is gene detection by real-time PCR equivalent to toxin detection for diagnosis of CDI?

47

Clostridium difficile Infection (CDI): Treatment Strategies

Ciarán P. Kelly, MD
Chief, Herrman L. Blumgart Internal Medicine Firm
Director, Gastroenterology Fellowship Training
Beth Israel Deaconess Medical Center
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

48

Disclosure of Conflicts of Interest

Ciarán P. Kelly, MD

Dr. Ciarán P. Kelly has affiliations with Actelion Pharmaceuticals (*Consultant* and *Research Grants*); Salix Pharmaceuticals, Inc.; Cubist Pharmaceuticals, Inc.; and ViroPharma Incorporated (*Consultant*).

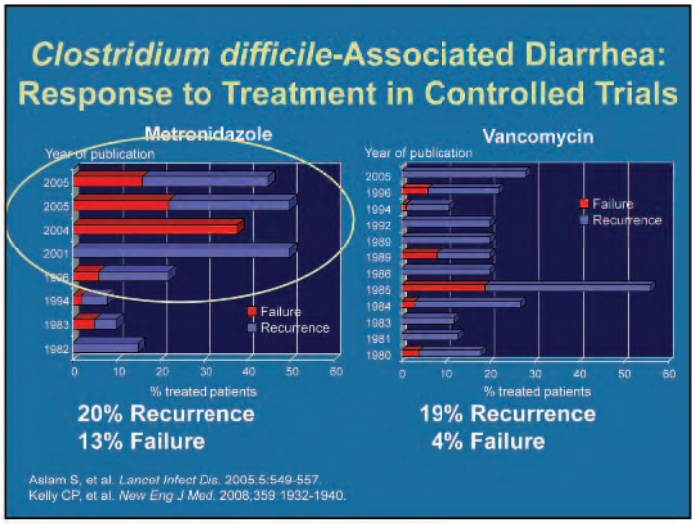
49

Clostridium difficile Infection (CDI): Treatment Strategies

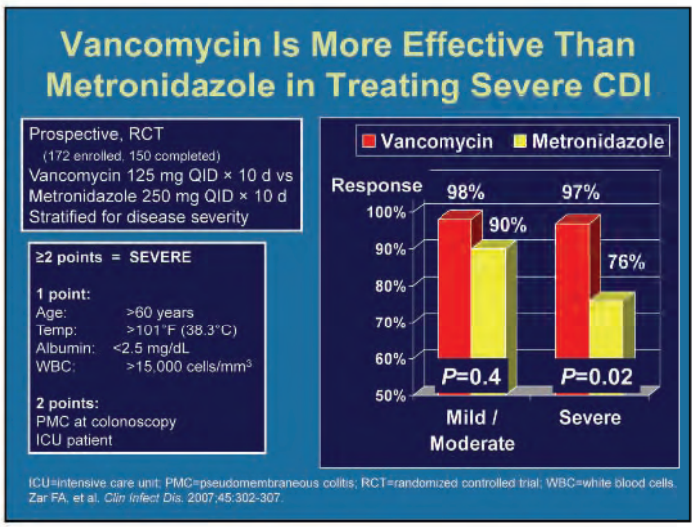
- Stratification of therapy by disease severity
- Fulminant and refractory CDI
- Recurrent CDI
- New agents for CDI

Aslam S et al. *Lancet Infect Dis*. 2005;5:549-557.

50


Clostridium difficile-Associated Diarrhea:
Response to Treatment in Controlled Trials
Metronidazole
Year of publication
2005
2005
2004
2001
1994
1983
1982
Failure
Recurrence
0 10 20 30 40 50 60
% treated patients
20% Recurrence
13% Failure
Vancomycin
Year of publication
2005
1996
1994
1992
1989
1989
1986
1985
1984
1983
1981
1980
Failure
Recurrence
0 10 20 30 40 50 60
% treated patients
19% Recurrence
4% Failure
Aslam S, et al. Lancet Infect Dis. 2005;5:549-557.
Kelly CP, et al. New Eng J Med. 2008;359:1932-1940.

51


Vancomycin Is More Effective Than
Metronidazole in Treating Severe CDI
Prospective, RCT
(172 enrolled, 150 completed)
Vancomycin 125 mg QID × 10 d vs
Metronidazole 250 mg QID × 10 d
Stratified for disease severity
≥2 points = SEVERE
1 point:
Age: >60 years
Temp: >101°F (38.3°C)
Albumin: <2.5 mg/dL
WBC: >15,000 cells/mm3
2 points:
PMC at colonoscopy
ICU patient
Vancomycin
Metronidazole
Response
100%
90%
80%
70%
60%
50%
98%
90%
97%
76%
P=0.4
P=0.02
Mild / Moderate
Severe
ICU=intensive care unit; PMC=pseudomembraneous colitis; RCT=randomized controlled trial; WBC=white blood cells.
Zar FA, et al. Clin Infect Dis. 2007;45:302-307.

52

Treatment of a First Episode of CDI

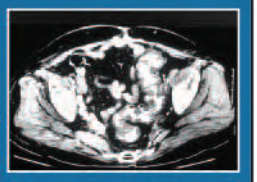
- Mild CDI
  - Discontinue inciting antibiotic (if possible)
  - Request stool toxin assay
  - Monitor course of disease
- Moderate or persisting CDI
  - Metronidazole (e.g., 500 mg TID) for 10 to 14 days
- Severe CDI (or metronidazole failure)
  - Vancomycin (e.g., 125 mg QID PO) for 10 to 14 days

Gerding DN, et al. *Infect Control Hosp Epidemiol*. 1995;16:459-477.
Poutanen SM, et al. *Can Med Assoc J*. 2004;171:51-58.
Kelly CP, et al. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. Philadelphia: WB Saunders, 2006:2393-2412.

53

Markers of Severe CDI

- Severe diarrhea (>10 bowel movements/day)
- Marked leukocytosis
  - >15,000 cells/mm^3 associated with severe CDI
  - >25,000 cells/mm^3 associated with increased fatality
- Rising serum creatinine
- Falling serum albumin
- Colonic thickening on computed tomography
- Ascites on computed tomography
- Pseudomembranous colitis (PMC) on endoscopy
- Hemodynamic instability
- Severe abdominal distention, pain



≥2 points = SEVERE

1 point:

Age:	>60 years
Temp:	>101°F (38.3°)
Albumin:	< 2.5 mg/dL
WBC:	>15,000 cells/mm^3

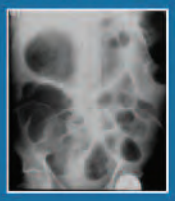
2 points:
PMC at colonoscopy
ICU patient

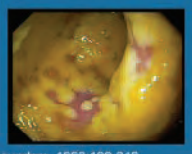
Zar FA, et al. *Clin Infect Dis*. 2007;45:302-307.

54

Colonic Distention and Small Bowel Ileus in Fulminant *Clostridium difficile* Colitis

- Severe/fulminant CDI may present as an acute abdomen and/or mimic acute colonic pseudo-obstruction
  - Little or no diarrhea
  - Sigmoidoscopy usually diagnostic



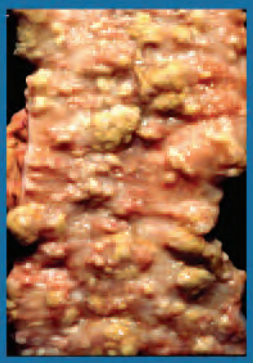


Kelly CP, LaMont JT. *Gastrointestinal Pharmacotherapy*. Philadelphia: WB Saunders, 1993;199-212.

55

Management of Fulminant or Refractory CDI

- Vancomycin 500 mg QID PO
- If ileus:
  - Metronidazole 500 mg IV TID plus
  - Vancomycin 500 mg QID via nasogastric tube or by enema
- If progressive or refractory:
  - Early surgery evaluation/consultation
  - Consider intravenous immunoglobulin (IVIG) 400 mg/kg
  - Monitor for progression
    - WBC >20,000 cells/mm³
    - Serum creatinine >1.5 × baseline
    - Rising serum lactate (>5 mmol/L)



56

Recurrent CDI

- Common
  - ~20% after first CDI episode
  - ~40% after first recurrence
  - >60% after 2 or more recurrences
- Mechanisms of recurrence
  - **Not** resistance to metronidazole or vancomycin
  - New infection common (≥50%)
    - Metronidazole and vancomycin both perpetuate loss of colonization resistance
  - Inadequate immune response important

Kyne L, Kelly CP. *Gut*. 2001;49:152-153.

57

Treatment of a First ~~Episode~~ Recurrence of CDI

- Mild CDI
  - Discontinue inciting antibiotic (if possible)
  - Request stool toxin assay
  - Monitor course of disease
- Moderate or persisting CDI
  - Metronidazole (e.g., 500 mg TID) for 10 to 14 days
- Severe CDI (or metronidazole failure)
  - Vancomycin (e.g., 125 mg QID PO) for 10 to 14 days

Gerding DN, et al. *Infect Control Hosp Epidemiol*. 1995;16:459-477.
Poutanen SM, et al. *Can Med Assoc J*. 2004;171:51-58.
Kelly CP, et al. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. Philadelphia: WB Saunders; 2006;2393-2412.

58

An Approach To Treating Recurrent CDI

- First recurrence
  - Metronidazole or vancomycin for 10–14 days
- Second recurrence
  - Oral vancomycin taper and pulsed dosing
- Third recurrence
  - Vancomycin 125 mg QID for 14 days *followed by* rifaximin 400 mg BID for 14 days
- Subsequent recurrences
  - IVIG (400 mg/kg; repeat after 3 weeks)
  - Vancomycin plus probiotic therapy?
    - *Lactobacillus* spp, *Saccharomyces boulardii*
    - Fecal transplantation

Vancomycin Taper and Pulsed Dosing

Week 1	*125 mg*	*QID*
Week 2	*125 mg*	*BID*
Week 3	*125 mg*	*QD*
Week 4	*125 mg*	*QOD*
Weeks 5–6	*125 mg*	*Q3D*

Kelly CP, LaMont JT. *N Engl J Med*. 2008;359:1932-1940.
Tedesco FJ, et al. *Am J Gastroenterol*. 1985;80:867-868.

59

Treatment of Multiply Recurrent CDI

Nonrandomized Study*

Vancomycin	*N*	Recurrence, *n* (%)	*P* Value
Medium dose (1 g to <2 g/day)	14	10 (71)	
Low dose (<1 g/day)	48	26 (54)	
High dose (≥2 g/day)	21	9 (43)	
Tapering dose	29	9 (31)	0.01
Pulse dosing	7	1 (14)	0.02
Other†	6	2 (33)	
All	125	57 (46)	
Metronidazole	***N***	**Recurrence, *n* (%)**	
Low dose (≤1 g/day)	29	13 (45)	
Medium dose (1.5 g/day)	5	2 (40)	
Other‡	4	1 (25)	
All	38	16 (42)	
Totals	163	73 (45)	

*Placebo/antibiotic cohort from 2 clinical trials of *Saccharomyces boulardii* as adjunctive treatment.
†Includes vancomycin and rifampin (*n*=3) and vancomycin and metronidazole (*n*=3).
‡Includes high dose (2 g/day), taper, or pulse dosing.

McFarland LV, et al. *Am J Gastroenterol*. 2002;97:1769-1775.

60

An Approach To Treating Recurrent CDI

- First recurrence
  - Metronidazole or vancomycin for 10–14 days
- Second recurrence
  - Oral vancomycin taper and pulsed dosing
- Third recurrence
  - Vancomycin 125 mg QID for 14 days *followed by* rifaximin 400 mg BID for 14 days
- Subsequent recurrences
  - IVIG (400 mg/kg; repeat after 3 weeks)
  - Vancomycin plus probiotic therapy?
    - *Lactobacillus* spp. *Saccharomyces boulardii*
    - Fecal transplantation

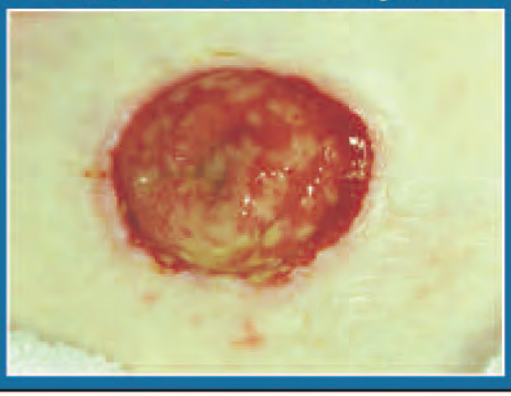
Vancomycin Taper and Pulsed Dosing

Week 1	*125 mg*	*QID*
Week 2	*125 mg*	*BID*
Week 3	*125 mg*	*QD*
Week 4	*125 mg*	*QOD*
Weeks 5–6	*125 mg*	*Q3D*

Kelly CP, LaMont JT. *N Engl J Med*. 2008;359:1932-1940.
Tedesco FJ, et al. *Am J Gastroenterol*. 1985;80:867-868.

61

Bedside Diagnosis: Pseudomembranous Colitis at a Colostomy Site



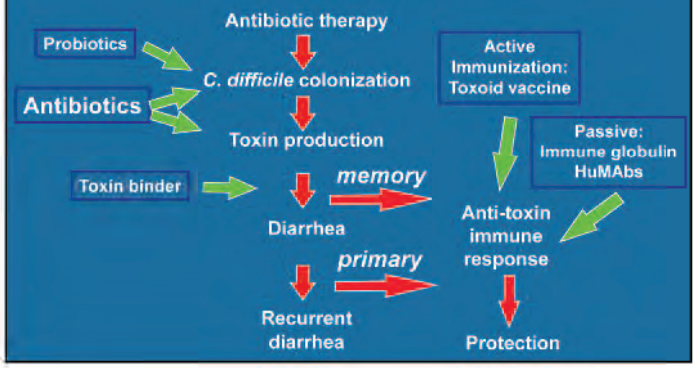
62

CDI: Unmet Medical Needs

- Increasing disease incidence
- Increasing disease severity
- Low cure rate (<75%)
  - 4% to 13% of patients don't respond to treatment
  - 2% to 7% of patients die
  - >20% have recurrence

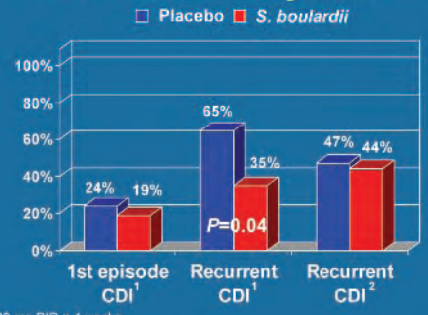
63

New Treatment Approaches for *C. difficile*–Associated Diarrhea



64

S. boulardii for Prevention of CDI: Inconsistent Study Results*



S. boulardii 500 mg BID × 4 weeks.

1. McFarland LV, et al. *J AM Med Assoc.* 1994;271:1913-1918.
2. Surawicz CM, et al. *Clin Infect Dis.* 2000;31:1012-1017.

65

New Antimicrobial Agents for CDI

Company	Antimicrobial	Human Studies
ActivBiotics	Rifalazil® (benzoxazinorifamycin)*	Phase II
Oscient	Ramoplanin	Phase III?
Optimer	Fidaxomicin (OPT-80)*	Phase III
Presutti	Tindamax® (tinidazole)†	–
Romark	Alinia® (nitazoxanide)†	Phase III?
Salix	Xifaxan® (rifaximin)†	Phase III

*Available for another medication.
†Animal data show reduced recurrence of CDI.

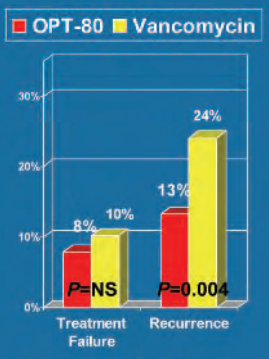
66

OPT-80 in CDI

- Minimal absorption from human gastrointestinal tract
- "Selective" anti-*C. difficile* antibiotic
- Preserves colonization resistance??

- 629 adults with CDI treated for 10 days
  - 200 mg OPT-80 BID (78% "cured")*
  - 125 mg vancomycin QID (67% "cured")*

*P=0.006



Optimer Pharmaceuticals, Inc. www.optimerpharma.com/news.asp?news_story=698-page_num=4.

67

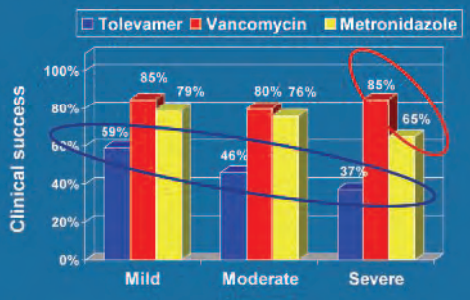
Tolevamer for CDI Therapy: Inferior to Vancomycin and to Metronidazole

- High-molecular-weight soluble polymer
- Binds *C. difficile* toxins A and B

Louie TJ, et al. 47th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) Meeting. September 17-20, 2007 [abstract K-425-a].

68

Tolevamer for CDI Therapy: Inferior to Vancomycin and to Metronidazole

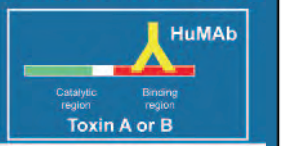


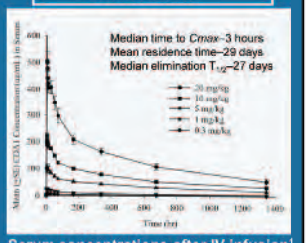
Louie TJ, et al. 47th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) Meeting. September 17-20, 2007 [abstract K-425-a].

69

Human Monoclonal Anti-Toxin A and B

- Anti-toxin HuMAbs from transchromic mice (Massachusetts Biologic Laboratories and Medarex)
- Clinical studies
  - Phase I safety and pharmacokinetics[1]
  - Phase II – Anti-A HuMAb - failed
- Phase II[2]
  - RCT in 200 patients with CDI
  - Standard antibiotic therapy PLUS anti-A & anti-B Mab infusion
  - Met primary objective: 70% reduction in recurrent CDI (active vs placebo: P=0.0004)

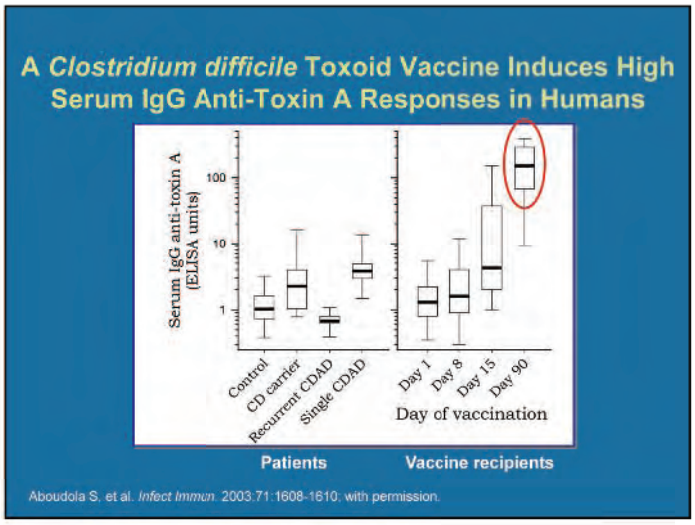




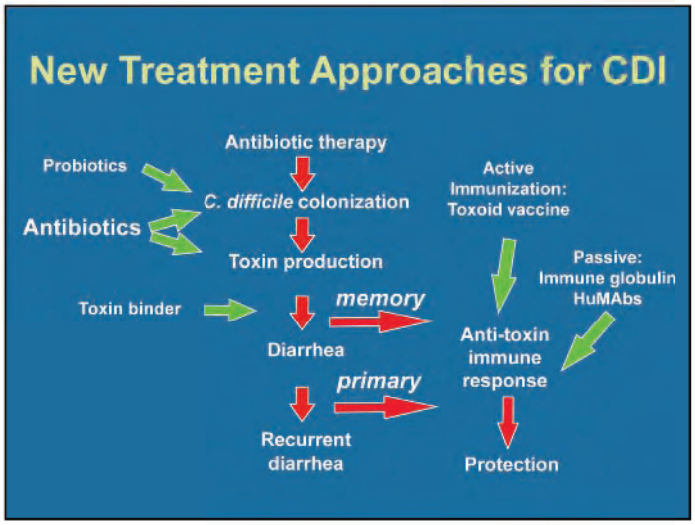
Serum concentrations after IV infusion[1]

Taylor CP, et al. Vaccine. 2008;26:3404-3409; with permission.
Medarex, Inc. www.medarex.com/cgi-local/item.pl/20061103-1220865.

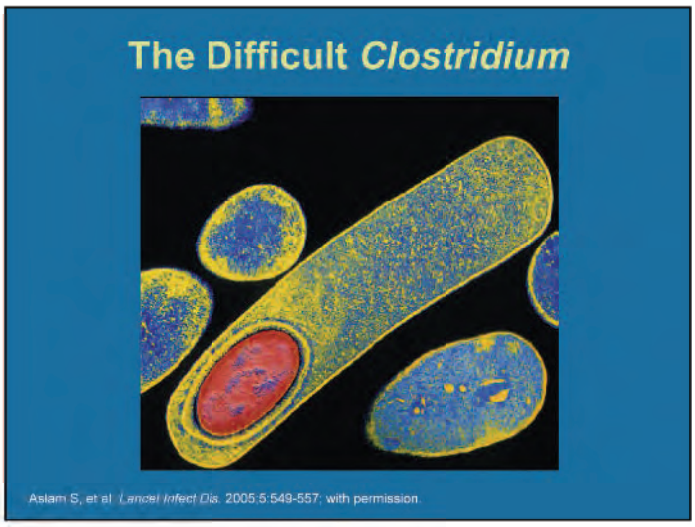
70


A Clostridium difficile Toxoid Vaccine Induces High Serum IgG Anti-Toxin A Responses in Humans
Serum IgG anti-toxin A (ELISA units)
100
10
1
Control
CD carrier
Recurrent CDAD
Single CDAD
Day 1
Day 8
Day 15
Day 90
Day of vaccination
Patients
Vaccine recipients
Aboudola S. et al. Infect Immun. 2003;71:1608-1610. with permission.

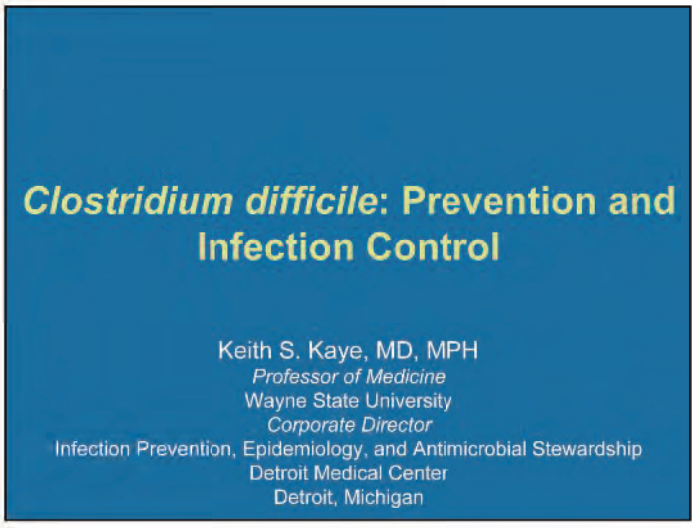
71


New Treatment Approaches for CDI
Antibiotic therapy
Probiotics
Antibiotics
C. difficile colonization
Toxin production
Toxin binder
memory
Diarrhea
primary
Recurrent diarrhea
Active Immunization: Toxoid vaccine
Passive: Immune globulin HuMAbs
Anti-toxin immune response
Protection

72


The Difficult *Clostridium*
Aslam S, et al. *Lancet Infect Dis.* 2005;5:549-557; with permission.

73


Clostridium difficile: Prevention and Infection Control
Keith S. Kaye, MD, MPH
Professor of Medicine
Wayne State University
Corporate Director
Infection Prevention, Epidemiology, and Antimicrobial Stewardship
Detroit Medical Center
Detroit, Michigan

74

Disclosure of Conflicts of Interest

Keith S. Kaye, MD, MPH

Dr. Keith S. Kaye has an affiliation with Cubist; Merck & Co., Inc.; Pfizer Inc.; Schering-Plough (*Speakers' Bureau*); Forest Laboratories, Inc.; Ortho-McNeil Pharmaceutical, Inc.; Schering-Plough; TheraDoc Inc.; Wyeth Pharmaceuticals (*Consultant*); Merck & Co., Inc. and Pfizer Inc. (*Research*).

75

The Impact of *Clostridium difficile* Infection (CDI)

- Leading cause of infectious nosocomial diarrhea in the United States
  - >300,000 cases diagnosed in 2005
  - Occurs in 3% to 29% of hospitalized patients who receive antibiotics
- Mortality ranges from 6% to 30%
- Persistent, resilient microbe
  - Challenging to diagnose
  - Spore former
  - Contamination of hands, carpet, and other environmental surfaces and equipment demonstrated
  - Symptomatic and asymptomatic patients act as reservoirs
  - Formation of spores that are resistant to heat, chemicals, and antibiotics

Elixhauser, A, Jhung, MA. HCUP Statistical Brief #50. April 2008. Agency for Healthcare Research and Quality, Rockville, MD, and unpublished data. Available at: www.hcup-us.ahrq.gov/reports/statbriefs/sb50.pdf.
Aslam S, et al. *Lancet Infect Dis*. 2005;5:549-557.

76

The Impact of CDI: Economic Burden

- Excess costs
  - $2380 to $3240 per index hospitalization
  - $3797 to $7179 inpatient costs over 180 days of follow-up
- Other outcomes
  - 2.8 days attributable excess length of stay
  - 19.3% attributable readmission (180 days)
  - 5.7% attributable mortality (180 days)
  - More likely discharged to long-term care

CDI prevention and infection control are critical

Dubberke ER. et al. *Clin Infect Dis.* 2008;46:497-504.
Dubberke ER. et al. 17th Annual Meeting of The Society for Healthcare Epidemiology of America (SHEA). April 14-17, 2007: Baltimore, MD; unpublished data.

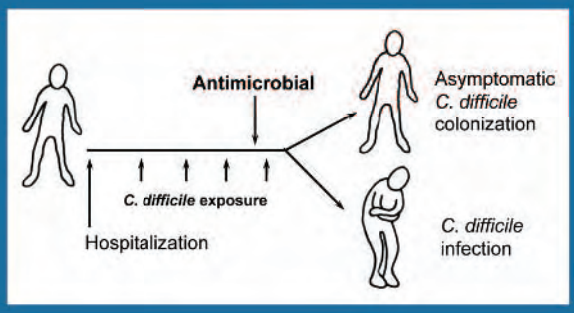
77

Prevention and Infection Control Strategies

- Hand hygiene
- Isolation and contact precautions
- Environmental disinfection
- Antimicrobial stewardship

78

Pathogenesis of CDI

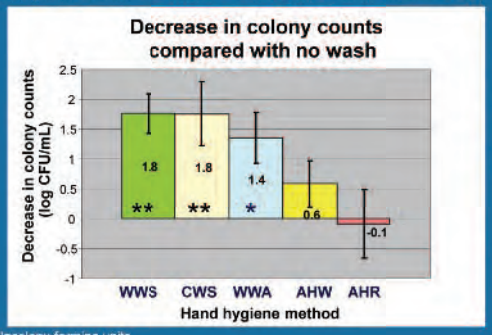


From Johnson S, Gerding DN. *Clin Infect Dis*. 1998;26:1027-1036; with permission.

79

Hand Hygiene

Soap and water are more effective than alcohol-based wipes and rubs



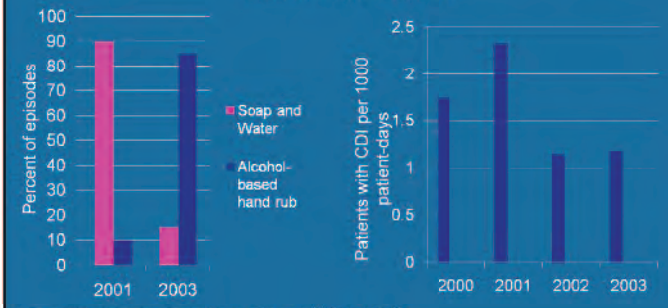
WWS = warm water and soap
CWS = cold water and soap
WWA = warm water and antibacterial
AHW = alcohol hand wipe
AHR = alcohol hand rub

CFU=colony-forming units.
*Different from AHR ($P<0.05$).
**Different from AHR and AHW ($P<0.05$).
Oughton M, et al. Presented at the 47th Annual ICAAC Meeting. 2007; Chicago, IL.

80

Hand Hygiene: Alcohol-Based Rubs and CDI Incidence

Significant increase in use of alcohol-based hand rubs with no parallel increase in CDI incidence

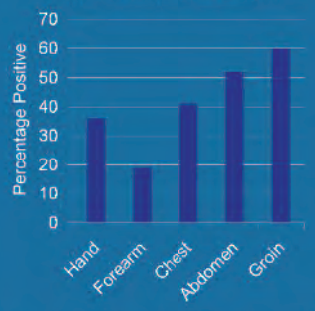


Boyce JM, et al. *Infect Control Hosp Epidemiol.* 2006;27:479-483.

81

Skin Contamination

Frequency of *C. difficile* contamination of skin sites (*N*=27 patients with CDI)



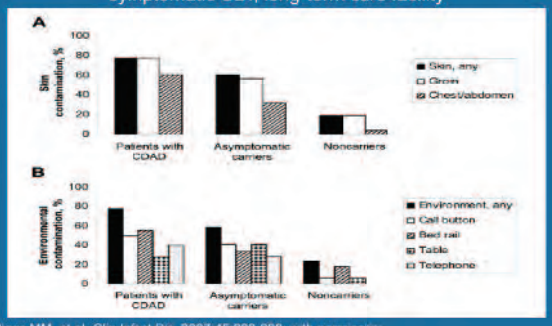
- 25 patients (93%) had contamination of ≥1 skin site
- Of 21 patients with CDI with molecular typing, 11 (52%) had epidemic NAP1 strains
- All NAP1 isolates had the binary toxin gene *cdtB* (polymerase chain reaction positive) and high-level resistance to moxifloxacin (minimum inhibitory concentration, 132 mg/mL)

Adapted from Bobulsky GS, et al. *Clin Infect Dis.* 2008;46:447-450; with permission.

82

Transmission of CDI From Asymptomatic Carriers

Asymptomatic carriers shed *C. difficile* spores at lower rates than patients with symptomatic CDI, long-term care facility



From Riggs MM, et al. *Clin Infect Dis.* 2007;45:992-998; with permission.

83

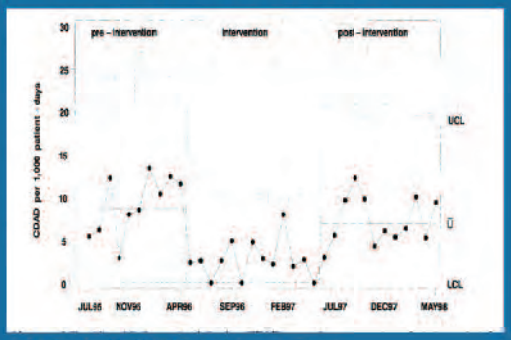
Environmental Disinfection

- Alcohol-based products do not kill *C. difficile* spores or remove *C. difficile* from environmental objects
- Commonly used hospital cleaning agents, such as quaternary ammonium–based (and other surfactant-based) detergents, are not sporicidal and may in fact encourage sporulation
- Disinfection with a 1:10 dilution of concentrated sodium hypochlorite (i.e., bleach) or high-concentration, vaporized hydrogen peroxide has been shown to be effective

Gerding DN, et al. *Clin Infect Dis.* 2008;46:S43-S49.

84

Effect of Hypochlorite in Highly Endemic Ward



From Mayfield JL. *Clin Infect Dis* 2000;31:995-1000; with permission.

85

Efficacy of Hydrogen Peroxide (H_2O_2)

Activity of a dry-mist hydrogen peroxide system against environmental *C. difficile* contamination

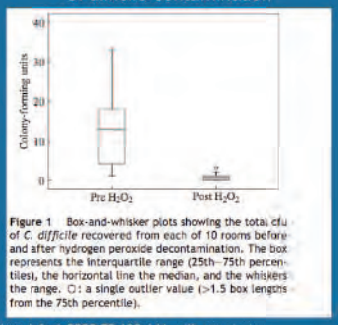
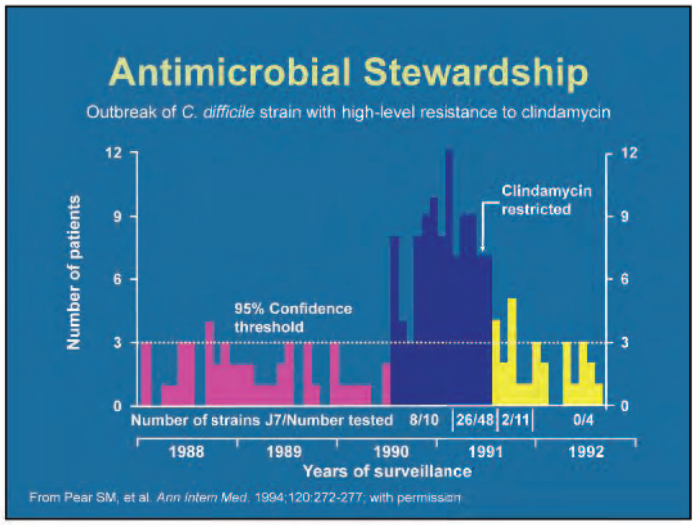


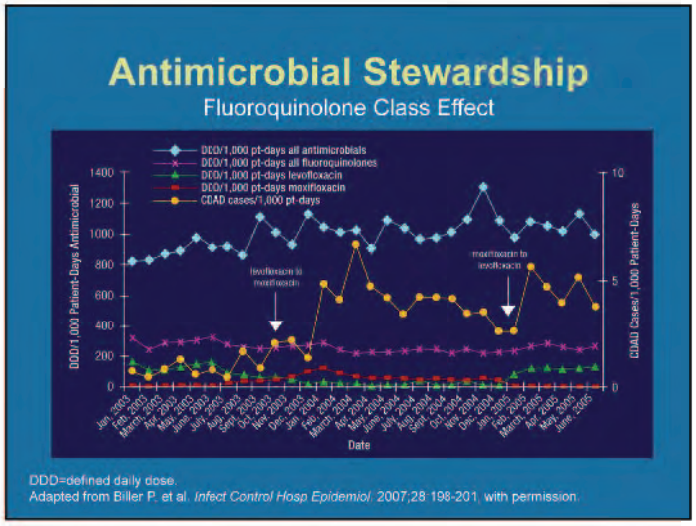
Figure 1 Box-and-whisker plots showing the total cfu of *C. difficile* recovered from each of 10 rooms before and after hydrogen peroxide decontamination. The box represents the interquartile range (25th–75th percentiles), the horizontal line the median, and the whiskers the range. ○: a single outlier value (>1.5 box lengths from the 75th percentile).

From Shapey S, et al. *J Hosp Infect* 2008;70:136-141; with permission.

86


Antimicrobial Stewardship
Outbreak of C. difficile strain with high-level resistance to clindamycin
Number of patients
12
9
6
3
0
95% Confidence threshold
Clindamycin restricted
Number of strains J7/Number tested 8/10 26/48 2/11 0/4
1988
1989
1990
1991
1992
Years of surveillance
From Pear SM, et al. Ann Intern Med. 1994;120:272-277; with permission

87


Antimicrobial Stewardship
Fluoroquinolone Class Effect
DDD/1,000 pt-days all antimicrobials
DDD/1,000 pt-days all fluoroquinolones
DDD/1,000 pt-days levofloxacin
DDD/1,000 pt-days moxifloxacin
CDAD cases/1,000 pt-days
DDD/1,000 Patient-Days Antimicrobial
CDAD Cases/1,000 Patient-Days
levofloxacin to moxifloxacin
moxifloxacin to levofloxacin
Date
DDD=defined daily dose.
Adapted from Biller P, et al. Infect Control Hosp Epidemiol. 2007;28:198-201; with permission.

88

Antimicrobial Stewardship

Fluoroquinolone Class Effect (2)

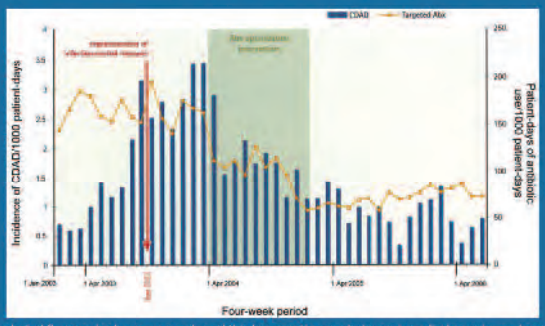
- Large case-control study of an outbreak, including 203 nosocomial *C. difficile* cases
- Independent risk factors include recent history of receiving clindamycin, cephalosporins, or levofloxacin (odds ratio, 2.0; 95% confidence intervals 1.2–3.3)
- Notable increase in levofloxacin use preceding outbreak and continuing during outbreak

Adapted from Muto C, et al. *Infect Control Hosp Epidemiol.* 2005;26:273-280

89

Antimicrobial Stewardship

Impact of reduction of high-risk antibiotics* on epidemic CDI



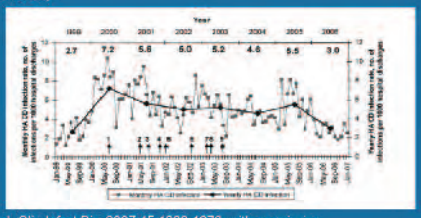
*Included fluoroquinolones, second- and third-generation cephalosporins, clindamycin, and macrolides.

From Valiquette L, et al. *Clin Infect Dis.* 2007;45:S112-S121; with permission

90

CDI "Bundle": Pittsburgh, PA

- Education
- Increased and early case finding (alerts)
- Expanded infection control measures
  - Contact precautions (CP) for the duration of hospitalization
  - Soap and water for hand hygiene
  - Sodium hypochlorite for environmental cleaning
- CD management team
- Antimicrobial management (approval for clindamycin, ceftriaxone, and levofloxacin)

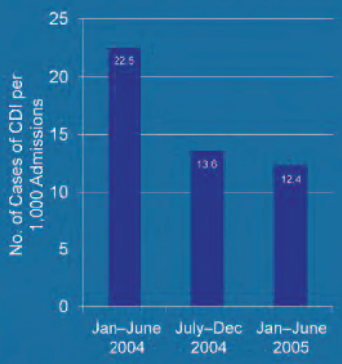


From Muto CA, et al. *Clin Infect Dis.* 2007;45:1266-1273; with permission.

91

CDI "Bundle": Quebec, Canada

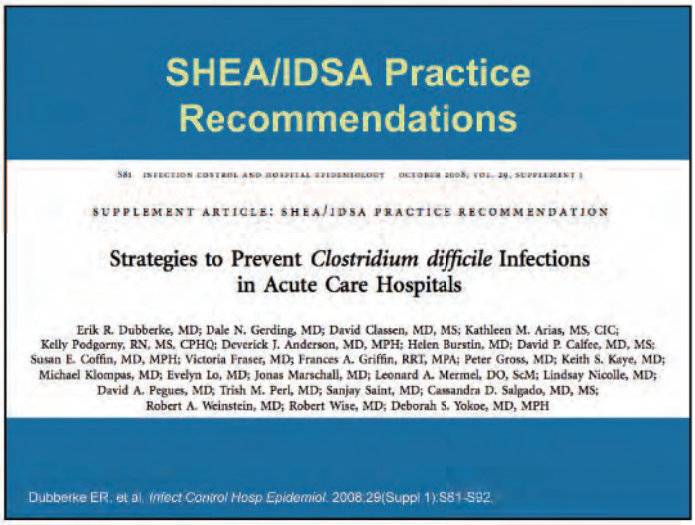
- Intensified environmental cleaning
- Dedicated equipment
- Enhanced hand-hygiene practices
- Case finding and early detection
- Contact isolation
- Antibiotic stewardship



Loo VG, et al. *Can Med Assoc J.* 2004;171:47-48.
Loo VG, et al. *N Engl J Med.* 2005;353:2442-2449.

92

SHEA/IDSA Practice Recommendations



S81 INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY OCTOBER 2008, VOL. 29, SUPPLEMENT 1

SUPPLEMENT ARTICLE: SHEA/IDSA PRACTICE RECOMMENDATION

Strategies to Prevent *Clostridium difficile* Infections in Acute Care Hospitals

Erik R. Dubberke, MD; Dale N. Gerding, MD; David Classen, MD, MS; Kathleen M. Arias, MS, CIC; Kelly Podgorny, RN, MS, CPHQ; Deverick J. Anderson, MD, MPH; Helen Burstin, MD; David P. Calfee, MD, MS; Susan E. Coffin, MD, MPH; Victoria Fraser, MD; Frances A. Griffin, RRT, MPA; Peter Gross, MD; Keith S. Kaye, MD; Michael Klompas, MD; Evelyn Lo, MD; Jonas Marschall, MD; Leonard A. Mermel, DO, ScM; Lindsay Nicolle, MD; David A. Pegues, MD; Trish M. Perl, MD; Sanjay Saint, MD; Cassandra D. Salgado, MD, MS; Robert A. Weinstein, MD; Robert Wise, MD; Deborah S. Yokoe, MD, MPH

Dubberke ER, et al. *Infect Control Hosp Epidemiol.* 2008;29(Suppl 1):S81-S92.

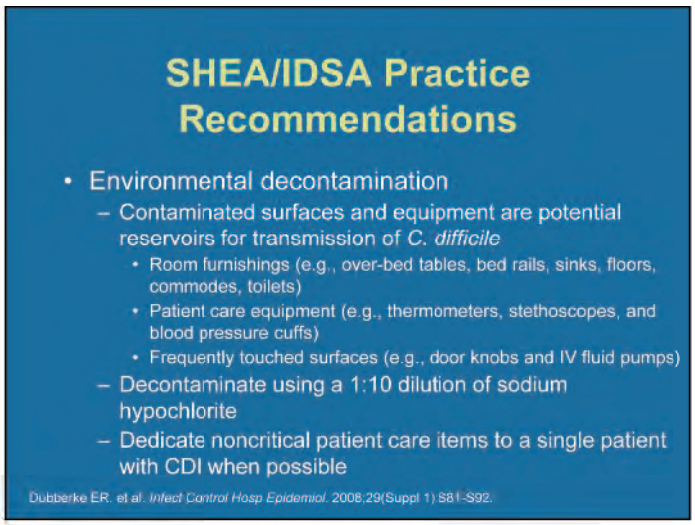
93

SHEA/IDSA Practice Recommendations

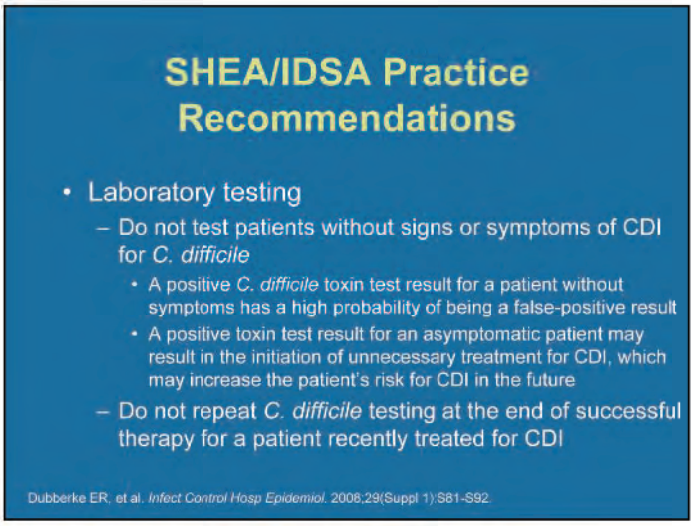
- Contact precautions (CP)
  - Use CP for infected patients; single-patient room preferred
  - Maintain CP for the duration of illness (CDC recommendations)
    - Some experts recommend CP for ≥48 h after diarrhea resolves
  - Asymptomatic colonized patients
    - Shed spores to a lesser degree than do patients with active CDI
    - No data to support isolation of asymptomatic patients
    - Do not treat or attempt to decolonize asymptomatic *C. difficile* carriers

Dubberke ER, et al. *Infect Control Hosp Epidemiol.* 2008;29(Suppl 1):S81-S92.

94


SHEA/IDSA Practice Recommendations
• Environmental decontamination
– Contaminated surfaces and equipment are potential reservoirs for transmission of C. difficile
• Room furnishings (e.g., over-bed tables, bed rails, sinks, floors, commodes, toilets)
• Patient care equipment (e.g., thermometers, stethoscopes, and blood pressure cuffs)
• Frequently touched surfaces (e.g., door knobs and IV fluid pumps)
– Decontaminate using a 1:10 dilution of sodium hypochlorite
– Dedicate noncritical patient care items to a single patient with CDI when possible
Dubberke ER, et al. Infect Control Hosp Epidemiol. 2008;29(Suppl 1):S81-S92.

95


SHEA/IDSA Practice Recommendations
• Laboratory testing
– Do not test patients without signs or symptoms of CDI for C. difficile
• A positive C. difficile toxin test result for a patient without symptoms has a high probability of being a false-positive result
• A positive toxin test result for an asymptomatic patient may result in the initiation of unnecessary treatment for CDI, which may increase the patient's risk for CDI in the future
– Do not repeat C. difficile testing at the end of successful therapy for a patient recently treated for CDI
Dubberke ER, et al. Infect Control Hosp Epidemiol. 2008;29(Suppl 1):S81-S92.

96

SHEA/IDSA Practice Recommendations

- Education
  - Educate healthcare workers, housekeeping, hospital administration, and patients and their families about CDI
    - Risk factors, routes of transmission, etc.
  - Ensure proper hand-hygiene technique using soap and water
- Laboratory-based alert system
  - Provide immediate notification to infection prevention and control personnel and clinical personnel about patient with newly diagnosed CDI

Dubberke ER, et al. *Infect Control Hosp Epidemiol*. 2008;29(Suppl 1):S81-S92.

97

SHEA/IDSA Practice Recommendations

- Internal reporting
  - Compliance with hand-hygiene guidelines:

$$\frac{\text{Number of observed proper hand-hygiene episodes}}{\text{Total number of observed opportunities for hand hygiene}} \times 100$$

  - Compliance with contact precautions:

$$\frac{\text{Number of observed patient care episodes in which contact precautions are appropriately implemented}}{\text{Number of observed patient care episodes in which contact precautions are indicated}} \times 100$$

- External reporting
  - Hospitals in states that have mandatory reporting requirements for CDI must collect and report the data required by the state

Dubberke ER, et al. *Infect Control Hosp Epidemiol*. 2008;29(Suppl 1):S81-S92.

98

SHEA/IDSA Practice Recommendations

- Surveillance
  - CDI rates should be calculated as follows:
    - Numerator: number of CDI cases in the population being monitored
    - Denominator: total number of patient days in the population being monitored
    - Multiply by 10,000 so that the measure is expressed as number of cases per 10,000 patient-days

$$\frac{\text{Number of CDI cases in the population}}{\text{Total number of patient days in the population}} \times 10{,}000$$

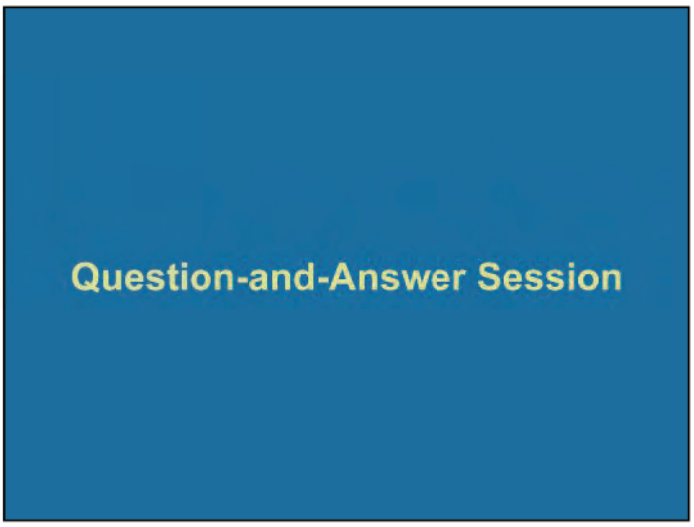
Dubberke ER, et al. *Infect Control Hosp Epidemiol.* 2008;29(Suppl 1):S81-S92.

99

Summary

- *C. difficile* is a persistent, resilient pathogen that is difficult to manage
- Multimodal and multidisciplinary strategies are likely most effective and include:
  - Hand hygiene, isolation, and the use of barrier precautions
  - Environmental and equipment cleaning use of dedicated equipment
  - Antibiotic stewardship
- Compliance with these processes will enhance epidemic prevention and endemic control

100



101

References

Stuart Johnson, MD, DTM&H

Al Saif N, Brazier JS. The distribution of *C. difficile* in the environment of South Wales. *J Med Microbiol*. 1996;45:133-137.

Chang HT, Krezolek D, Johnson S, Parada JP, Evans CT, Gerding DN. Onset of symptoms and time to diagnosis of *Clostridium difficile*-associated disease following discharge from an acute care hospital. *Infect Control Hosp Epidemiol.* 2007;28:926-931.

Cheknis A, Citron DM, Nagaro KJ, Sambol SP, Johnson S, Gerding DN. Epidemic BI/NAP1 is the dominant strain of *Clostridium difficile* found in patients in the OPT-80 vs. vancomycin clinical trial in North America and the European Union. Presented at the 48th Annual Interscience Conference of Antimicrobial Agents and Chemotherapy (ICAAC)/Infectious Diseases Society of America (IDSA) 46th Annual Meeting. October 25-28, 2008; Washington, DC.

Cheknis AK, Davidson D, Nagaro KJ, Sambol SP, Johnson S, Gerding DN. Prevalence of epidemic REA types of *Clostridium difficile* from a recent European clinical treatment trial. Presented at the 9th Biennial Congress of the Anaerobe Society of the Americas. June 24-27, 2008; Long Beach, CA.

Eggertson L, Sibbald B. *Can Med Assoc J*. 2004;171:19-21.

Elixhauser A, Jhung MA. Healthcare Cost and Utilization Project statistical brief #50: *Clostridium difficile*-associated disease in U.S. hospitals, 1993-2005. Rockville, MD: Agency for Healthcare Research and Quality; April 2008. Available at: www.hcup-us.ahrq.gov/reports/statbriefs/sb50.jsp. Accessed May 4, 2009.

Garey KW, Jiang ZD, Yadov Y, Mullins B, Wong K, Dupont HL. Peripartum *Clostridium difficile* infection: case series and review of the literature. *Am J Obstet Gynecol*. 2008;199:332-337.

Goorhuis A, Bakker D, Corver J, Debast SB, Harmanus C, Notermans DW, et al. Emergence of *Clostridium difficile* infection due to a new hypervirulent strain, polymerase chain reaction ribotype 078. *Clin Infect Dis*. 2008;47:1162-1170.

Jhung MA, Thompson AD, Killgore GE, Zukowski WE, Songer G, Warny M, et al. Toxinotype V *Clostridium difficile* in humans and food animals. *Emerg Infect Dis*. 2008;14:1039-1045.

Kuijper EJ, Barbut F, Brazier JS, Kleinkauf N, Eckmanns T, Lambert ML, et al. Update of *Clostridium difficile* infection due to PCR ribotype 027 in Europe, 2008. *Eurosurveillance*. 2008;13:1-7.

Kutty PK, Benoit S, Woods C, Sena A, Naggie S, Frederick J, et al. Emerging *Clostridium difficile*–associated disease in the community and the role of non-antimicrobial risk factors. In: Program and abstracts of the 44th Annual Meeting of Infectious Disease Society of America; October 12-15, 2006; Toronto, Ontario [Abstract LB-28].

Kutty PK, Benoit SR, Woods CW, Sena AC, Naggie S, Frederick J, et al. Assessment of *Clostridium difficile*-associated disease surveillance definitions, North Carolina, 2005. *Infect Control Hosp Epidemiol*. 2008;29:197-202.

Loo VG, Poirier L, Miller MA, Oughton M, Libman MD, Michaud S, et al. A predominantly clonal multi-institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. *N Engl J Med*. 2005;353:2442-2449.

McDonald LC, Coignard B, Dubberke E, Song X, Horan T, Kutty PK; and the Ad Hoc *Clostridium difficile* Surveillance Working Group. Recommendations for surveillance of *Clostridium difficile*-associated disease. *Infect Control Hosp Epidemiol*. 2007:28:140-145.

McDonald LC, Killgore GE, Thompson A, Owens RC Jr, Kazakova SV, Sambol SP, et al. An epidemic, toxin gene-variant strain of *Clostridium difficile*. *N Engl J Med*. 2005;353:2433-2441.

Miller M, Gravel D, Mulvey M, Gardam M, McGeer A, Hutchinson J, et al. *Clostridium difficile* strain type and patient age are highly predictive of severe outcomes due to *C. difficile* infection. Presented at the 48th Annual Interscience Conference of Antimicrobial Agents and Chemotherapy (ICAAC)/Infectious Diseases Society of America (IDSA) 46th Annual Meeting. October 25-28, 2008; Washington DC.

Redelings MD, Sorvillo F, Mascola L. Increase in *Clostridium difficile*-related mortality rates, United States, 1999-2004. *Emerg Infect Dis*. 2007;13:1417-1419.

Rodriguez-Palacios A, Stämpfli HR, Duffield T, Peregrine AS, Trotz-Williams LA, Arroyo LG, Brazier JS, Weese JS. *Clostridium difficile* PCR ribotypes in calves, Canada. *Emerg Infect Dis*. 2006;12:1730-1736.

Rodriguez-Palacios A, Stämpfli HR, Duffield T, Weese JS. *Clostridium difficile* in retail ground meat, Canada. Emerg Infect Dis. 2007;13:485-487.

Rouphael NG, O'Donnell JA, Bhatnagar J, Lewis F, Polgreen PM, Beekmann S, et al. *Clostridium difficile*-associated diarrhea: an emerging threat to pregnant women. *Am J Obstet Gynecol*. 2008;198:635.e1-e6.

Songer JG. The emergence of *Clostridium difficile* as a pathogen of food animals. *Anim Health Res Rev*. 2004;5:321-326.

Songer JG, Anderson MA. *Clostridium difficile*: an important pathogen of food animals. *Anaerobe*. 2006;12:1-4.

Suetens C. *Clostridium difficile*: summary of actions in the European union. *Euro Surveill*. 2008;13:18944.

Valiquette L, Low DE, Pépin J, McGeer A. *Clostridium difficile* infection in hospitals: a brewing storm. *Can Med Assoc J*. 2004;171:27-29.

Dale N. Gerding, MD, FACP, FIDSA

Alfa MJ, Kabani A, Lyerly D, Moncrief S, Neville LM, Al-Barrak A, et al. Characterization of a toxin A-negative, toxin B-positive strain of *Clostridium difficile* responsible for a nosocomial outbreak of *Clostridium difficile*-associated diarrhea. *J Clin Microbiol*. 2000;38:2706-2714.

Barbut F, Braun M, Burghoffer B, Petit J. Rapid diagnosis of toxigenic strains of *Clostridium difficile* in diarrheal stools by real-time PCR [Abstract D-2279]. Presentation at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and the Infectious Diseases Society of America (IDSA) 46th Annual Meeting, October 25-28, 2008; Washington, DC.

Chang T-W, Bartlett JG, Gorbach SL, Onderdonk AB. Clindamycin-induced enterocolitis in hamsters as a model of pseudomembranous colitis in patients. *Infect Immun.* 1978;20:526-529.

Delmée M, Van Broeck J, Simon A, Janssens M, Avesani V. Laboratory diagnosis of *Clostridium difficile*-associated diarrhoea: a plea for culture. *J Med Microbiol*. 2005;54:187-191.

References

Gelone S. *Clostridium difficile*-associated disease: results of an international web-based surveillance project. Late breaking abstract. 16th Annual Meeting of the Society for Healthcare Epidemiology of America (SHEA). March 18-21, 2006; Chicago, IL.

George WL, Sutter VL, Citron D, Finegold SM. Selective and differential medium for isolation of *Clostridium difficile*. *J Clin Microbiol*. 1979;9:214-219.

Kato N, Ou CY, Kato H, Bartley SL, Luo CC, Killgore GE, et al. Detection of toxigenic *Clostridium difficile* in stool specimens by the polymerase chain reaction. *J Infect Dis*. 1993;167:455-458.

Loo VG, Fenn S, Rowsome F. Rapid detection of *Clostridium difficile* toxin B gene in fecal specimens by BD GeneOhm Cdiff assay. Presentation at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and the Infectious Diseases Society of America (IDSA) 46th Annual Meeting, October 25-28, 2008; Washington, DC.

Lyerly DM, Barroso LA, Wilkins TD. Identification of the latex test-reactive protein of *Clostridium difficile* as glutamate dehydrogenase. *J Clin Microbiol*. 1991;29:2639-2642.

Lyerly DM, Sullivan NM, Wilkins TD. Enzyme-linked immunosorbent assay for *Clostridium difficile* toxin A. *J Clin Microbiol*. 1983;17:72-78.

O'Connor D, Hynes P, Cormican M, Collins E, Corbett-Feeney G, Cassidy M. Evaluation of methods for detection of toxins in specimens of feces submitted for diagnosis of *Clostridium difficile*-associated diarrhea. *J Clin Microbiol*. 2001;39:2846-2849.

Peterson LR, Manson RU, Paule SM, Hacek DM, Robicsek A, Thomson RB Jr., et al. Detection of toxigenic *Clostridium difficile* in stool samples by real-time polymerase chain reaction for the diagnosis of *Clostridium difficile*–associated diarrhea. *Clin Infect Dis*. 2007;45:1152-1160.

Reller ME, Lema CA, Perl TM, Cai M, Ross TL, Speck KA, et al. Yield of stool culture with isolate toxin testing versus a two-step algorithm including stool toxin testing for the detection of toxigenic *Clostridium difficile*. *J Clin Microbiol*. 2007;45:3601-3605.

Ribes J, Overman S, Kenley M, Morgan L, Jacobs B. Comparison of 3 *Clostridium difficile* common antigen EIAs with cytotoxin assay and bacterial culture [Abstract D-2277]. Presentation at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and the Infectious Diseases Society of America (IDSA) 46th Annual Meeting, October 25-28, 2008; Washington, DC.

Sloan LM, Duresko BJ, Gustafson DR, Rosenblatt JE. Comparison of real-time PCR for detection of the tcdC gene with four toxin immunoassays and culture in diagnosis of *Clostridium difficile* infection. *J Clin Microbiol*. 2008;46:1996-2001.

Snell H, Ramos M, Longo S, John M, Hussain Z. Performance of the TechLab C. DIFF CHEK-60 enzyme immunoassay (EIA) in combination with the *C. difficile* Tox A/B II EIA kit, the Triage *C. difficile* panel immunoassay, and a cytotoxin assay for diagnosis of *Clostridium difficile*-associated diarrhea. *J Clin Microbiol*. 2004;42:4863-4865.

Ticehurst JR, Aird DZ, Dam LM, Borek AP, Hargrove JT, Carroll KC. Effective detection of toxigenic *Clostridium difficile* by a two-step algorithm including tests for antigen and cytotoxin. *J Clin Microbiol.* 2006;44:1145-1149.

Ciarán P. Kelly, MD

Aboudola S, Kotloff KL, Kyne L, Warny M, Kelly EC, Sougioultzis S, et al. *Clostridium difficile* vaccine and serum immunoglobulin G antibody response to toxin A. *Infect Immun*. 2003;71:1608-1610.

Aslam S, Hamill RJ, Musher DM. Treatment of *Clostridium difficile*-associated disease: old therapies and new strategies. *Lancet Infect Dis*. 2005;5:549-557.

Gerding DN, Johnson S, Peterson LR, Mulligan ME, Silva J Jr. *Clostridium difficile*-associated diarrhea and colitis. SHEA position paper. *Infect Control Hosp Epidemiol*. 1995;16:459-477.

Kelly CP, LaMont JT. *Clostridium difficile*—more difficult than ever. *N Engl J Med*. 2008;359:1932-1940.

Kelly CP, LaMont JT. Pseudomembranous colitis and antibiotic-associated diarrhea. In: Feldman M, Friedman LS, Brandt LJ, eds. Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 8th ed. Philadelphia: WB Saunders, 2006;2393-2412.

Kelly CP, LaMont JT, Treatment of *Clostridium difficile* diarrhea and colitis. In: Wolfe MM, ed. Gastrointestinal Pharmacotherapy. Philadelphia: WB Saunders, 1993;199-212.

Kyne L, Kelly CP. Recurrent *Clostridium difficile* diarrhoea. *Gut*. 2001;49: 152-153

Kyne L, Warny M, Qamar A, Kelly CP. Association between antibody response to toxin A and protection against recurrent *Clostridium difficile* diarrhoea. *Lancet*. 2001;357:189-193.

Leung DY, Kelly CP, Boguniewicz M, Pothoulakis C, LaMont JT, Flores A. Treatment with intravenously administered gamma globulin of chronic relapsing colitis induced by *Clostridium difficile* toxin. 1991;118:633-637.

Louie T. Results of a phase III trial comparing tolevamer, vancomycin and metronidazole in *Clostridium difficile*–associated diarrhea (CDAD)[abstract K-425-a]. Presentation at the 47th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, September 17-20, 2007; Chicago, IL.

McFarland LV, Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent *Clostridium difficile* disease. *Am J Gastroenterol*. 2002:97:1769-1775.

McFarland LV, Surawicz CM, Greenberg RN, Fekety R, Elmer GW, Moyer KA, et al. A randomized placebo-controlled trial of Saccharomyces boulardii in combination with standard antibiotics for *Clostridium difficile* disease. *J Am Med Assoc*. 1994;271:1913-1918.

Medarex, Inc. Medarex and Massachusetts Biologic Laboratories Announce Primary Objective Achieved in Phase 2 Trial of Monoclonal Antibody Combination for the Treatment of *Clostridium difficile* Associated Diarrhea (CDAD) [November 3, 2008 press release]. Available at www.medarex.com/cgi-local/item.pl/20081103-1220865. Accessed May 18, 2009.

Optimer Pharmaceuticals, Inc. OPT-80 Achieves its Primary Endpoint of Clinical Cure with a Lower Recurrence Rate vs. Vancocin® [November 10, 2008 press release]. Available at: www.optimerpharma.com/news.asp?news_story=698-page_num=4. Accessed May 18, 2009.

References

Poutanen SM, Simor AE. *Clostridium difficile*-associated diarrhea in adults. *Can Med Assoc J*. 2004;171:51-58.

Surawicz CM, McFarland LV, Greenberg RN, Rubin M, Fekety R, Mulligan ME, et al. The search for a better treatment for recurrent *Clostridium difficile* disease: use of high-dose vancomycin combined with Saccharomyces boulardii. *Clin Infect Dis*. 2000;31:1012-1017.

Taylor CP, Tummala S, Molrine D, Davidson L, Farrell RJ, Lembo A, et al. Open-label, dose escalation phase I study in healthy volunteers to evaluate the safety and pharmacokinetics of a human monoclonal antibody to *Clostridium difficile* toxin A. *Vaccine*. 2008;26:3404-3409.

Tedesco FJ, Gordon D, Fortson WC. Approach to patients with multiple relapses of antibiotic-associated pseudomembranous colitis. *Am J Gastroenterol*. 1985;80:867-8680.

Wilcox MH. Descriptive study of intravenous immunoglobulin for the treatment of recurrent *Clostridium difficile* diarrhea. *J Antimicrob Chemother*. 2004;53:882-884.

Zar FA, Bakkanagari SR, Moorthi K, Davis MB. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. *Clin Infect Dis*. 2007;45:302-307.

Keith S. Kaye, MD, MPH

Aslam S, Hamill RJ, Musher DM. Treatment of *Clostridium difficile*-associated disease: old therapies and new strategies. *Lancet Infect Dis*. 2005;5:549-557.

Biller P, Shank B, Lind L, Brennan M, Tkatch L, Killgore G, et al. Moxifloxacin therapy as a risk factor for *Clostridium difficile*-associated disease during an outbreak: attempts to control a new epidemic strain. *Infect Control Hosp Epidemiol*. 2007;28:198-201.

Bobulsky GS, Al-Nassir WN, Riggs MM, Sethi AK, Donskey CJ. *Clostridium difficile* skin contamination in patients with *C. difficile*-associated disease. *Clin Infect Dis*. 2008;46:447-450.

Boyce JM, Ligi C, Kohan C, Dumigan D, Havill NL. Lack of association between the increased incidence of *Clostridium difficile*-associated disease and the increasing use of alcohol-based hand rubs. *Infect Control Hosp Epidemiol.* 2006;27:479-483.

Dubberke ER, Gerding DN, Classen D, Arias KM, Podgorny K, Anderson DJ, et al. SHEA/IDSA practice recommendation: strategies to prevent *Clostridium difficile* infections in acute care hospitals. *Infect Control Hosp Epidemiol.* 2008;29(Suppl 1):S81-S92.

Dubberke ER, Reske KA, Olsen MA, McDonald LC, Fraser VJ. Short- and long-term attributable costs of *Clostridium difficile*–associated disease in nonsurgical inpatients. *Clin Infect Dis*. 2008;46:497-504.

Elixhauser A, Jhung MA. *Clostridium difficile*-Associated Disease in U.S. Hospitals, 1993–2005. HCUP Statistical Brief #50. Available at: www.hcup-us.ahrq.gov/reports/statbriefs/sb50.pdf. Accessed May 21, 2009.

Gerding DN, Muto CA, Owens RC Jr. Measures to control and prevent *Clostridium difficile* infection. *Clin Infect Dis*. 2008;46(Suppl 1):S43-S9.

Johnson S, Gerding DN. Clostridium difficile-associated diarrhea. *Clin Infect Dis*. 1998;26:1027-1036.

Loo VG, Libman MD, Miller MA, Bourgault AM, Frenette CH, Kelly M, et al. *Clostridium difficile*: a formidable foe. *Can Med Assoc J*. 2004;171:47-48.

Loo VG, Poirier L, Miller MA, Oughton M, Libman MD, Michaud S, et al. A predominantly clonal multi-institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. *N Engl J Med*. 2005;353:2442-2449.

Mayfield JL, Leet T, Miller J, Mundy LM. Environmental control to reduce transmission of *Clostridium difficile*. *Clin Infect Dis*. 2000;31:995-1000.

Muto CA, Blank MK, Marsh JW, Vergis EN, O'Leary MM, Shutt KA, et al. Control of an outbreak of infection with the hypervirulent *Clostridium difficile* BI strain in a university hospital using a comprehensive "bundle" approach. *Clin Infect Dis*. 2007;45:1266-1273.

Muto CA, Pokrywka M, Shutt K, Mendelsohn AB, Nouri K, Posey K, et al. A large outbreak of *Clostridium difficile*-associated disease with an unexpected proportion of deaths and colectomies at a teaching hospital following increased fluoroquinolone use. *Infect Control Hosp Epidemiol*. 2005;26:273-280.

Oughton M, Loo V, Fenn S, Lynch A, Libman M. Alcohol rub and antiseptic hand wipes are inferior to soap and water for removal of *C. difficile* by handwashing [late-breaking abstract K-1376a]. Presentation at the 47th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, September 17-20, 2007; Chicago, IL.

Pear SM, Williamson TH, Bettin KM, Gerding DN, Galgiani JN. Decrease in nosocomial *Clostridium difficile*-associated diarrhea by restricting clindamycin use. Ann Intern Med. 1994;120:272-277

Riggs MM, Sethi AK, Zabarsky TF, Eckstein EC, Jump RL, Donskey CJ. Asymptomatic carriers are a potential source for transmission of epidemic and nonepidemic *Clostridium difficile* strains among long-term care facility residents. *Clin Infect Dis*. 2007;45:992-998.

Shapey S, Machin K, Levi K, Boswell TC. Activity of a dry mist hydrogen peroxide system against environmental *Clostridium difficile* contamination in elderly care wards. *J Hosp Infect*. 2008;70:136-141.

Valiquette L, Cossette B, Garant MP, Diab H, Pépin J. Impact of a reduction in the use of high-risk antibiotics on the course of an epidemic of *Clostridium difficile*-associated disease caused by the hypervirulent NAP1/027 strain. *Clin Infect Dis*. 2007;45:S112-S121.

ROBERT MICHAEL
EDUCATIONAL INSTITUTE LLC

101 Laurel Road • Voorhees, New Jersey 08043

Additional educational activities offered by
Robert Michael Educational Institute LLC can be found at
www.RMEI.com or by calling toll-free to 866-770-RMEI.

03-09-079-VL