CHALLENGES AND OPPORTUNITIES IN MANAGING SERIOUS BACTERIAL INFECTIONS

A Role for Pathogen-Directed Therapy

Wednesday, October 8, 2014
8:00 – 10:00 PM
Pennsylvania Convention Center
Philadelphia, PA

EDUCATIONAL OVERVIEW

The pandemic of multidrug-resistant (MDR) bacteria and their continuing spread is well recognized. The growing prevalence of MDR pathogens in the community and healthcare settings has challenged clinicians in maintaining a high quality of care. Of particular concern are infections caused by Gram-positive bacteria (i.e., methicillin-resistant *S. aureus* [MRSA], vancomycin-resistant enterococci [VRE]), Gram-negative pathogens (MDR *P. aeruginosa*, ESBL-producing and carbapenem-resistant Enterobacteriaceae), and *Clostridium difficile*. Compared to susceptible organisms, infections caused by these pathogens are associated with higher failure rates, mortality, and healthcare resource utilization. When an MDR infection is suspected, it is critical to consider multiple patient-, pathogen-, and drug-related factors in selecting an optimal therapeutic option.

This educational program utilizes a case-based approach to demonstrate how management strategies are tailored to patient and pathogen factors. Understanding how these factors can influence therapeutic selection is a critical component for successful outcomes and underscores the importance of collaboration among the various disciplines when addressing the challenges of MDR infections. The program is divided into three learning blocks that focus on 1) Gram-positive pathogens, 2) Gram-negative pathogens, and 3) *C. difficile*. Each block is designed to open and conclude with an interactive patient case scenario that reflects the challenges and decision-making process that occurs regularly in clinical practice when managing these difficult infections.

TARGET AUDIENCE

Optimal management of serious bacterial infections requires an interdisciplinary approach that includes all healthcare providers (HCPs) involved in the management of patients with or at risk for these infections. Therefore, this continuing medical education activity targets healthcare providers at the forefront of diagnosing, managing, and preventing infections at healthcare institutions. These include ID specialists, infection control specialists, hospital epidemiologists, clinical microbiologists, and clinical pharmacists.

LEARNING OBJECTIVES

Healthcare professionals participating in this educational activity will be able at its conclusion to:

- Apply evidence-based guideline recommendations into clinical practice when managing hospitalized patients with serious bacterial infections
- Identify strategies to optimize the use of available antimicrobial agents to treat multidrug-resistant bacterial infections in a pathogen-directed approach
- Evaluate new and emerging therapeutic options for treating serious bacterial infections

FACULTY

Thomas M. File, Jr., MD, MS, MACP, FIDSA, FCCP
Chair, Infectious Disease Division
Summa Health System
Akron, OH
Professor, Internal Medicine
Master Teacher; Chair, Infectious Disease Section
Northeast Ohio Medical University
Rootstown, OH

Marin H. Kollef, MD, FACP, FCCP
Professor of Medicine, Division of Pulmonary and Critical Care Medicine
Virginia E. & Sam J. Golman Chair in Respiratory Intensive Care Medicine
Director, Critical Care Research
Director, Respiratory Care Services
Barnes-Jewish Hospital
St. Louis, MO

Carlene A. Muto, MD, MS
Associate Professor of Medicine
Medical Director of Infection Control and Hospital Epidemiology
Center for Quality Improvement and Innovation
UPMC Health System
Pittsburgh, PA

EDUCATIONAL PROGRAM

Registration: 7:30 PM – 8:00 PM
Educational Program: 8:00 PM – 10:00 PM

8:00 – 8:10 PM **MDR-GLOBAL PUBLIC HEALTH THREAT**

8:10 – 9:50 PM **IMPROVING PATIENT CARE**

Practice Case 1 Gram-Positive Infections
Optimized Approaches in Managing Gram-Positive Infections
Back to Practice Case 1
Thomas M. File, Jr., MD, MS, MACP, FIDSA, FCCP

Practice Case 2 Gram-Negative Infections
Optimized Approaches in Managing Gram-Negative Infections
Back to Practice Case 2
Marin H. Kollef, MD, FACP, FCCP

Practice Case 3 *Clostridium difficile* Infections
Optimized Approaches in Managing *C. difficile* Infections
Back to Practice Case 3
Carlene A. Muto, MD, MS

9:50 – 10:00 PM **OPEN FORUM: Q&A**

ACCREDITATION

PHYSICIANS

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 providership of the Center for Independent Healthcare Education (Center) and Vemco MedEd. Center is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Center designates this live activity for a maximum of 2.0 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

PHARMACISTS

Center for Independent Healthcare Education is accredited by the Accreditation Council for Pharmacy Education as a provider for continuing pharmacy education. Center has assigned 2.0 contact hours (0.2 CEUs) of continuing pharmacy education credits for participating in this activity.

ACPE UAN: 0473-9999-14-007-L01-P
Activity type: Application-based

For questions regarding accreditation, please contact info@jointsponsor.com.

INSTRUCTIONS FOR CREDIT

To receive a Certificate of Credit, participants must register for the symposium, document attendance, and complete and return the evaluation form.

Physicians: A Certificate of Credit will be emailed to you 4 weeks after the symposium.

Pharmacists: The information that you participated will be uploaded to CPE Monitor and you will be able to access your credits from the profile you set up with NABP. For more information, please visit http://www.nabp.net/.

DISCLOSURE OF CONFLICTS OF INTEREST

In accordance with policies set forth by the Accreditation Council for Continuing Medical Education (ACCME), Center for Independent Healthcare Education requires all faculty members and spouses/significant others with an opportunity to affect the content of a continuing education activity to disclose any relevant financial relationships during the past 12 months with commercial interests. A commercial interest is any entity producing, marketing, reselling or distributing health care goods or services consumed by or used on patients. Relationships with commercial interests and conflicts of interest resulting from those relationships must be revealed to the audience and resolved prior to the activity.

Relevant relationships include roles such as speaker, author, consultant, independent contractor (including research), employee, investor, advisory committee member, board member, review panelist, and investigator. If a potential speaker or author indicates a possible conflict of interest, the conflict will be resolved by choosing another speaker or author for that topical area, or the slides, handouts, and/or monograph will be reviewed and approved by a qualified commercially-disinterested peer.

PLANNING COMMITTEE MEMBERS

Thomas M. File, Jr., MD, MS, MACP, FIDSA, FCCP

Marin H. Kollef, MD, FACP, FCCP

Carlene A. Muto, MD, MS

Paul DeLisle

Marco Cicero, PhD

Maja Drenovac, PharmD, CCMEP

DISCLOSURE OF FINANCIAL INTEREST SUMMARY

Thomas M. File, Jr., MD (Faculty/Planner) has relevant financial relationships with commercial interests as follows:

- Advisory Board: Cubist Pharmaceuticals, Forest Laboratories, GlaxoSmithKline, Merck & Co., Pfizer, Tetraphase
- Grant Recipient/Research Support: Pfizer, Cempra

Dr. File intends to discuss the off-label use of following: Non-approved uses of drugs for MDR pathogens.

Marin H. Kollef, MD (Faculty/Planner) has relevant financial relationships with the following commercial interests:

- Advisory Board: Cubist Pharmaceuticals and Merck & Co.
- Consultant: Cardeas, Accelerate
- Speaker's Bureau: Cubist Pharmaceuticals and Merck & Co.

Dr. Kollef does not intend to discuss the off-label use of any products.

Carlene A. Muto, MD, MS (Faculty/Planner) does not have relevant financial relationships with commercial interests.

Dr. Muto does not intend to discuss the off-label use of any products.

COMMERCIAL SUPPORT

This activity is supported by an educational grant from **Cubist Pharmaceuticals**.

FACULTY BIOS

Thomas M. File, Jr., MD, MS, MACP, FIDSA, FCCP

Chair, Infectious Disease Division
Summa Health System
Akron, OH
Professor, Internal Medicine
Master Teacher; Chair, Infectious Disease Section
Northeast Ohio Medical University
Rootstown, OH

Dr. Thomas File is Chair of the Infectious Disease Division at Summa Health System in Akron, Ohio, USA and Professor of Internal Medicine, Master Teacher, and Chair of the Infectious Disease Section at Northeast Ohio Medical University in Rootstown, Ohio. After graduating from medical school at the University of Michigan, Ann Arbor, in 1972, Dr. File received his Master of Science in medical microbiology from Ohio State University in Columbus, in 1977, where he also completed his fellowship in infectious diseases.

Dr. File is Past President of the Board of Directors of the National Foundation for Infectious Diseases. He is a Master of the American College of Physicians, a Fellow and past member of the Board of Directors of the Infectious Diseases Society of America (IDSA), and a fellow of the American College of Chest Physicians. He is a member of many other professional societies, including the American Society for Microbiology, the American Thoracic Society (ATS), and the European Society of Clinical Microbiology and Infectious Diseases. He is a past Chairperson of the Standards and Practice Guidelines Committee of the IDSA and has also served as a member of the IDSA and ATS committees for guidelines on community-acquired pneumonia; and is a member of the IDSA guidelines panels for hospital-acquired pneumonia, influenza, and sinusitis. He is a past-president of the Infectious Disease Society of Ohio, and is a past president of the Northeastern Ohio Task Force on AIDS.

Primary research interests that Dr. File has pursued include community-acquired respiratory tract infections, immunizations in adults, bacterial resistance in respiratory infections, infections in patients with diabetes, soft tissue infections, antimicrobial stewardship, and evaluation of new antimicrobial agents. A frequent lecturer both nationally and internationally, Dr. File has published more than 250 articles, abstracts, and textbook chapters, focusing on the diagnosis, etiology, and treatment of infectious diseases, especially on respiratory tract infections. He co-authored File TM Jr. and Stevens DL *Contemporary Diagnosis and Management of Skin and Soft Tissue Infections, 3rd Ed* (2011, published by Handbooks in Health Care Co.) and co-edited Tan JS, File TM Jr., Salata RA, Tan MJ (eds.) *Expert Guide to Infectious Diseases, 2nd edition*(2008, published by ACP Press, Phil.). He authors sections on community-acquired pneumonia, acute bronchitis, and hospital-acquired pneumonia in UpToDate. In addition, he is Editor-in-Chief of *Infectious Diseases in Clinical Practice*.

Marin H. Kollef, MD, FACP, FCCP

Professor of Medicine, Division of Pulmonary and Critical Care Medicine
Virginia E. & Sam J. Golman Chair in Respiratory Intensive Care Medicine
Director, Critical Care Research
Director, Respiratory Care Services
Barnes-Jewish Hospital
St. Louis, MO

Dr. Marin Kollef is a Professor of Medicine at Washington University School of Medicine and Director of the Medical Intensive Care Unit and Respiratory Care Services at Barnes-Jewish Hospital in St. Louis, Missouri. He is a member of the Barnes-Jewish Hospital Critical Care Committee. Dr. Kollef was awarded Virginia E. and Sam J. Golman Chair in Respiratory Intensive Care Medicine in 2009.

After completing his Bachelor of Science from the US Military Academy in West Point, NY, Dr. Kollef went on to receive his Doctor of Medicine degree from University of Rochester School of Medicine and Dentistry. Dr. Kollef then completed his residency in Internal Medicine and fellowship in Pulmonary Diseases and Critical Care at the Madigan Army Medical Center in Tacoma, Washington. He is a fellow of the American College of Physicians and the American College of Chest Physicians.

Dr. Kollef has lectured extensively on numerous critical care topics, including ventilator-associated pneumonia, antibiotic resistance, and optimization of antibiotic therapy. Dr. Kollef has authored peer-reviewed manuscripts, letters, case reports, editorials, and invited publications. He currently serves on the editorial boards of *Respiratory Care, Critical Care, Critical Care Medicine, Informed Decisions/Clinical Strategies,* and *Journal of Surgical Infections* and is a reviewer for many journals including *Chest, JAMA,* and the *New England Journal of Medicine*.

Dr. Kollef is the recipient of numerous honors and awards including selection to "Best Doctors in America," Central Region and Barnes-Jewish Hospital Team Awards for Quality Improvement for programs directed to VAP prevention, bloodstream infection prevention, and the "Surviving Sepsis Initiative." He has received teaching awards and is a recognized expert in the performance of clinical outcomes research in the ICU setting. His clinical research focus has been the understanding and prevention of nosocomial infections and the improved care of mechanically-ventilated patients. He is also a member of the American Thoracic Society, Society of Critical Care Medicine, American Association for Respiratory Care, and American Society of Clinical Investigation.

Carlene A. Muto, MD, MS

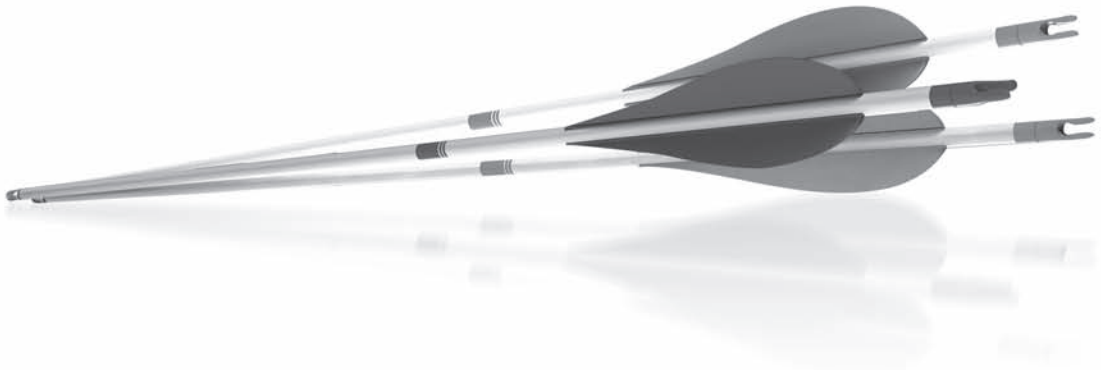
Associate Professor of Medicine
Medical Director of Infection Control and Hospital Epidemiology
Center for Quality Improvement and Innovation
UPMC Health System
Pittsburgh, PA

Dr. Carlene Muto is Associate Professor, Epidemiology and Medicine, Division of Infectious Diseases at the University of Pittsburgh School of Medicine in Pittsburgh, PA. Dr. Muto also serves as the Medical Director of Infection Control and Hospital Epidemiology at the Center for Quality Improvement and Innovation at the UPMC Health System.

After completing her Master of Science in Health Evaluation Sciences at the University of Virginia, Virginia Graduate School of Arts and Sciences in Charlottesville, VA, Dr. Muto went on to receive her Doctor of Medicine from Temple University School of Medicine in Philadelphia, PA. Dr. Muto then completed her internal medicine residency at Temple University Hospital and her infectious diseases fellowship at the University of Virginia Health Center.

A nationally recognized leader in reducing hospital infection rates, Dr. Muto's research interests include the control of antibiotic-resistant organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and *Clostridium difficile*. She has also studied the use of electronic surveillance to identify important pathogens and the effects of mandatory public reporting of hospital-acquired infections. As a result of her groundbreaking work, she has been invited to lecture around the world on effective infection control strategies.

Dr. Muto chairs the Society for Healthcare Epidemiology of America's (SHEA) Antibiotic Resistance Task Force and was the first author of the SHEA Guideline on Preventing Spread of Antibiotic Resistance. She is also a member of and medical advisor to the Southwestern Pennsylvania Professionals in Infection Control (SWPPIC) Regional MRSA Prevention Collaborative.

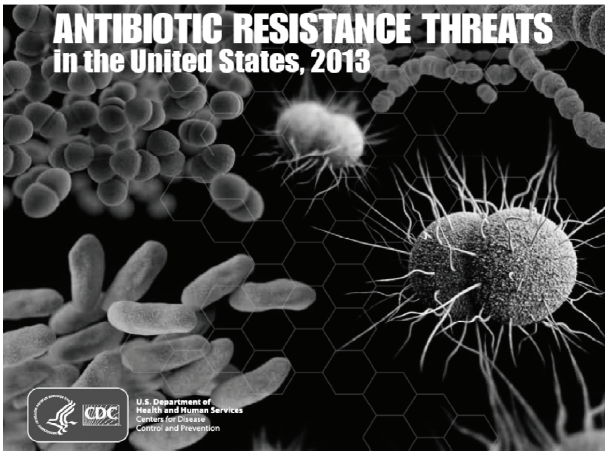


MDR – Global Public Health Threat

Thomas M. File, Jr., MD, MS, MACP, FIDSA, FCCP

Chair, Infectious Disease Division
Summa Health System
Akron, OH
Professor, Internal Medicine
Master Teacher; Chair, Infectious Disease Section
Northeast Ohio Medical University
Rootstown, OH

More Americans die each year from antibiotic-resistant bacteria than AIDS, and there are no new drugs coming
By Tim Fernholz — November 7, 2013



World Health Organization

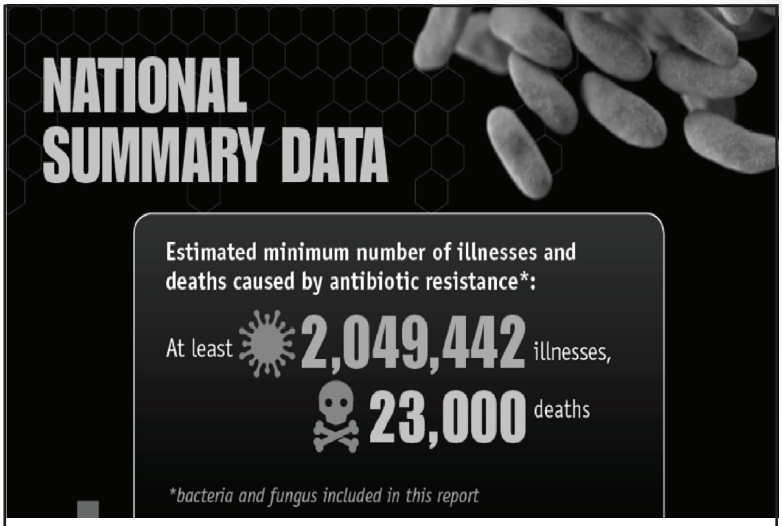
Antibiotic resistance: a threat to global health security

May, 2013

Antimicrobial Resistance: Concern by Developers

'Drug resistance follows the drug like a faithful shadow'.
Paul Erhlich, 1854–1915

"….there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant."
Alexander Fleming, Nobel Prize lecture, Dec 11, 1945



CDC. Antibiotic Resistance Threats in the United States, 2013. Available at: http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf. Accessed September 20, 2014.

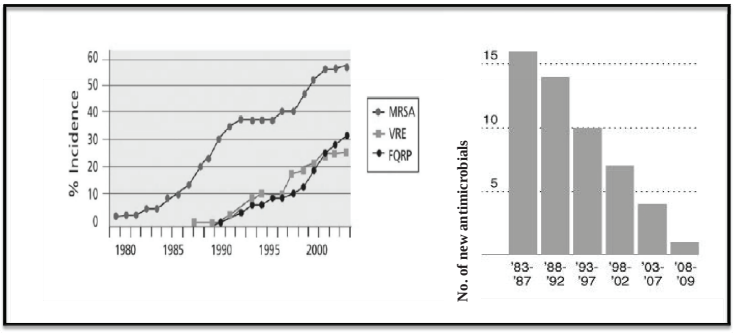
Morbidity and Mortality of MDR Organisms

Organism	Infections included	Est. # of cases	Est. annual # deaths
MRSA	**Invasive**	**80,000**	**11,000**
VRE	**HAIs**	**20,000**	**1,300**
DRSP	**All infections**	**1,200,000**	**7,000**
ESBL-producing	HAI; *E. coli*, *K. pneumoniae*	26,000	1,700
CRE	HAIs; *E. coli*, *K. pneumoniae*	9,300	610
MDR *Pseudomonas* spp.	HAIs	6,700	440
MDR *Acinetobacter* spp.	HAIs	7,300	500

DRSP, drug-resistant *S. pneumoniae*; HAI, hospital-acquired infection; MDR, multidrug-resistant; CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum beta-lactamase; VRE, vancomycin-resistant enterococci
CDC. Antibiotic Resistance Threats in the United States, 2013. Available at: http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf. Accessed September 20, 2014.

IDSA Call-to-Action: Bad Bugs, No Drugs

As resistance increases . . . number of new antimicrobials diminishes



VRE, vancomycin-resistant enterococci; FQRP, fluoroquinolone-resistant *Pseudomonas.*
Kallen AJ, et al. *JAMA.* 2010;304:641-8.
Boucher HW, et al. *Clin Infect Dis.* 2013;56:1685-1694.

HAZARD LEVEL: URGENT

These are high-consequence antibiotic-resistant threats because of significant risks identified across several criteria. These threats may not be currently widespread but have the potential to become so and require urgent public health attention to identify infections and to limit transmission.

Clostridium difficile (C. difficile), Carbapenem-resistant Enterobacteriaceae (CRE), Drug-resistant *Neisseria gonorrhoeae* (cephalosporin resistance)

HAZARD LEVEL: SERIOUS

These are significant antibiotic-resistant threats. For varying reasons (e.g., low or declining domestic incidence or reasonable availability of therapeutic agents), they are not considered urgent, but these threats will worsen and may become urgent without ongoing public health monitoring and prevention activities.

Multidrug-resistant *Acinetobacter*, Drug-resistant *Campylobacter*, Fluconazole-resistant *Candida* (a fungus), Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs), Vancomycin-resistant *Enterococcus* (VRE), Multidrug-resistant *Pseudomonas aeruginosa*, Drug-resistant Non-typhoidal *Salmonella*, Drug-resistant *Salmonella* Typhi, Drug-resistant *Shigella*, Methicillin-resistant *Staphylococcus aureus* (MRSA), Drug-resistant *Streptococcus pneumonia*, Drug-resistant tuberculosis (MDR and XDR)

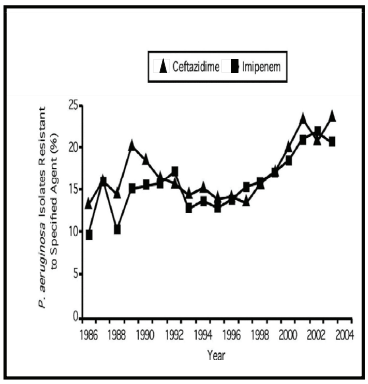
HAZARD LEVEL: CONCERNING

These are bacteria for which the threat of antibiotic resistance is low, and/or there are multiple therapeutic options for resistant infections. These bacterial pathogens cause severe illness. Threats in this category require monitoring and in some cases rapid incident or outbreak response.

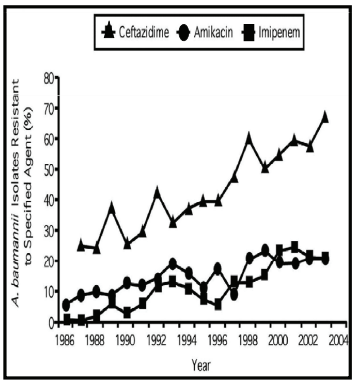
Vancomycin-resistant *Staphylococcus aureus* (VRSA), Erythromycin-resistant *Streptococcus* Group A, Clindamycin-resistant *Streptococcus* Group B

Increasing Drug Resistance

P. aeruginosa

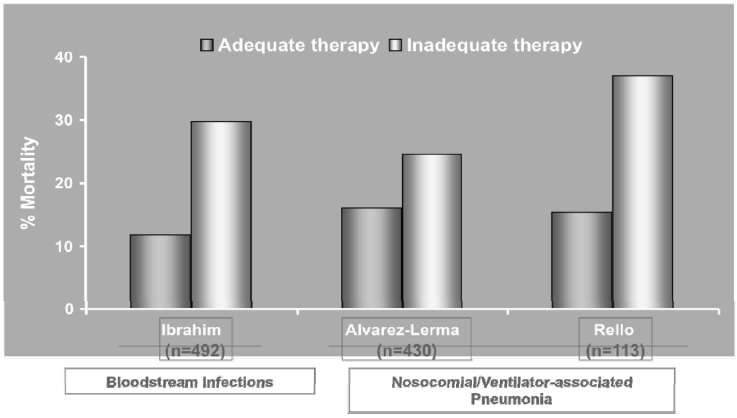


A. baumannii



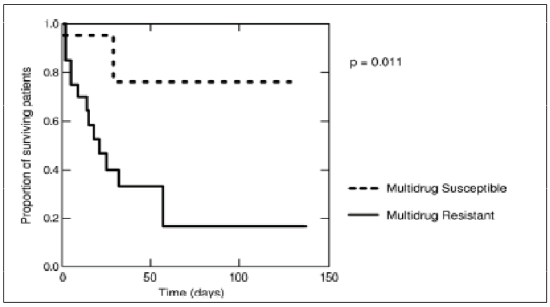
Rahal JJ. *Clin Infect Dis.* 2009;49:S4-S10.

Inadequate Antimicrobial Therapy Associated with Increased Mortality



Ibrahim EH, et al. *Chest*. 2000;118:146-155.; Alvarez-Lerma F, et al. *Intensive Care Med*. 1996;22:387-394.; Rello J, et al. *Am J Respir Crit Care Med*. 1997;156:196-200.

MDR Pseudomonas-Impact



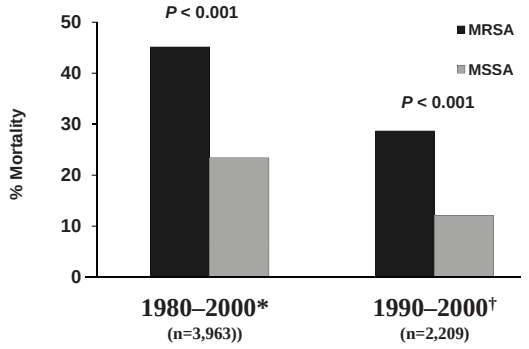
Tam VH, et al. *Antimicrob Agents Chemother*. 2010;54:3717- 22.

Extensively Drug Resistant (XDR) *Pseudomonas aeruginosa* Containing bla_{VIM-2} and Elements of *Salmonella* Genomic Island 2: A New Genetic Resistance Determinant in Northeast Ohio

Federico Perez[1,2‡], Andrea M. Hujer[1,2‡], Steven H. Marshall[1], Amy J. Ray[2,6], Philip N. Rather[7,8], Nuntra Suwantarat[6], Donald Dumford III[6], Patrick O'Shea[1], T. Nicholas J. Domitrovic[1], Robert A. Salata[2,6], Kalyan D. Chavda[9], Liang Chen[9], Barry N. Kreiswirth[9], Alejandro J. Vila[10], Susanne Haussler[11], Michael R. Jacobs[2,3,6], and Robert. A. Bonomo#[1,2,4,5]

Perez F, et al. *Antimicrob Agents Chemother*. 2014;58:5929-35.

Mortality Associated With MRSA: Two Meta-analyses



*Cosgrove SE, *et al. Clin Infect Dis.* 2003;36:53-59.
†Whitby M, *et al. Med J Aust.* 2001;175:264-267.

The Impact of Antimicrobial Resistance

- Affects clinical outcomes
  - Associated with higher mortality
- Results in higher healthcare costs
- Leads to prolonged hospitalization
- Increases challenge for appropriate management
  - Empiric therapy
  - Directed therapy

File TM, Jr. *Chest*. 1999;115(suppl):3S-8S..

FOUR CORE ACTIONS

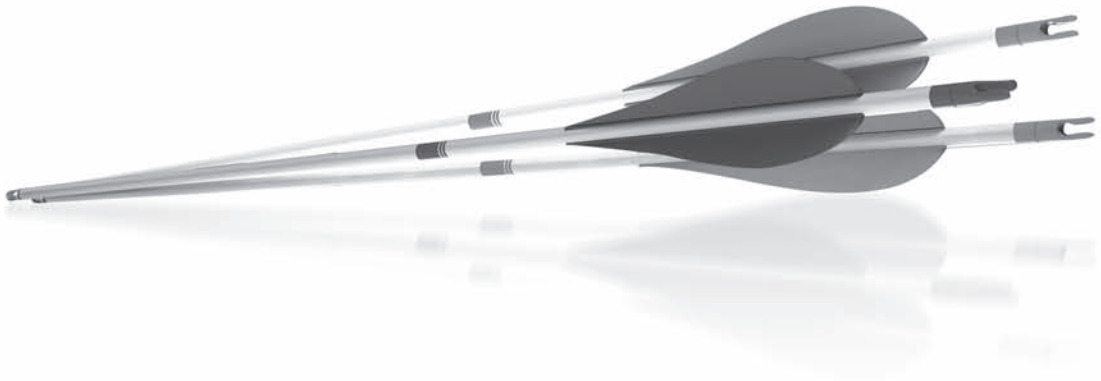
PREVENTING INFECTIONS, PREVENTING SPREAD.

TRACKING RESISTANCE PATTERNS.

IMPROVING USE OF ANTIBIOTICS.

DEVELOPING NEW ANTIBIOTICS AND DIAGNOSTIC TESTS.

CDC. Antibiotic Resistance Threats in the United States, 2013. Available at: http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf. Accessed September 20, 2014.



Practice Case 1
Gram-Positive Infections

Optimized Approaches in Managing Gram-Positive Infections

Thomas M. File, Jr., MD, MS, MACP, FIDSA, FCCP

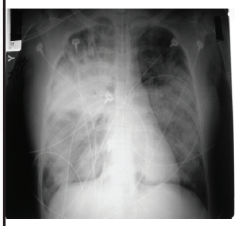
Chair, Infectious Disease Division
Summa Health System
Akron, OH
Professor, Internal Medicine
Master Teacher; Chair, Infectious Disease Section
Northeast Ohio Medical University
Rootstown, OH

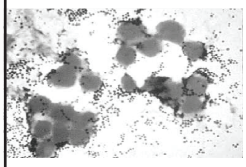
Morbidity and Mortality of MDR Organisms

Organism	Infections included	Est. # of cases	Est. annual # deaths
MRSA	**Invasive**	**80,000**	**11,000**
VRE	**HAIs**	**20,000**	**1,300**
DRSP	**All infections**	**1,200,000**	**7,000**
ESBL-producing	HAI; *E. coli*, *K. pneumoniae*	26,000	1,700
CRE	HAIs; *E. coli*, *K. pneumoniae*	9,300	610
MDR *Pseudomonas* spp.	HAIs	6,700	440
MDR *Acinetobacter* spp.	HAIs	7,300	500

DRSP, drug-resistant *S. pneumoniae*; HAI, hospital-acquired infection; MDR, multidrug-resistant; CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum beta-lactamase; VRE, vancomycin-resistant enterococci
CDC. Antibiotic Resistance Threats in the United States, 2013. Available at: http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf. Accessed September 20, 2014.

Case: **30 y/o female presents to ER with fever and respiratory distress; immediate intubation; history of ILI (influenza-like illness); Ceftriaxone and azithromycin initiated at time of intubation. Gram stain obtained.**





CXR, Stain courtesy of T File MD.

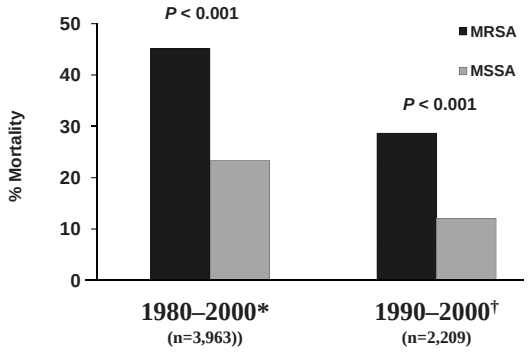
Based on Gram stain, what is your choice of antimicrobial ?

A. Clindamycin
B. Ceftaroline
C. Telavancin
D. Vancomycin
E. Linezolid

Challenges

- MRSA
  - Impact (vs MSSA)
  - Diagnosis
  - Surveillance
  - Treatment
- DRSP
  - Increasing resistance
  - Treatment

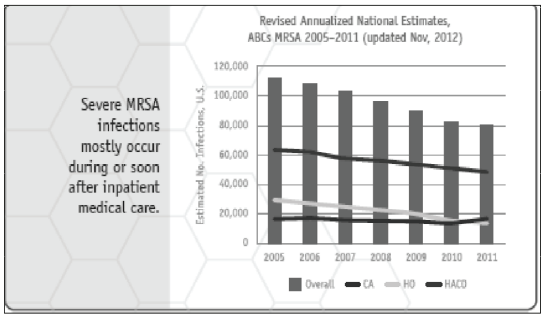
Mortality Associated With MRSA: Two Meta-analyses



*Cosgrove SE, *et al. Clin Infect Dis.* 2003;36:53-59.
†Whitby M, *et al. Med J Aust.* 2001;175:264-267.

MRSA: Decreasing Incidence

- Decreasing Trend (from CDC; 2013)

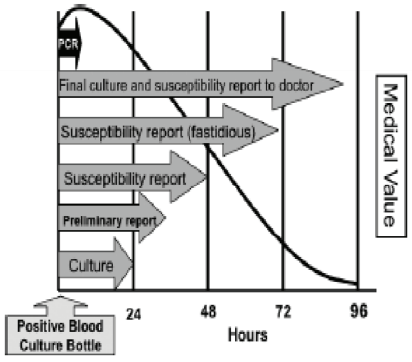


- Why
  - Better awareness, isolation, treatment

Dantes R, et al. *JAMA Intern Med.* 2013;173:1970-8.

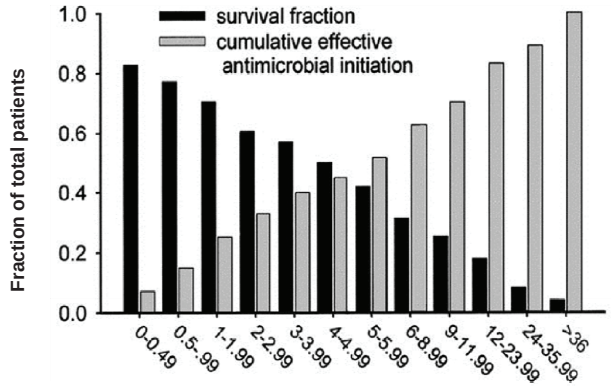
MRSA: Diagnostic Testing

- **Rapid Diagnostic Tests**
  - **PNA FISH, PCR, MALDI-TOF, Automated Microscopy**



Goff DA, et al. *Pharmacother.* 2012;32:677-88.

Effect of Antimicrobial Timing on Survival



Kumar A, et al. *Crit Care Med*. 2006;34:1589-96.

MRSA: Stewardship

- Impact on antimicrobial stewardship
  - Antimicrobial stewardship program's impact with rapid PCR MRSA/MSSA blood cultures
    - LOS was 6.2 days shorter (p=0.07) and the mean hospital costs were $21,387 less (p=0.02)[1]
  - Evaluation and use of a rapid *Staphylococcus aureus* assay by an antimicrobial stewardship program
    - Use of immunochromatographic PBP2a test led to more rapid appropriate use of antimicrobial[2]

1. Bauer KA, et al. *Clin Infect Dis*. 2010;51:1074-80.
2. Trienski T, et al. *Am J Health-Syst Pharm*. 2013;70:1908-12.

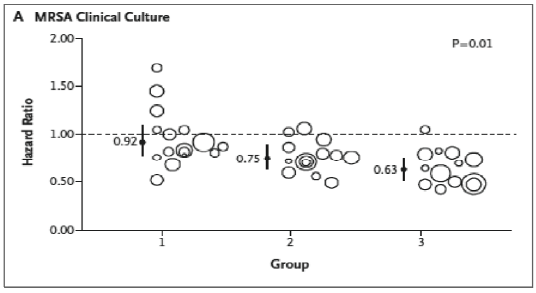
MRSA Surveillance

The policy in my ICU for assessing patients colonized with MRSA is:

A. Screen and isolate
B. Screen and decolonize if positive
C. Universal decolonization
D. No specific policy

MRSA: Surveillance

- Impact of surveillance testing
  - Controversial
  - Screen & Isolate (1) vs. Targeted Decolonization (2) vs. Universal Decolonization (3) in ICU



Huang SS, et al. *N Engl J Med*. 2013;368:2255-65.

Back to the Case

The patient with MRSA respiratory infection is started on vancomycin therapy. Susceptibility results reveal a vancomycin MIC of 1 mg/L. She remains critically ill on vent. What do you do?

A. Continue with vancomycin
B. Switch to linezolid
C. Switch to ceftaroline
D. Switch to telavancin
E. Other

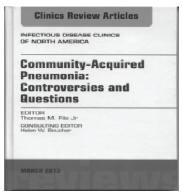
How Important is MRSA as a Cause of CAP?[1]

Important pathogen. While currently causing a relatively low percentage of CAP cases, the disproportionate frequency of otherwise healthy young people with this infection drives concern and therefore empiric antibiotic therapy."[1]

EMERGEncy ID Net study (2006-2007)[2]
- N=595 CAP patients, pathogen identified in 17%
- *S. pneumoniae:* 9.6%; MRSA, 2.4%; MSSA: 1.5%; *K. pneumoniae:* 0.7%; *H. influenzae:* 0.3%

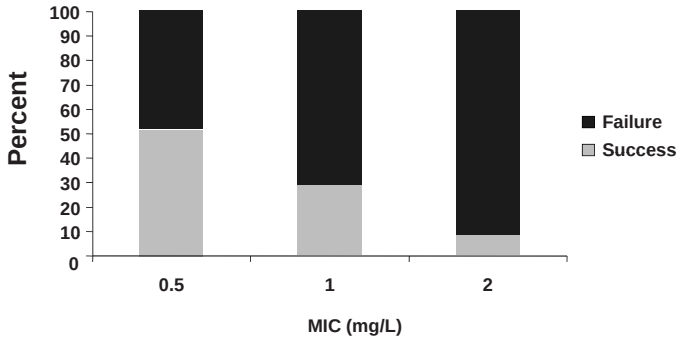
Clinical features suggesting increased risk of CA-MRSA pneumonia[1]
- Cavitary pneumonia
- Lung necrosis
- Neutropenia
- Hemoptysis

Antimicrobials for MRSA pneumonia[1]
- Appropriate: vancomycin, linezolid
- Approved for HAP/VAP: telavancin
- Not approved: ceftaroline
- Unclear: clindamycin, trimethoprim/sulfa



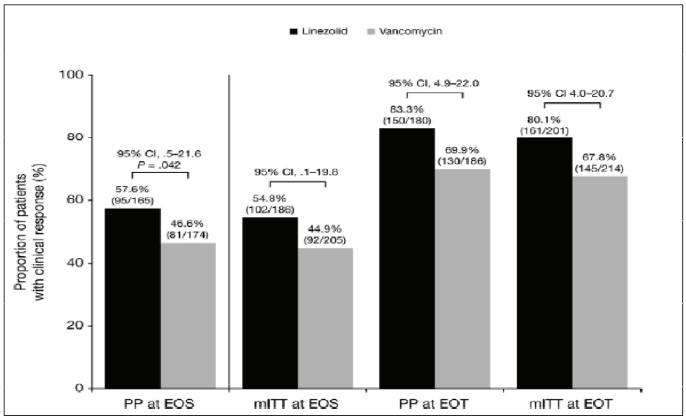
1. Wunderink RG. *Infect Dis Clin North Am.* 2013;27(1):177-188.
2. Moran G, et al. *Clin Infect Dis.* 2012;54:1126-1133.

Influence of Vancomycin MIC on Outcome in *S. aureus* Infection



Moise-Broder, et al. *Clin Infect Dis*. 2004;38:1700-1705.

MRSA: Vancomycin or Linezolid for Pneumonia?

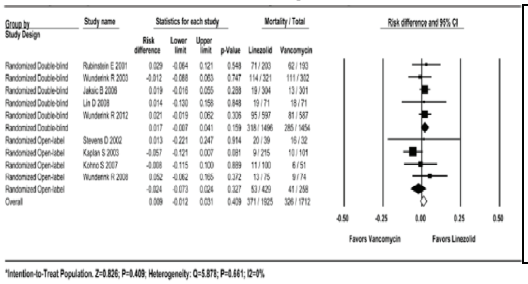


Wunderink RG. *Clin Infect Dis*. 2012;54:621-9.

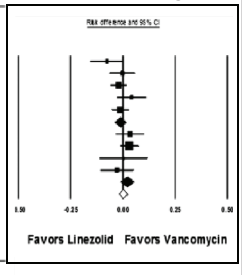
MRSA: Vancomycin or Linezolid for Pneumonia?

- Guidelines: either
- Meta-analysis

Clinical Response



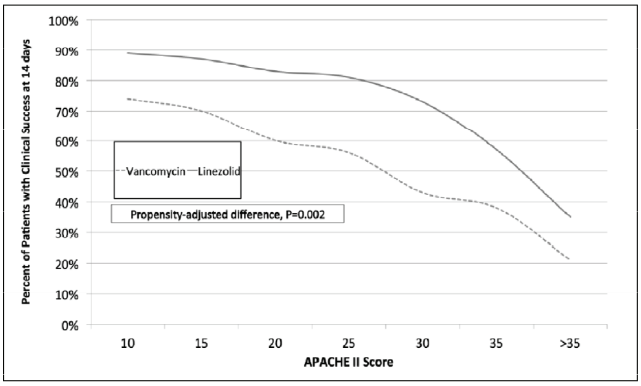
Mortality



*Intention-to-Treat Population. Z=0.826; P=0.409; Heterogeneity: Q=5.873; P=0.661; I2=0%

Kalil AC, et al. *BMJ Open*. 2013;3:e003912.

Higher Clinical Success in Patients with VAP due to MRSA Treated with Linezolid Compared to Vancomycin



Peyrani P, et al. Presented at the Infectious Diseases Society of America Annual Meeting; 2012 Oct 17-21; San Diego, CA, USA.

MRSA: Vancomycin or Linezolid for Pneumonia?

- Multi-center observational evaluation in VAP

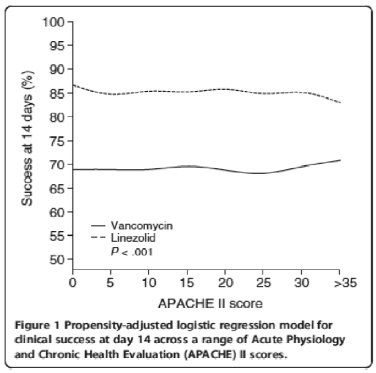


Figure 1 Propensity-adjusted logistic regression model for clinical success at day 14 across a range of Acute Physiology and Chronic Health Evaluation (APACHE) II scores.

- No difference in mortality
- No difference nephrotoxicity, anemia, thrombocytopenia

Peyrani P, et al. *Crit Care*. 2014;18:Rii8.

Telavancin

- ATTAIN Studies*
  - 1503 pts; All treated cure: TEL 58.9% VANC 59.5%; Per Protocol: TEL 82.4%; VANC 80.7%
- 2013 FDA-approved for MRSA HAP or VAP
  - "when alternative cannot be used"
- Warnings:
  - Pre-existing renal impairment had increased mortality compared to vancomycin
  - New-onset renal impairment
  - Avoid during pregnancy unless potential benefit outweighs potential risk to fetus

*Rubinstein E, et al. *Clin Infect Dis*. 2011;52:31-40.

CAPTURE Study:
Experience in Patients with Community-Acquired Bacterial Pneumonia (CABP) Due to Methicillin-Resistant *S. aureus* (MRSA) Treated with Ceftaroline

- Multicenter, retrospective study: 49 patients (12% of cohort) with MRSA from blood or sputum
- Mean age: 62; ICU: 53%
- Ceftaroline 2nd-line agent 92%
  - Most with 600 mg q12h concurrent ABX 55% (vancomycin most common)
  - Mean duration: 7.3 days
- RESULTS: Clinical success 63% (ICU 50%)
- Comments: Ongoing MRSA CAP study underway using q8h dosing

Pasquale T, et al. Presented at 2013 ICAAC. Abstract #L1329a.

MRSA: Combination Therapy?

- Vancomycin + rifampin
  - Not good for bacteremia
  - Prosthetic body
- Daptomycin plus ?? for vancomycin failure for bacteremia (IDSA MRSA guideline)
  - Ceftaroline + daptomycin
    - Report of 26 cases*

*Sakoulas G, et al. *Clin Ther*. 2014 July 10;[Epub ahead of print].

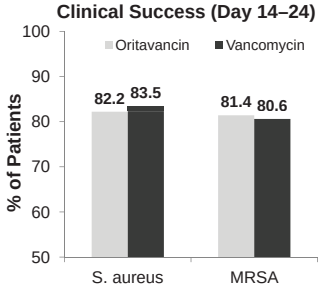
MRSA: New/Investigational Agents

- New Cephalosporins
  - Ceftaroline; ceftobiprole (Europe)
- New Glycopeptides
  - Dalbavancin, Oritavancin, (Telavancin)
- New Oxazolidinones
  - Tedizolid
- New Fluoroquinolones
  - Delafloxacin and others

New Gram-positive Agents: Oritavancin and Dalbavancin for ABSSSIs

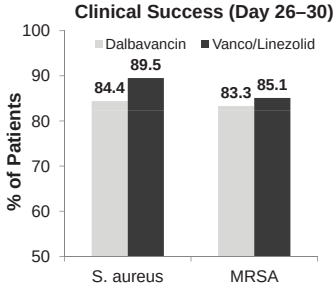
Pooled analyses from 2 phase 3 trials comparing oritavancin (single 1200 mg IV dose) vs. vancomycin (1 g or 15 mg/kg q12h IV for 7–10 days)[1]

Clinical Success (Day 14–24)



Pooled analyses from 2 phase 3 trials comparing two weeks of treatment with dalbavancin (1000 mg IV followed by 500 mg 1 week later) vs. vancomycin (1 g or 15 mg/kg q12h, with option to switch to linezolid after 3 days)[2]

Clinical Success (Day 26–30)

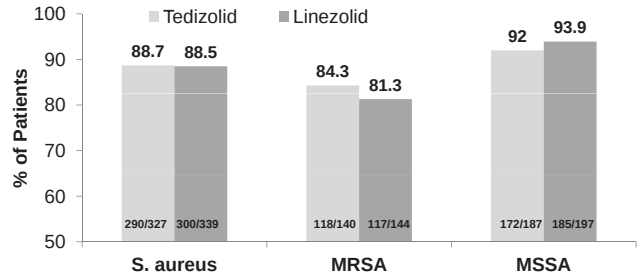


1. Orbactiv™ (oritavancin) for injection Prescribing Information. The Medicines Company, Parsippany, NJ. August, 2014.
2. Dalvance™ (dalbavancin) for injection Prescribing Information. Durata Therapeutics, Chicago, IL. May 2014.

New Gram-positive Agents (cont'd): Tedizolid vs. Linezolid for ABSSSIs

Pooled analyses from 2 phase 3 trials comparing tedizolid 200 mg QD for 6 days vs. linezolid 600 mg BID for 10 days for the treatment of ABSSSI.

Clinical Response at Post-Therapy Evaluation* by Pathogen



*7-14 days after the end of therapy

Prokocimer P, et al. *JAMA*. 2013;309;559-69.
Moran GJ, et al. *Lancet Infect Dis*. 2014;14:696-705.

Vancomycin-Resistant Enterococci (VRE): Impact

- Most prevalent in *E. faecium*
- Significant burden of infection [3]
  - Common nosocomial pathogen
  - Intra-abdominal, urinary tract infections, bacteremia
- Infection control and antimicrobial stewardship both needed to control[2]
  - A variety of antibiotic classes have been implicated as influencing rates of resistance
  - High prevalence of colonization (estimates up to 10.6% in ICU patients) an important determinant of infection[1]

	Percent of all *Enterococcus* healthcare-associated infections resistant to vancomycin	Estimated number of infections	Estimated number of deaths attributed
Vancomycin-resistant *Enterococcus faecium*	77%	10,000	650
Vancomycin-resistant *Enterococcus faecalis*	9%	3,100	200
Vancomycin-resistant *Enterococcus* (species not determined)	40%	6,900	450
Totals		20,000	1,300

from reference 3

1. Ziakas PD, et al. *PLoS ONE*. 2013;8(9):e75658.
2. Rubinstein E, et al. *Crit Care Clin*. 2013;29(4):841-52.
3. CDC. Antibiotic Resistance Threats in the United States, 2013. Available at: http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf.

Parenteral Therapy for Infections Due to VRE

Regimen	Dosage* and route
Ampicillin-susceptible enterococci	
Monotherapy:	
Ampicillin (+/- sulbactam)•	6-12 g per 24 hours in 6 equally divided doses
Combination therapy:	
Above plus one of the following: (for bactericidal activity)Δ	
Gentamicin◇	3 mg/kg per 24 hours in 3 equally divided doses
Streptomycin§	15 mg/kg per 24 hours in 2 equally divided doses
Ampicillin-resistant E faecium: One of the following	
High-dose ampicillin¥	18-30 g per day‡
Linezolid	1200 mg per 24 hours in 2 equally divided doses
Daptomycin†	For E faecalis: 4 mg/kg every 24 hours (approved dose for complicated skin and soft tissue infection)
	Higher dosing (8 to 12 mg/kg every 24 hours) may be more efficacious for life threatening infections due to E. faecalis or E. faecium.
Tigecycline**	100 mg loading dose followed by maintenance dosing 50 mg every 12 hours
Quinupristin-dalfopristin	22.5 mg/kg per 24 hours in 3 equally divided doses

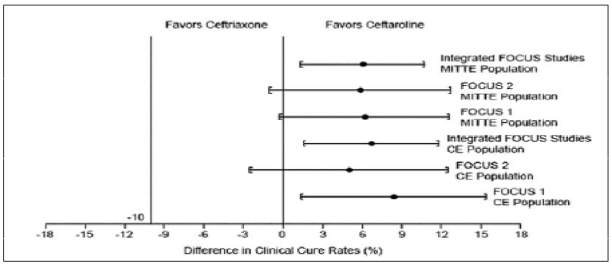
* Dosages recommended are for patients with normal renal function.

Murray BE. *UpToDate*, 2014. Available at: http://www.uptodate.com/contents/treatment-of-enterococcal-infections.

CABP: Unmet Needs

- Increasing resistance
  - Macrolide resistant *S. pneumoniae*: now > 40% in US
  - Penicillin/Ceftriaxone resistant *S. pneumoniae* increasing – approaching 10% adults (Wenzler et al. *Infect Dis Clin Pract*. 2014)
  - Macrolide resistant *Mycoplasma:* now > 90% parts of Asia
  - MRSA (3-5% of CAP)
  - GNR- common in some locations; multiple resistance patterns
- Collateral 'Damage' of existing regimens
  - Fluoroquinolones: resistant GNR; *C. difficile* infection; AEs: QTc, tendons, liver, phototoxicity
  - Azithromycin: QTc
  - Ceftriaxone: *C. difficile* infection
- Monotherapy options

Ceftaroline vs. Ceftriaxone in Patients with CAP



FOCUS 1/2: 1200+ patients (all PORT III/IV); mean age: 61 years; ceftriaxone 1 gm QD[1]

- Clinical cure for *S. pneumoniae*:
  - Ceftaroline 59/69 (85.5%) vs. ceftriaxone 48/70 (68.6%)
  - Ceftaroline has greater affinity for PBP 2x; much lower MICs

New double-blind study from Asia (700+ patients) showing clinical superiority of ceftaroline vs. ceftriaxone (2 gm QD)[2]

- Clinical Response:
  - Ceftaroline (84.1%) vs. ceftriaxone (74.2%) (95% CI, 2.8 to 17.1)

1. File TM, et al. *Clin Infect Dis*. 2010;51:1395-1405. 2. Presented at ECCMID 2014.

Ceftriaxone Non-Susceptibility in Emerging (35B) and Persisting (19A, 19F) *S. pneumoniae* Serotypes in the USA (2011–2012)

Only ceftaroline retains activity among beta-lactams

Serotype (no. tested)	Percentage of non-susceptible rates[a] and $MIC_{50/90}$ values (2011-2012 collection):					
	Ceftriaxone (MIC for non-susceptible)			Ceftaroline (MIC for non-susceptible)		
	CLSI (≥2 µg/ml)	EUCAST (≥1 µg/ml)	$MIC_{50/90}$	CLSI (≥1 µg/ml)	EUCAST (≥0.5 µg/ml)	$MIC_{50/90}$
19A (165)	49.4[b]	78.0[b]	1/2	0.0	4.3	0.12/0.25
19F (35)	14.3	22.9	≤0.06/2	0.0	2.9	≤0.015/0.12
35B (92)	4.3[c]	80.4[c]	1/1	0.0	0.0	0.12/0.12
All (1,190)	8.7	21.0	≤0.06/1	0.0	0.7	≤0.015/0.12

a. Calculated by CLSI (also USA-FDA) or EUCAST breakpoints for nonmeningitis isolates.
b. Dominantly in USA Census regions 5 (South Atlantic) and 6 (East South Central).
c. Strains from all USA Census regions, and non-S rates ranged 70.0-100.0% per region.

Mendes, et al. Presented at ICAAC 2013, abstract #C2-539a.

Decrease in Mortality of Severe Pneumococcal Pneumonia (2000–2013)

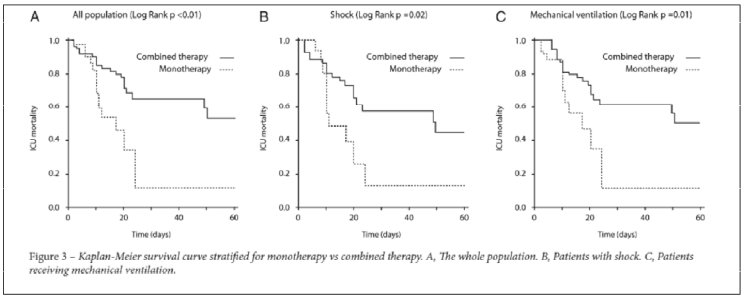


Figure 3 – *Kaplan-Meier survival curve stratified for monotherapy vs combined therapy. A, The whole population. B, Patients with shock. C, Patients receiving mechanical ventilation.*

Gattarello S, et al. *Chest.* 2014;146:22-31.

CABP: Possible Future Agents

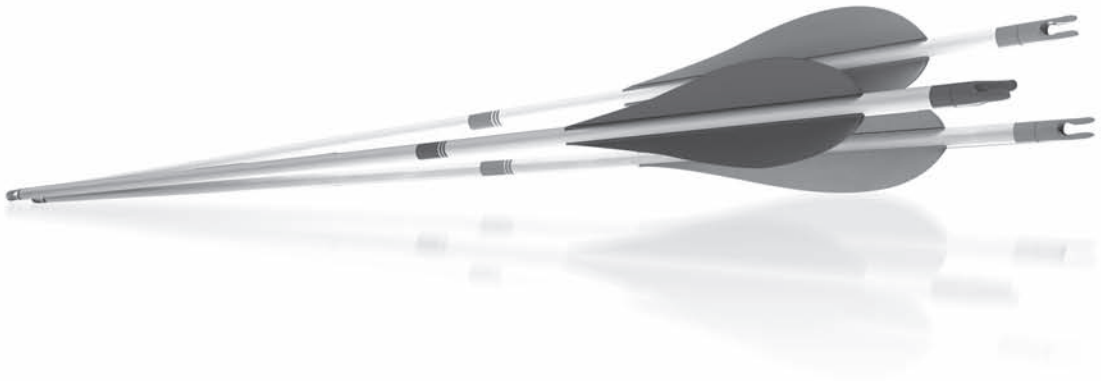
	S. pneumoniae	*Haemophilus*	Atypicals	MRSA (300)	GNR
Ceftobiprole (β-lactam; Basilea)	+	+	0	+	+
Delafloxacin (Fluoroquinolone; Melinta)	+	+	+	+	+
Tedizolid (oxazolidinone; Cubist)	+	0	0	+	0
Omadacycline (tetracycline; Paratek)	+	+	+	+	+
Eravacycline (tetracycline; tetraphase)	+	+	+	+	+
GSK1322322 (peptide deformylase inhibitor; GSK)	+	+	+	+	0
BC-3781 (pleuromutilin; Nabriva)	+	+	+	+	0
Solithromycin (fluoroketolide; Cempra)	+	+	+	+	0

MRSA: Challenges Considered

- Which agent for specific patient?
  - MRSA IDSA Guidelines*
    - For HA-MRSA or CA-MRSA pneumonia, IV vancomycin (A-II) or linezolid (A-II) or clindamycin (B-III), if the strain is susceptible, for 7–21 days, depending on the extent of infection
  - Other agents: ?Ceftaroline, telavancin
- Role of new diagnostic tests
  - New paradigm of pathogen-directed therapy
- Role of surveillance: still debated

*Liu C, et al. *Clin Infect Dis*. 2011;52:e18-55.

NOTES



Practice Case 2
Gram-Negative Infections

Optimized Approaches in Managing Gram-Negative Infections

Marin H. Kollef, MD, FACP, FCCP

Professor of Medicine, Division of Pulmonary and Critical Care Medicine
Virginia E. & Sam J. Golman Chair in Respiratory Intensive Care Medicine
Director, Critical Care Research
Director, Respiratory Care Services
Barnes-Jewish Hospital
St. Louis, MO

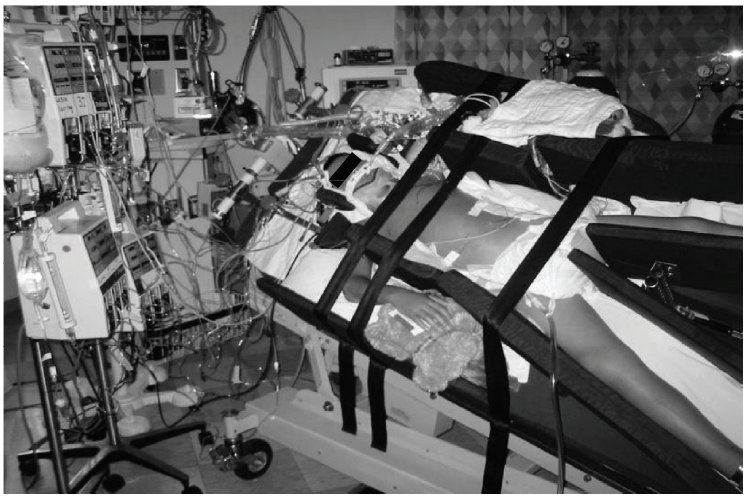
What are the Challenges of Emerging Resistant Gram-Negative Bacteria?

- **Extended-spectrum beta-lactamase (ESBL)**
  - *Escherichia coli*
  - *Klebsiella* species
- **Carbapenemase producers**
  - *Escherichia coli*
  - *Klebsiella* species
- **Multiple mechanisms (pumps, porins, beta-lactamases)**
  - *Pseudomonas aeruginosa*

Global Emergence of Carbapenem-Resistant Enterobacteriaceae (CRE)

- *Klebsiella pneumoniae* carbapenemase (KPC) producers in New York City and Israel
- 21% of *Klebsiella pneumoniae* isolates reported to the Centers for Disease Control and Prevention in 2006–2007 from NYC were carbapenem-resistant
- CRE reported in >35 states and 30 countries
- Carbapenem resistance among Enterobacteriaceae in the USA is most commonly caused by KPC

Gram-Negative Pneumonia in the ICU

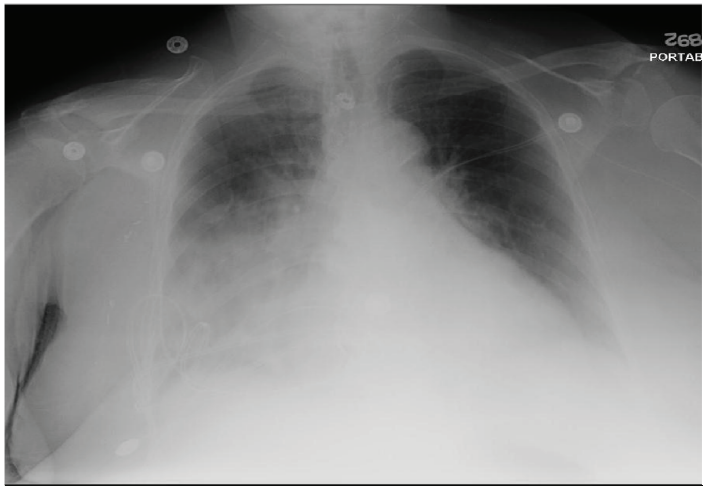


Case Presentation

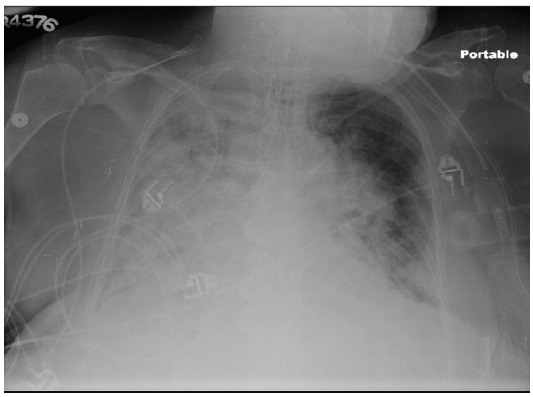
- 55 yo woman s/p CVA 3 years earlier (nursing home resident) comes in with SBO
- Intubated in the ED; goes to OR
- Multiple hospitalizations for UTIs and SSTIs treated with antibiotics, including meropenem
- Temperature: 39.1ºC; WBC 18,500/mm^3
- Vancomycin 1 g q12h and piperacillin-tazobactam 4.5 g q6h begun empirically
- BAL performed in ICU

CVA, cerebrovascular accident; SBO, small bowel obstruction; SSTI, skin and soft tissue infection; UTI, urinary tract infection

Pre-Op Chest X-ray



Post-Op Day 8 Chest X-ray; T 39.5°C; WBC 22,300



Despite 8 days of vancomycin and pipercillin-tazobactam – abdominal wound is clean, passing gas and stool.

Audience Question

What diagnostic test should you order?

A. Computed tomography of the chest

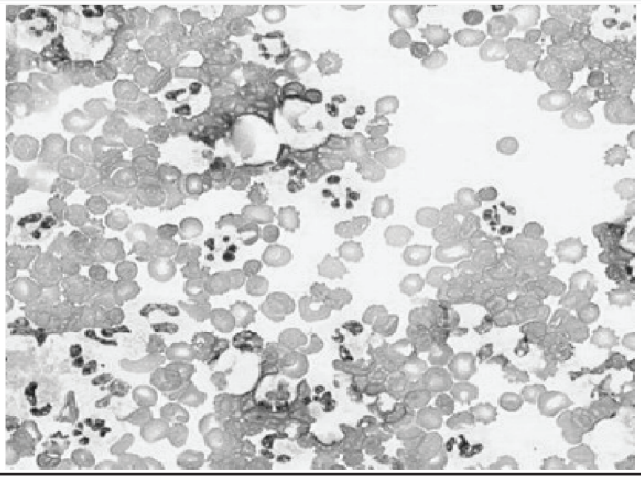
B. Ventilation-perfusion scan

C. Bronchoalveolar lavage

D. Serum procalcitonin

E. Abdominal computed tomography

BAL

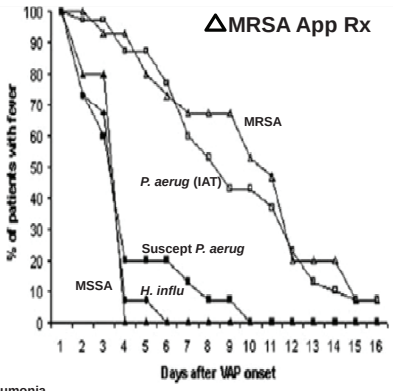


BAL Results

- **798 nucleated cells**
- **82% neutrophils**
- ***Pseudomonas aeruginosa* >10^5 cfu/mL**

Clinical Resolution of VAP: Pathogens Do Differ!

- Prospective observational study of VAP patients in three teaching ICUs
  - 60 episodes appropriate therapy
  - 30 episodes initial inappropriate therapy (IAT)
- Significant delay (multiple regression model) in the resolution of hypoxemia in VAP episodes due to:
  - MRSA
  - *P. aeruginosa* with IAT (median time to resolution)
- Among survivors, the median duration of MV after VAP onset was significantly longer
  - for MRSA (17 days)
  - *P. aeruginosa* IAT (11 days)
- Multiple regression analysis, adjusted for disease severity, confirmed that MRSA required significantly ($R2$ 0.132; $p < 0.01$) longer respiratory support than other organisms even when treated adequately



MV, mechanical ventilation; VAP, ventilator-associated pneumonia.
Vidaur L. *Chest*. 2008;133:625–33.

Audience Question

What do you do with your antibiotics?

A. Continue vancomycin and pip-tazo

B. Change to linezolid and cefepime

C. Change to ceftaroline

D. Change to tigecycline

E. Change to meropenem and colistin

Case (cont'd): *Pseudomonas aeruginosa* Susceptibility Testing

Agent	Interpretation
Amikacin	S
Ampicillin	R
Cefazolin	R
Ceftazidime	R
Ceftriaxone	R
Cefepime	R
Ciprofloxacin	R
Colistin	S
Gentamicin	I/R
Imipenem	R
Meropenem	R
Doripenem	R
Piperacillin-Tazobactam	R
Tobramycin	S

Audience Question

Is VAP still a problem in the US?

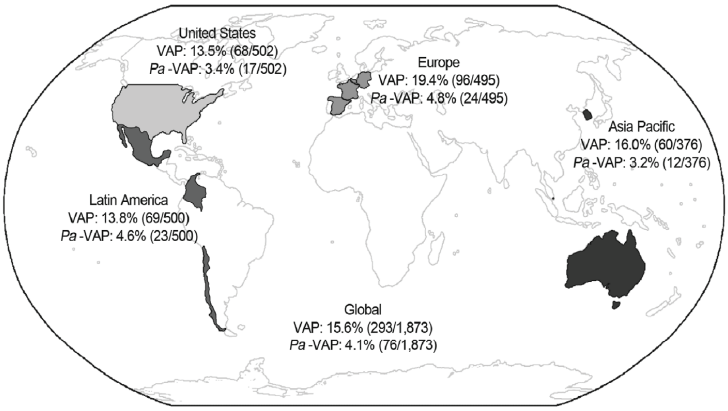
A. No

B. Yes

C. Maybe

D. The CDC is switching to ventilator-associated conditions, so it does not matter

Prevalence of *Pseudomonas aeruginosa* VAP



United States = continental United States; Europe = Belgium, France, Germany, and Spain; Latin America = Chile, Colombia, and Mexico; Asia Pacific = Australia, Singapore, and South Korea.

Kollef MH, et al. *Crit Care Med*. 2014;(In Press).

Audience Question

Is Carbapenem Resistance and/or MDR in *Pseudomonas* a Common Problem?

A. No

B. Yes

C. Maybe

D. Not in the US

Joint Definitions ECDC and CDC

Aminoglycosides:
Gentamicin Tobramycin Amikacin Netilmicin

Antipseudomonal carbapenems:
Imipenem Meropenem Doripenem

Antipseudomonal cephalosporins:
Ceftazidime Cefepime

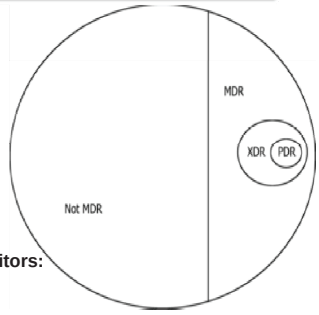
Antipseudomonal fluoroquinolones:
Ciprofloxacin Levofloxacin

Antipseudomonal penicillins + β-lactamase inhibitors:
Ticarcillin-clavulanic acid Piperacillin-tazobactam

Monobactams
Aztreonam

Phosphonic acids
Fosfomycin

Polymyxins
Colistin Polymyxin B



Magiorakos AP, et al. *Clin Microbiol Infect.* 2012;18:268-81.

BAD BUGS, NO DRUGS

As Antibiotic Discovery Stagnates ...
A Public Health Crisis Brews

First understand your local problem with MDR/XDR!

IDSA
Infectious Diseases Society of America

July 2004

GNB: Resistant Isolates in the US per CDC

TABLE 1. Pooled Mean Percentage of Resistance for 2 Definitions of Multidrug Resistance, With and Without Facilities That Contribute Large Numbers of Resistant Isolates, as Reported to the National Healthcare Safety Network, 2006–2007

	No. of resistant isolates/no. of eligible isolates (pooled mean resistance, %)			
	3-class resistance[a]		4-class resistance[b]	
Organism	All	Modified[c]	All	Modified[c]
Pseudomonas aeruginosa	676/6,489 (10)	631/6,400 (10)	84/3,724 (2)	79/3,672 (2)
Acinetobacter baumannii	1,201/1,987 (60)	1,081/1,830 (59)	489/1,454 (34)	394/1,309 (30)
Klebsiella pneumoniae	679/4,527 (15)	640/4,472 (14)	223/3,029 (7)	170/2,916 (6)

[a] Antimicrobial classes were penicillins, cephalosporins, aminoglycosides, fluoroquinolones, and carbapenems for *P. aeruginosa* and *K. pneumoniae*. Antimicrobial classes were penicillins, cephalosporins, aminoglycosides, fluoroquinolones, carbapenems, and sulbactam for *A. baumannii*.

[b] Antimicrobials tested for all organisms were β-lactams (penicillins and cephalosporins), aminoglycosides, fluoroquinolones, and carbapenems.

[c] Excluding large contributor facilities that contributed more than 5% of the resistant isolates.

Kallen AJ, et al. *Infect Control Hosp Epidemiol.* 2010;31:528-31.

GNB: Resistant Isolates in the US per CDC

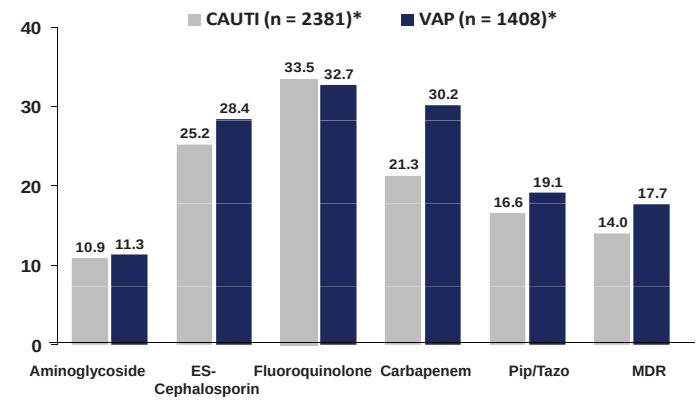
TABLE 2. No. (%) of Causative Agents with 3-Class or 4-Class Resistance within Each Infection Type, as Reported to the National Healthcare Safety Network, 2006–2007

Organism	Ventilator-associated pneumonia	Central line–associated bloodstream infection	Catheter-associated urinary tract infection	Surgical site infection
With 3-class resistance[a]				
Pseudomonas aeruginosa (n = 676)	242 (36)	111 (16)	292 (43)	31 (5)
Acinetobacter baumannii (n = 1,201)	590 (49)	372 (31)	188 (16)	51 (4)
Klebsiella pneumoniae (n = 679)	89 (13)	237 (35)	309 (46)	44 (6)
With 4-class resistance[b]				
P. aeruginosa (n = 84)	34 (40)	8 (10)	38 (45)	4 (5)
A. baumannii (n = 489)	244 (50)	173 (35)	59 (12)	13 (3)
K. pneumoniae (n = 223)	31 (14)	90 (40)	83 (37)	19 (9)

[a] Antimicrobial classes tested were penicillins, cephalosporins, aminoglycosides, fluoroquinolones, and carbapenems for *P. aeruginosa* and *K. pneumoniae*. Penicillins, cephalosporins, aminoglycosides, fluoroquinolones, carbapenems, and sulbactam were tested for *A. baumannii*.
[b] Antimicrobials tested for all organisms included β-lactams (penicillins and cephalosporins), aminoglycosides, fluoroquinolones, and carbapenems.

Kallen AJ, et al. *Infect Control Hosp Epidemiol*. 2010;31:528-31.

Pseudomonas Resistance in HAI



*Isolates reported to the National Healthcare Safety Network (NHSN), 2009–2010.
Sievert DM, et al. *Infect Control Hosp Epidemiol*. 2013;34:1-14.

Pseudomonas Resistance to Carbapenems

European Antimicrobial Resistance Surveillance Network (EARS-NET). Available at: http://www.ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/database/Pages/database.aspx.

Audience Question

Does Delayed Treatment of VAP Increase Mortality?

A. No

B. Yes

C. Maybe

D. I do not see cases of VAP in my hospital

Impact of Initial Antibiotic Therapy (IAT) on Mortality

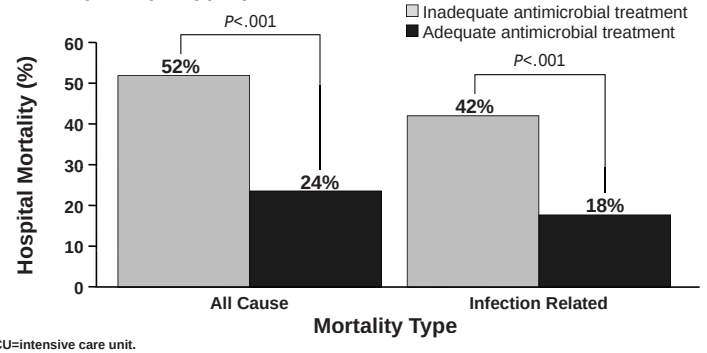
Study	Patient population (n)			Mortality risk (OR or RR)
		Inappropriate IAT	Appropriate IAT	
Kollef et al. 1999[1]	ICU admission (2000)	52.1	12.2	4.26
Kollef et al. 1999[1]	ICU admission with documented infection (655)	52.1	23.5	2.22
Peralta et al. 2007[2]	*E. coli* bacteremia (663)	11.3	4.2	2.26
Kuti et al. 2008[3]*	VAP (813)	NR	NR	2.34
Kuti et al. 2008[3]*	Bloodstream infection (11,483)	NR	NR	2.33
Micek et al. 2010[4]	GNB sepsis (760)	51.7	36.4	2.30
Muscedere et al. 2012[5]	VAP (350)	48.7	19.5	3.05

1. Kollef MH, et al. *Chest*. 1999;115:462-74. 2. Peralta G, et al. *J Antimicrob Chemother*. 2007;60:855-63.
3. Kuti EL, et al. *J Crit Care*. 2008;23:91-100. 4. Micek ST, et al. *Antimicrob Agents Chemother*. 2010;54:1742-8.
5. Muscedere G, et al. *J Crit Care*. 2012;27:322.e7-322.e14.

Increased Mortality With Inadequate Antibiotic Therapy in Infections Requiring ICU Admission

655 (32.8%) infected
169 (25.8%) inappropriate treatment

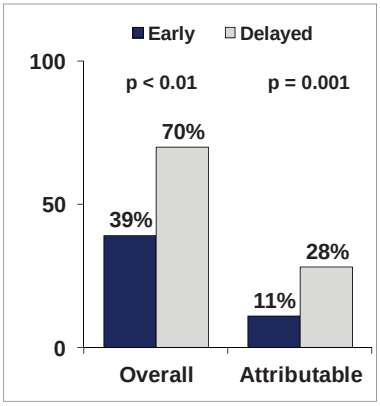
Prospective, single-center, cohort study



ICU=intensive care unit.
Site of infection includes bloodstream, lung, wound, gastrointestinal tract, urinary tract, and miscellaneous (includes peritoneal infection, meningitis, endocarditis, and infections of the skin and fascia).
Kollef MH, et al. *Chest*. 1999;115:462-474.

Early Appropriate Therapy is Critical in ICU NP/VAP

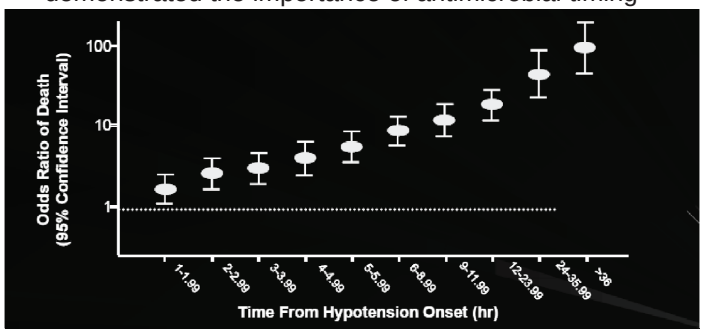
- 107 patients with VAP
- Mean time from diagnosis of VAP to initiation of appropriate therapy was 28.6 hr in delayed group vs 12.5 hr in early group



NP/VAP, nosocomial pneumonia/ventilator-associated pneumonia.
Iregui M, et al. *Chest*. 2002;122:262-268.

Appropriate Initial Therapy

An earlier study of septic shock (n=2,731) explicitly demonstrated the importance of antimicrobial timing



- **Each hour of delay was associated with an average survival decrease of 7.6%**
- **OR for mortality increased from 1.67 in Hour 2 to 92.54 with delays >36 hours**

Kumar A, et al. *Crit Care Med*. 2006;34:1589-1596.

Audience Question

Can Combination Empiric Treatment of Serious GNB Infections Improve Appropriate Treatment?

A. No

B. Yes

C. It depends on local susceptibility patterns

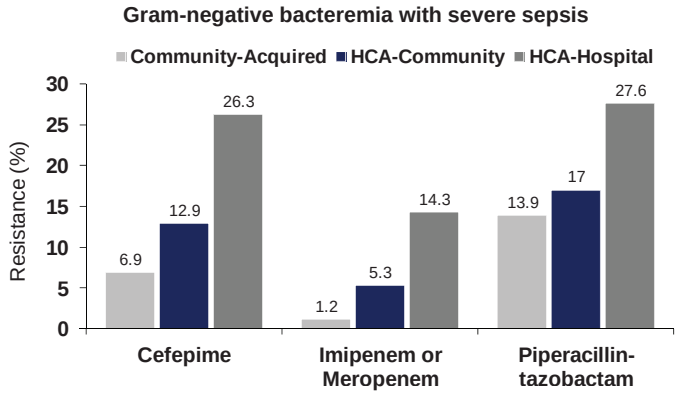
Adequacy of Antibiotic Combinations Against All Gram-negative Isolates in VAP (n=139)

Add-On Antibiotic

Drugs	None	Cipro	Gentamicin	Amikacin
Pip-Tazo	80%	82%	81%	96%
Cefepime	81%	83%	82%	96%
Meropenem	82%	83%	83%	96%

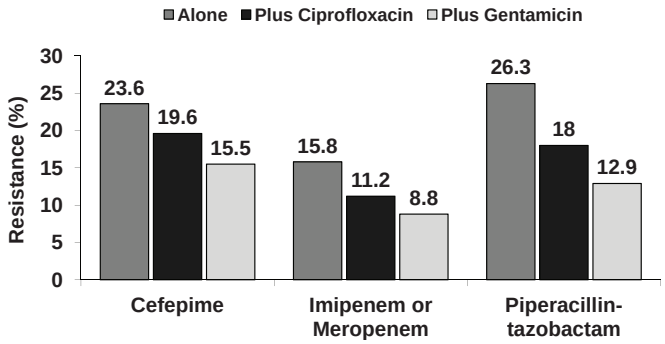
Beardsley JR, et al. *Chest*. 2006;130:787-793.

Selection: Patient Risk



HCA, healthcare-associated.
Micek ST, et al. *Antimicrob Agents Chemother*. 2010:54:1742-1748.

The Impact of Combination Antibiotic Therapy: Hospital-Acquired Infection



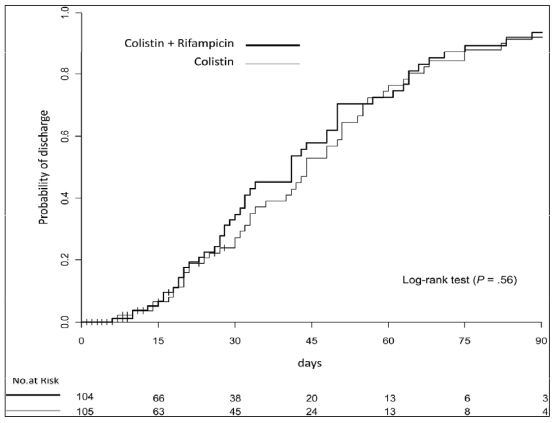
Micek ST, et al. *Antimicrob Agents Chemother*. 2010:54:1742-1748.

Antimicrobial Agents for the Treatment of MDR Gram-Negative Infections

Medication	Dosage	Route
Sulbactam (amp/sulb in the US)	6 g per day	IV
Imipenem-cilastatin	500 mg every 6 h up to 1g	IV
Meropenem	500 mg to 1g every 8 h	IV
Doripenem	500 mg every 8 h	IV
Amikacin	15 mg/kg daily	IV
Tobramycin	4-7 mg/kg daily	IV
Colistin (colistimethate)	5 mg/kg/day, 2-4 divided doses	IV
Minocycline	100 mg every 12 h	IV
Tigecycline	100 mg then 50 mg every 12 h	IV

Fishbain J, et al. *Clin Infect Dis*. 2010;51:79-84.

Probability of Hospital Discharge for Treatment of Serious Infections Due to MDR *A. baumannii*



Durante-Mangoni E, et al. *Clin Infect Dis*. 2013;57:349-358.

Investigational Antimicrobial Agents Against Gram-negative Organisms

- β-Lactamase Inhibitor Combinations
  - Ceftolozane + Tazobactam
  - Avibactam (NXL-104)
    - w/ Ceftazidime
    - w/ Ceftaroline
- MK-7655
  - w/ Imipenem-cilastatin
- Key target enzymes
  - Class A β-lactamases (e.g., KPCs)
  - Class C β-lactamases (e.g., ampC)
- None of these inhibitor combinations are active against metallo beta-lactamases (e.g., NDM)

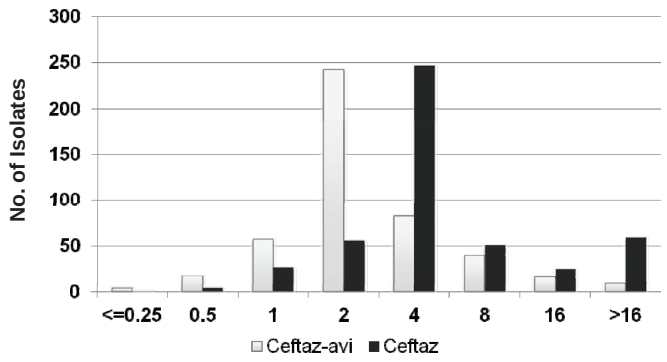
Ceftazidime-Avibactam

- Avibactam is a non-β-lactam, β-lactamase inhibitor
- Inhibits Ambler class A, C and some D β-lactamases
  - ESBL, AmpC, KPC
- 4–1024-fold more active vs. Enterobacteriaceae compared to ceftazidime alone
  - ~4-fold more active vs. *Pseudomonas aeruginosa*

Genotype	Ceftazidime $MIC_{50/90}$	Ceftazidime-avibactam $MIC_{50/90}$ (fold >)
ESBL *E. coli* (n = 161)	16/64	0.12/0.25 (256)
ESBL *K. pneumoniae* (n = 29)	64/>64	0.5/1 (>64)
AmpC *E. coli* (n = 94)	16/64	0.12/0.5 (128)
ESBL and AmpC *E. coli* (n = 8)	32/>64	0.12/0.12 (>512)

Lagace-Wiens PR, et al. *Antimicrob Agents Chemother.* 2011;55:2434–2437.

Activity of Ceftazidime-Avibactam vs. *Pseudomonas aeruginosa* (n=470)



- 66% ceftazidime-R = ≤8 mg/mL ceftazidime-avibactam
- 60% MDR = ≤8 mg/mL ceftazidime-avibactam

Walkty A, et al. *Antimicrob Agents Chemother.* 2011;55; 2992–2994.

Ceftolozane-Tazobactam

- Ceftolozane is a novel, broad-spectrum cephalosporin with potent antipseudomonal activity
  - High affinity for PBP
  - Poor affinity for efflux pumps
- Tazobactam inhibits Ambler class A and some class C β-lactamases (ESBL CTX-M-15)

Genotype/Phenotype	Ceftolozane-Tazobactam $MIC_{50/90}$
All *E. coli* (n = 1146)	≤0.12/0.25
ESBL *E. coli* (n = 84)	0.25/1
All *K. pneumoniae* (n = 395)	≤0.12/0.5
ESBL *K. pneumoniae* (n = 15)	0.5/2

Boucher HW, et al. *Clin Infect Dis.* 2013;56:1685-1694.
Zhanel GG, et al. Poster presentation at ICAAC 2013 (Presentation No. E-1689).

Activity of Ceftolozane-Tazobactam vs. *Pseudomonas aeruginosa* (n=2435)

Agent	All Isolates $MIC_{50/90}$	MDR (158) $MIC_{50/90}$
Ceftazidime	4/32	>32/>32
Ceftolozane/ Tazobactam	**0.5/1**	**2/16**
Ciprofloxacin	0.25/4	4/>16
Colistin	1/2	1/2
Meropenem	0.5/8	8/>32
Piperacillin/ Tazobactam	4/32	128/512
Tobramycin	≤0.5/2	4/64

- **95% ceftazidime-R = ≤8mg/mL ceftolozane/tazobactam**
- **89% of MDR strains inhibited by ≤8 µg/mL of ceftolozane/tazobactam**

Walkty A, et al. *Antimicrob Agents Chemother*. 2013;57:5707-5709.

Back To Our Case

- Switched to aerosolized colistin and meropenem
- Colistin: 150 mg of colistimethate sodium diluted in 2 mL sterile water twice per day
- Meropenem: 1 gram every 8 hours IV
- Improved over 7 to 8 days, completed 2 weeks of therapy

Clinical Cure & All-Cause 28-Day Mortality

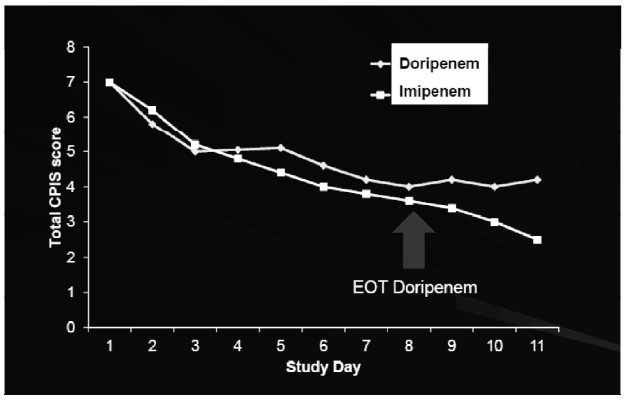
	Doripenem 7-day course			Imipenem 10- day course				
	n	N	%	n	N	%	Diff (%)	95% CI
Clinical cure rate								
MITT	36	79	**45.6**	50	88	**56.8**	-11.2	**(-26.3; 3.8)**
ME	28	57	**49.1**	36	59	**66.1**	-17.0	**(-34.7; 0.8)**
Creatinine clearance* (MITT)								
≥ 150 mL/min	8	18	**44.4**	20	28	**71.4**	-27.0	**(-55.4; 1.4)**
≥80 - 150	31	15	48.4	37	19	51.4	-3.0	-26.8; 20.9
>50 - <80	23	12	52.2	18	9	50.0	2.2	-28.7; 33.0
>30 - ≤50	5	0	0	2	1	50.0	-50.0	
≤30	2	1	50.0	3	1	33.3	16.7	
All cause 28-day mortality								
MITT	17	79	**21.5**	13	88	**14.8**	6.7	**(-5.0; 18.5)**

MITT = Microbiological ITT, ME = Microbiologically Evaluable

* Calculated using Cockcroft -Gault formulas relating serum creatinine with age & body weight

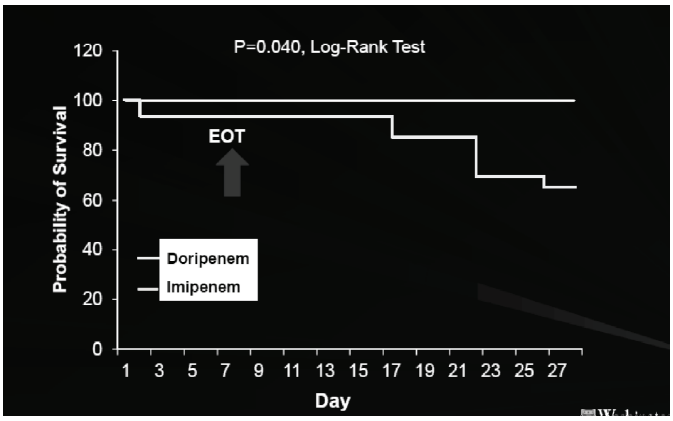
Kollef, MH, et al. *Crit Care*. 2012;16(6):R218.

CPIS for *Pseudomonas aeruginosa* MITT



CPIS, Clinical Pulmonary Infection Score.
Kollef, MH, et al. *Crit Care*. 2012;16(6):R218.

28-Day All-Cause Mortality: *P. aeruginosa*

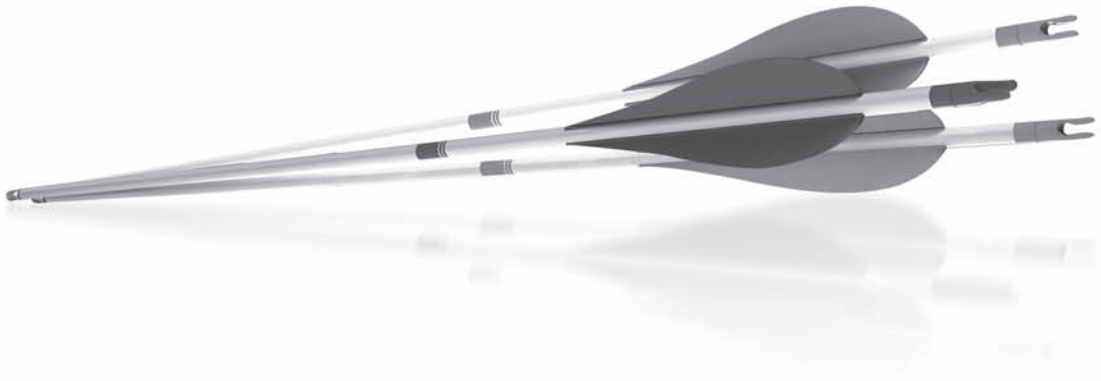


Kollef, MH, et al. *Crit Care*. 2012;16(6):R218.

Summary

- Resistant GNR infections are emerging risk factors for severe morbidity and high mortality.
- Expanding regional and global threat
- Critical public health need for
  - Improved detection of MDR GNR colonization and infection
  - Effective preventive measures
  - Development of novel antimicrobial agents

NOTES



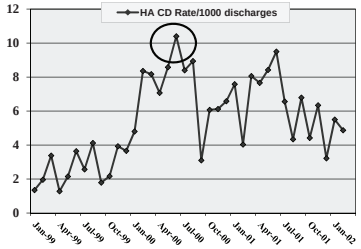
Practice Case 3
Clostridium difficile Infections

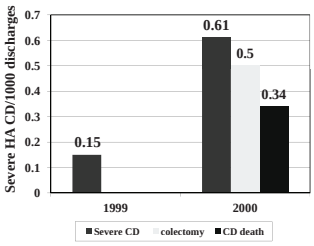
Optimized Approaches in Managing *C. difficile* Infections

Carlene A. Muto, MD, MS

Associate Professor of Medicine
Medical Director of Infection Control and Hospital Epidemiology
Center for Quality Improvement and Innovation
UPMC Health System
Pittsburgh, PA

The Pittsburgh Story



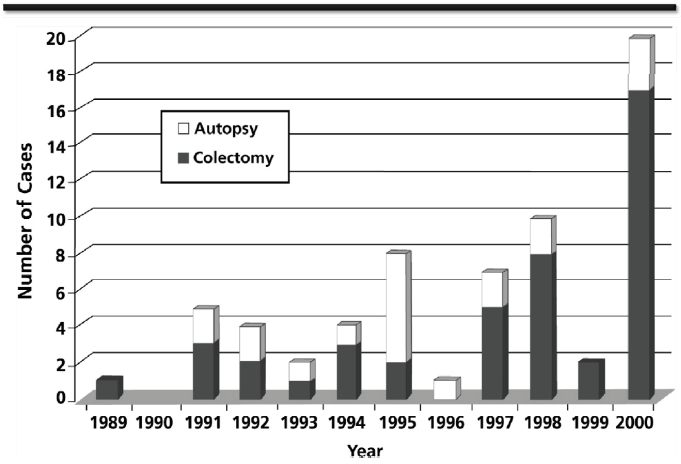


- Hospital-acquired (HA) CD infection (I) rate began increasing in 2000
- Peaked 6/00 at 10.4 cases/1000 discharges
- From "99 to "00 annual incidence increased significantly from 2.7 to 7.2 ($p<10^{-7}$, 95% CI=2.1-3.6)

- Accompanied by an increase in AE rate from 0.15 to 0.61 cases/1000 discharges
  p=0.01, 95% CI 1.31-14.3)
  ~Half of the colectomy cases were associated with CD death

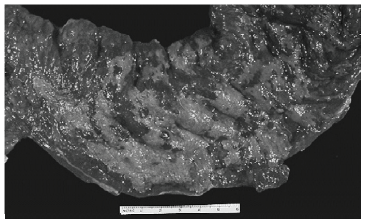
•No obvious changes in patient population, cleaning or infection control policies.
•The only formulary changes were switching ceftazidime to cefepime and cipro to levo

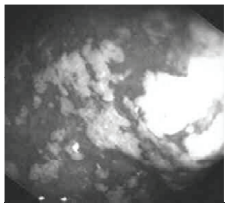
Severe CDI in Pittsburgh



Dallal RM, et al. *Ann Surg*. 2002;3:363-72.

CD Colitis: Background



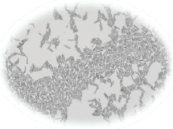


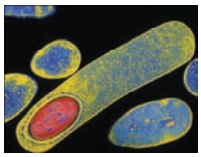
- Infectious diarrhea or pseudomembranous colitis caused by antibiotic use
- Pathogenesis: Inflammatory response secondary to toxin-induced cytokines in the colon
- Symptoms: fever, increased WBCs* (often as has high as 50,000), bandemia, abdominal pain with/or without diarrhea
- Caused by eliminating normal flora and allowing CD to overgrow
- Can occur up to 8–12 weeks after antibiotic therapy

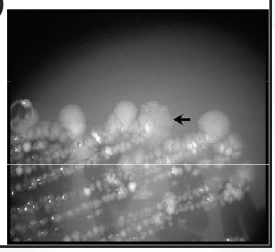
*Most infectious/ inflammatory conditions do not typically elevate WBCs >25,000.

Microbiology

- Ubiquitous
- Anaerobic Gram-positive spore-forming rod
- When the normal gastrointestinal (GI) flora is disrupted, CD exposure may result in CDI
- Slow doubling time (20–40 minutes)

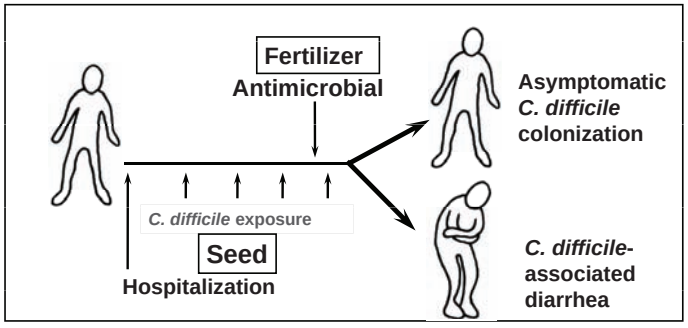






Aslam S, et al. *Lancet Infect Dis.* 2005;5:549-557.
Bouza E, et al. *Med Clin North Am.* 2006;90:1141-1163.

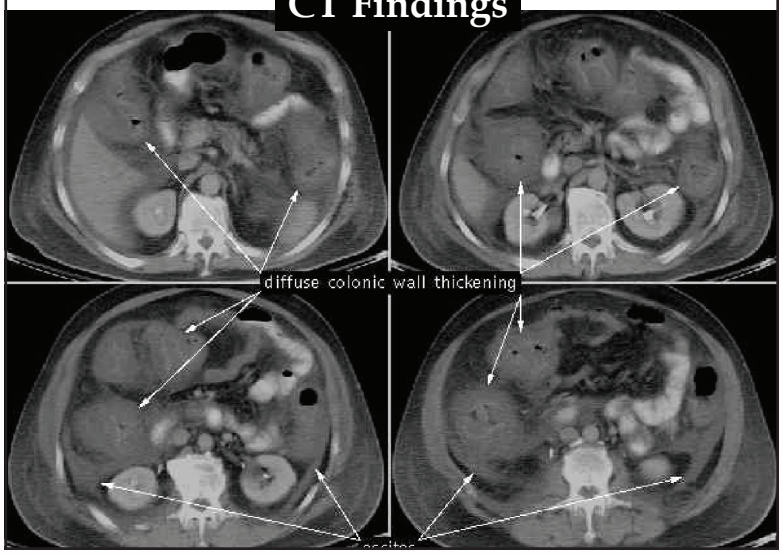
Pathogenesis



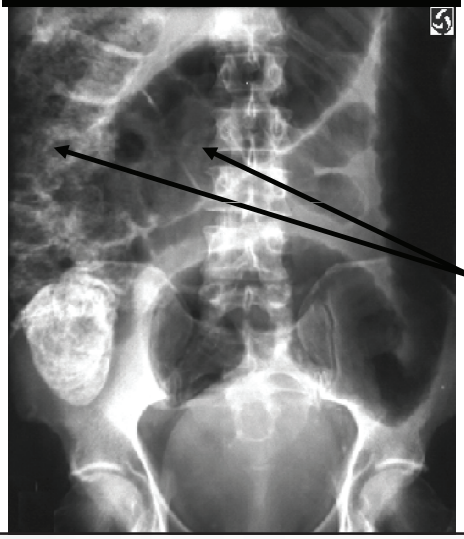
Stop Delivering the Seed or Use Less Fertilizer

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

CT Findings



Abdominal Flat Plate



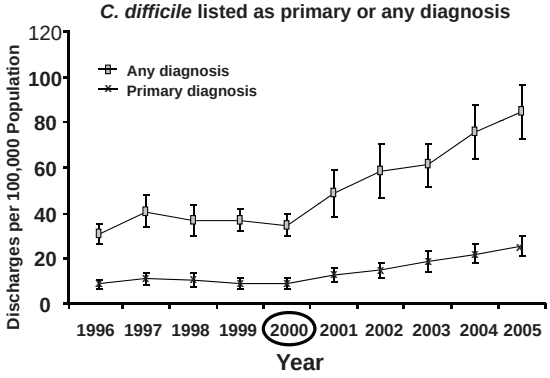
CD Epidemiology

- Present in soil and environment
- Hospitals major reservoirs
- ~ 20% to 40% of hospitalized patients become colonized
- Spread primarily on the hands of HCW
- Transmitted by fecal-enteral route

C. difficile spores have been recovered from:
hospital toilets/commodes metal bedpans
floors thermometers
Spores can exist on surfaces for months

National Hospital Discharge Survey

Estimates of short-stay hospital discharges with *C. difficile* listed as primary or any diagnosis



Tripling of rates in US Hospitals between 2000 and 2005

McDonald LC, et al. *Emerg Infect Dis*. 2006;12:409-415., and unpublished CDC data.

Case

- **An 84-year-old female presented with diarrhea.**
- **One month PTA she presented to her PCP with C/O of an exquisitely tender leg and fever and was diagnosed with *Strep. pyogenes* (Group A Strep) necrotizing fasciitis - now S/P surgical debridement.**
- **She was treated with nafcillin + clindamycin throughout surgical debridements – 1 week.**
- **Then received an additional 2 weeks of nafcillin. Her last dose was 1 week PTA.**
- **She did well until 2 days PTA when she developed diarrhea and abdominal pain.**
  - **10 bowel movements per day, worsening abdominal pain, and nausea/vomiting, tactile temps at home.**
  - **Denied weight loss, and bloody stool.**
  - **She has had no sick contacts, denied travel and well water use and has not eaten outside her home.**
  - **Other medical history is only significant for peptic ulcer disease for which she takes pantoprazole.**

Case (cont'd)

- **On exam the patient was awake but disoriented.**
- **T = 101.5ºC HR = 122/min RR = 24/min BP = 90/55**
- **She had lower quadrant tenderness and distention. Bowel sounds were absent.**
- **The surgical site was without erythema/discharge. Otherwise the exam was unremarkable.**
- **Lab values**
  - **WBC = 49,500 (55% neutrophils, 40% bands)** **LFTs = normal**
  - **Albumin = 2.1** **Lactate = 5.5**
  - **Creatinine = 2.5 (1.3 last admission)**
- **Despite fluid resuscitation BP remained low so vasopressors initiated and admitted to the ICU**
- **Broad-spectrum antibiotics were not given.**

Audience Question

What is the empiric management for this patient?

A. Contact precautions + enteral metronidazole
B. Contact precautions + enteral metronidazole + enteral vancomycin
C. Contact precautions + IV metronidazole + enteral vancomycin + surgical evaluation
D. Contact precautions + enteral fidaxomicin + surgical evaluation
E. Contact precautions + fecal microbiota transplantation

Historical Response to Initial Treatment

Agent	Response Rate*	Relapse Rate	Time to Resolution
Metronidazole	94%–95%	5%–16%	2.4–3.2 days
Vancomycin	94%–100%	15%–16%	2.6–3.1 days

*Successful treatment of the initial episode of CDI

Metronidazole - 500 mg PO TID for 10–14 d
Historical first-line agent
- Advantages
  - Comparable to vanc
  - Preferred according to guidelines
  - Low cost
- Disadvantages
  - High relapse or reinfection rate
  - Less effective than vanc in some studies

Vancomycin - 125 mg PO/per rectum QID for 10–14 d
Historically reserved for severe disease
- Advantages
  - The only FDA-approved CDI therapy
  - In vitro activity against all strains
  - Preferred for pregnant/lactating women
- Disadvantages
  - High relapse or reinfection rate
  - Promotion of acquisition of VRE??
  - High cost

Johnson SJ, Gerding DN. *Clostridium difficile*. In: *Antimicrobial Therapy & Vaccines*. Yu V, et al., eds. New York: Apple Trees Productions; 2002.
Fekety R. *Am J Gastroenterol.* 1997;92:739-750.
Gerding DN, et al. *ICHE.* 1995;16:459-477.
ASHP. *Am J Health-Syst Pharm.* 1998;55:1407-1411.

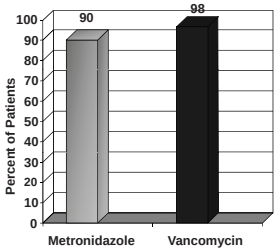
Enteral Vancomycin vs. Metronidazole in Mild and Severe Disease

172 patients enrolled and 150 completed the trial

Patients stratified by "disease severity" for N ≥ 2 points

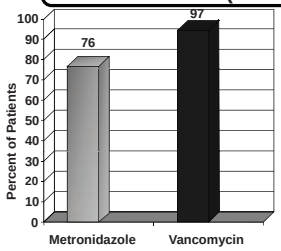
Age> 60 (1 point)	Temp >38.3ºC (1 point)
Albumin <2.5 (1 point)	WBC > 15K (1 point)
Pseudomembranous colitis (2 points)	ICU care (2 points)

Clinical Cure in Mild Disease (n=81)



P = NS

Clinical Cure in Severe Disease (n=69)

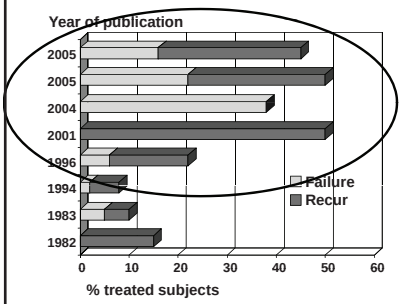


P = 0.02

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

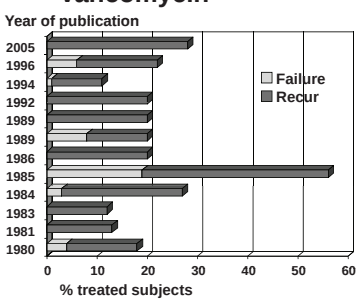
CDI - Response to Treatment in Controlled Trials

Metronidazole



20% Recurrence
13% Failure

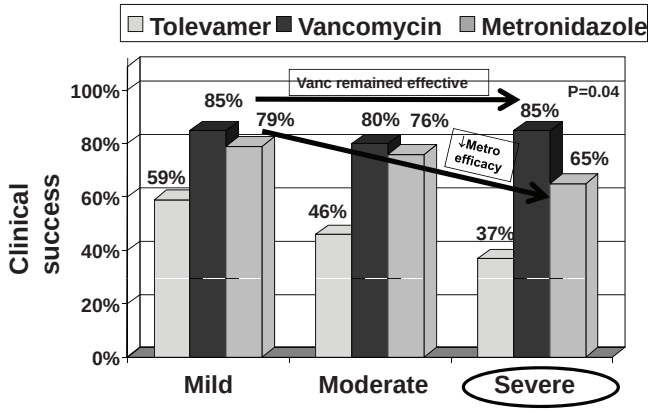
Vancomycin



19% Recurrence
4% Failure

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

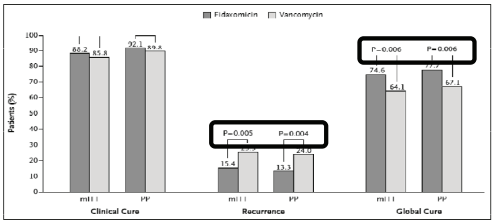
Tolevamer Study Data: Vancomycin is More Effective Than Metronidazole in Treating Severe CDI



Louie T, et al. The 47th Annual ICAAC Meeting, Sept. 17-20, 2007; Chicago, IL. Abstract K-425a.

Newer CDI Therapy: Fidaxomicin (FD)

- Rate of clinical cure with fidaxomicin non-inferior to that of vancomycin (V) - Phase 3 trial results
- FD 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)



- FD was also non-inferior to V in achieving clinical cure and superior to prevent recurrence.
- Subsequent post hoc analyses of these trials showed that, when patients received systemic antibiotics concurrent with CDI treatment, the cure rate was significantly higher for FD compared to V (90% vs. 79.4%; p=0.04), and recurrence rates were lower for FD (16.9% vs. 29.2%; p=0.048)

Louie TJ, et al. *N Engl J Med*. 2011;364:422-431.
Mullane KM, et al. *Clin Infect Dis*. 2011;53:440-7.
Cornely OA, *et al. Lancet Infect Dis*. 2012;12:281-9.

Fidaxomicin

- Approved by FDA on May 27, 2011
- Indication and dosing[1]
  - Treatment of CDI in adults (≥18 years of age)
  - Recommended dose - 200 mg PO BID for 10 days
- 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)
- Challenges include
  - Which patients should receive fidaxomicin treatment?
  - Hospital formulary inclusion
  - Post approval monitoring for unanticipated side affects, resistance??
- Cost[3]
  - $135 per 200 mg dose vs $0.72 for 500 mg dose of metronidazole, and 31.81 for a 125 mg capsule of Enteral V

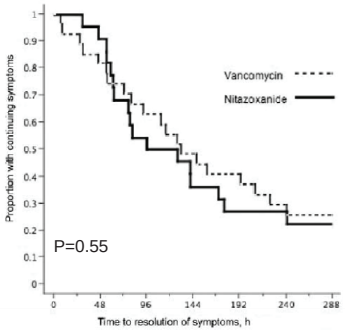
1. Dificid [package insert]: Cubist Pharmaceuticals; 2014.
2. Tannock GW, et al. *Microbiology.* 2010;156(Pt11):3354-9.
3. Lancaster JW, Matthews SJ. *Clin Ther.* 2012;34:1-13.

Alternative CDI Therapies: Nitazoxanide

(Not FDA-Approved for CDI Treatment)

- **May be effective in patients who failed treatment with metronidazole[1]**
  - **66% cure rate in 35 patients who failed treatment with metronidazole**
- **Non-inferior to vancomycin in small study of 50 patients (Figure)[2]**
  - **Initial response:**
    - **Vancomycin: 87%**
    - **Nitazoxanide: 94%**
  - **Similar time to complete resolution of symptoms**

Time to resolution of symptoms



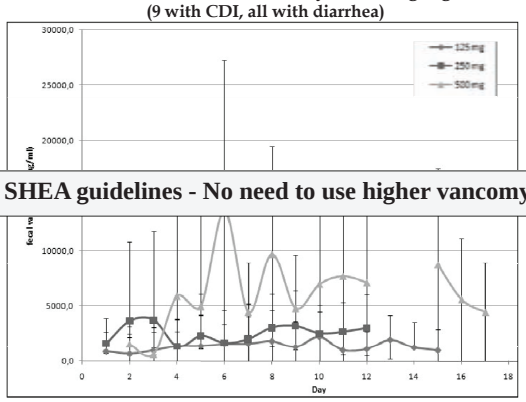
1. Musher DM, et al. *J Antimicrob Chemother*. 2007;59:705-710.
2. Musher DM, et al. *Clin Infec Dis*. 2009;48:e41-e46; with permission.

Severe and Severely Severe CDI

Severe CDI	Severe Complicated CDI
• Peripheral white cell count ≥15,000 cells/μL or • Increase in serum creatinine ≥1.5 times above baseline	• Admission to ICU for CDI • Systemic inflammatory response syndrome (SIRS) criteria • Hypotension with or without required use of vasopressors • Ileus or megacolon • Mental status change • Elevated serum lactate • Presence of end-organ failure

Do you really need a higher dose of enteral vancomycin?

Fecal levels with 3 different enteral vancomycin dosing regimens, 15 patients (9 with CDI, all with diarrhea)



Despite SHEA guidelines - No need to use higher vancomycin dose!

- **Lowest levels 15 and 33 μg/mL for day 1 for 125 mg dosing.**
- **MIC_{90} for *C. difficile* is 0.5–1. μg/mL.**
  - **All doses achieve 100 to 1000× this level.**

Gonazales M, et al. *BMC Infect Dis*. 2010. 30;10:363.

Management of Fulminant or Severe Complicated Disease

- Empiric treatment includes enteral vancomycin with IV metronidazole (ileus)
  - Vancomycin 125 mg enterally QID
  - Vancomycin may also be administered rectally via enema
- Immediate surgical evaluation/consultation
  - Colectomy may be life-saving
  - Total abdominal colectomy with end ileostomy is procedure of choice
  - Diverting ileostomy with vancomycin washout
    - Colon sparing

Lamontagne F, et al. *Ann Surg.* 2007;245:267-272.
Neal MD, et al. *Ann Surg.* 2011;254:423-7.

Alternative Adjunctive Therapies for Severe CDI

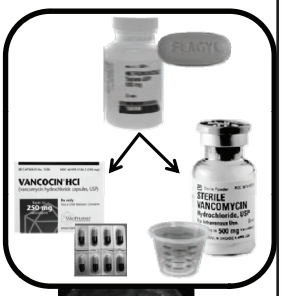
(Not FDA-Approved for CDI Treatment)

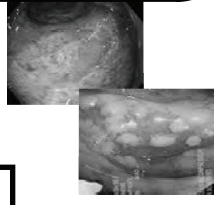
- Tigecycline[1-3]
  - Case reports and small case series with IV tigecycline
  - Usually given in conjunction with other therapies for severe CDI
- Intravenous Immunoglobulin (IVIG)[4,5]
  - Several case series in severe CDI, but evidence for benefit is inconclusive

1. Lu CL, et al. *Int J Antimicrob Agents.* 2010;35:311-312.
2. Herpers BL, et al. *Clin Infect Dis.* 2009;48:1732-1735.
3. Kopterides P, et al. *Anaesth Intensive Care.* 2010;38:755-758.
4. Abougergi MS, et al. *J Hosp Med.* 2010;5:E1-E9.
5. O'Horo J, et al. *Int J Infect Dis.* 2009;13:663-667.

Case Continued

- The patient was treated with IV metronidazole and enteral vancomycin (per rectum)
- CT abdomen/pelvis revealed diffuse colitis consistent with *C. difficile*.
- She remained febrile, had increasing abdominal pain and profuse watery diarrhea.
- WBC remained elevated and lactate was increasing so on hospital day # 2 the patient was taken to the OR, found and received a loop ileostomy
- Post op WBC was decreased and BP normalized.
- The patient made a full recovery…





- 1 month later the patient had a respiratory illness, likely viral.
- She was treated with moxifloxacin.
- 2 days later she developed diarrhea and again had a positive PCR for tox CD.

- Had mild abdominal pain
- WBC = 16,000

Audience Question

What is the BEST management for recurrent CDI? (1st episode)

A. Contact precautions + enteral metronidazole
B. Contact precautions + enteral vancomycin
C. Contact precautions + IV metronidazole + enteral vancomycin
D. Contact precautions + enteral fidaxomicin
E. Contact precautions + fecal microbiota transplantation

Case Continued

- **The patient was treated with enteral vancomycin × 14 days**
- **She did well**
- **4 days after completing therapy she had explosive diarrhea and abdominal pain AGAIN!!!**
- **PCR still positive for tox CD**

Audience Question

What is the BEST 1st-line management for recurrent CDI? (Multiple episodes)

A. Vancomycin 125 mg enterally QID for 14 days followed by rifaximin
B. Vancomycin 125 mg enterally QID for 14 days with concominant rifaximin
C. Vancomycin 125 mg enterally QID for 14 days followed by vancomycin taper over 6 weeks
D. Passive antibody – IVIG
E. Fecal Microbiota Transplantation (FMT)

Recurrent CDI

- Recurrence of symptoms within 8 weeks after symptom resolution, confirmed with a positive stool test.
- Rates of recurrent CDI:
  - 20% after first episode
  - 65% after third episode
- Risk of recurrence is higher with
  - Older age
  - Concomitant antibiotic exposure
  - Presence of comorbidities
  - ↓ levels of serum IgG anti-toxin A
- Antibiotic resistance after treatment not reported
- Repeated, prolonged courses of metronidazole not recommended
- Several empirical approaches have been advocated but most have no controlled data

McFarland LV, et al. *Am J Gastroenterol.* 2002:97:1769-1775.
Khanna S, Pardi D. *Mayo Clin Proc.* 2012;87: 1106–1117.
Hu M, et al. *Gastroenterol.* 2009;136:1206–1214.

Treatment of Multiple Recurrences

(Mostly Uncontrolled Observational Studies with Limited Numbers)

- Tapering/pulsed vancomycin regimens[1]
  - Full course + 6-week taper
- Probiotic approaches
  - *Saccharomyces boulardii* [2]
  - *Lactobacillus plantarum* 299v (*P*=NS)[3]
- Fecal Microbiota Transplantation (FMT)/ Fecal transplantation[4]
- Immunologic approaches
  - Passive vaccination (IVIG)[5]
  - Active vaccination (toxoid preparation)[6]
- Rifaximin "chaser"[7]
  - Resistance already described
- ? Fidaxomicin – case series[8]

1. McFarland LV, et al. *Am J Gastroenterol.* 2002;97:1769-1775.
2. Surawicz CM, et al. *Clin Infect Dis.* 2000;31;1012-1017.
3. Wullt M, et al. *Scand J Infect Dis.* 2003;35:385-367.
4. Aas J, et al. *Clin Infect Dis.* 2003;36:580-585.
5. Beales ILP. *Gut.* 2002;51:456.
6. Giannasca PJ, et al. *Vaccine.* 2004;22:848-856.
7. Johnson S, et al. *Clin Infect Dis.* 2007; 44:846-848.
8. Johnson S, Gerding DN. *Clin Infect Dis.* 2013;56:309-310.

Multiple Recurrent CDI: A Retrospective Study*

Vancomycin	N	Recurrence, n (%)	*P-Value*
Medium dose (1, <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)	

* In 163 cases; 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.

And the Winner is….
Fecal Microbiota Transplantation (FMT)

PUT DOWN THAT Coffee

- **Preparation of donor specimen**
  - **Fresh (<6 hours)**
  - **~30 g or ~2 cm^3 volume**
  - **Add 50 mL 0.9 normal saline**
  - **Homogenize with blender**
  - **Filter suspension with paper coffee filter**
  - **Refilter**

McDonald's New Dessert Item

Fecal McFlurry

Aas J, et al. *Clin Infect Dis.* 2003;36:580-585.

Fecal Flora Restoration

- **Data:**
  - **1958 to 2000: 9 reports (68 patients); cure rate ~90%.**
  - **2003: 18 patients; fecal filtrate (stool transplant); 1 of 16 survivors had a single subsequent recurrence; pre-treated with vancomycin and omeprazole; instilled through nasogastric tube.**
- **Test donor for enteric pathogens, *C. difficile*, ova and parasites, HAV, HBV, HCV, HIV, RPR prior to transplanting stool.**

Persky SE, Brandt LJ. *Am J Gastroenterol.* 2000;95:3283-3285.
Borody TJ. *Am J Gastroenterol*. 2000;95:3028-3029.
Palmer R. *Nat Med*. 2011;17:150-152.

CDI - Recurrent Disease

- **First recurrence: Treat with anti-CD antibiotic (which resolved initial episode) for 14 days**
- **Second recurrence: Treat with vancomycin 125 mg PO QID for 14 days**
- **Third recurrence: Treat with vancomycin 125 mg PO QID for 14 days followed by**
  - **Vancomycin taper (49 caps)**
    - Vancomycin 125 mg PO TID x 7 days, then
    - Vancomycin 125 mg PO BID x 7 days, then
    - Vancomycin 125 mg PO daily x 7 days, then
    - Vancomycin 125 mg PO every other day x 4 doses, then
    - Vancomycin 125 mg PO every third day x 3 doses, then STOP

Investigational Therapies for CDI

Company	Product Name (Type)	Patient Response	Development
Sanofi Pasteur	*C. difficile* vaccine *Cdiffense*	**Phase II** 445 volunteers age 40 – 75 4-fold ↑ in toxins A and B detectable antibodies. Peak responses at day 60	**Phase III** 15,000 volunteers, age ≥ 50 randomize in a 2:1 ratio to vaccine or placebo group*
Pfizer	*C. difficile* vaccine (PF-06425090)	Pending	Phase II
Rebiotix	RBX2660 (microbiota suspension), "fake poop" ready-to-use enema format	40 patients at 13 US centers	Phase II
Merck/ Medarex	MK-3415A (actoxumab + bezlotoxumab)	6.9% vs 25% recurrent CDI	Phase III
ViroPharma	VP 20621, spores of a non-toxigenic *C. difficile* strain (NTCD)	168 patients randomized and dosed following antibiotic treatment for CDI. VP20621 reduced the incidence of CDI recurrence by ≥ 50 % vs. placebo, CDI recurrence rate was 2% (2/86) in the treatment group colonized with VP20621.	Phase II

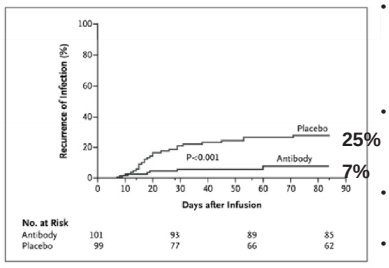
*planning an upcoming hospitalization or have had at least 2 hospital stays and have received systemic antibiotics in the past year.

CD Monoclonal Antibodies
Secondary CDI Prevention

- Multicenter, randomized, double- blind, placebo-controlled trial
- Two novel neutralizing human monoclonal antibodies
  - *C. difficile* toxins A (CDA1)
  - *C. difficile* toxins B (CDB1)
- 484 eligible patients at 30 centers in the US and Canada
- 200 were enrolled in the study
- Patients were given standard therapy for *C. difficile* infection and were randomly assigned to receive
  - A single intravenous infusion of either CDA1+CDB1
  - Saline placebo
- Patients were followed for 84 days
- The primary outcome measure was recurrent *C. difficile* infection.

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

Monoclonal Ab Results



- Intention-to-treat
  - Recurrent infection developed in 7 of 101 patients (7%) in the antibody group, as compared with 25 of 99 patients (25%) in the placebo group
  - Relative reduction of 72%.
- Patients with multiple recurrences were particularly likely to benefit, with a relative reduction of 82% in the recurrence rate, as compared with the placebo group.
- CDA1+CDB1 had no effect on the duration or severity of initial episodes of infection.
- The monoclonal antibodies
  - Were not immunogenic
  - Had an adverse event profile similar to that of placebo.

Conclusion – The addition of monoclonal antibodies against CD to antibiotic agents significantly reduced the recurrence of CDI

The trial results are consistent with previous studies showing that inadequate circulating antibody levels against CD toxins predispose patients to symptomatic and recurrent infection

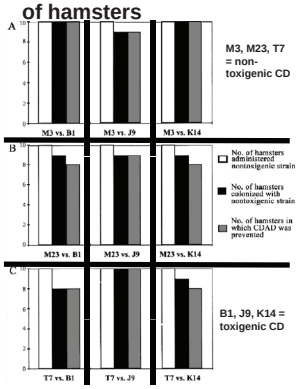
Lowy I, et al. *N Engl J Med*. 2010;362:197-205.

Potential Future CDI Therapies: Nontoxigenic *C. difficile*

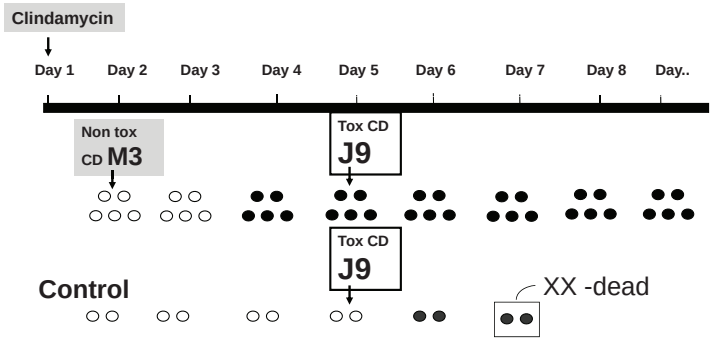
- Nontox CD strains occur naturally
- Natural asymptomatic CD colonization (toxigenic or nontoxigenic) decreases risk of CDI
- Nontox CD can be administered enterally as spores to provide protection against CDI
  - Mechanism by which nontoxigenic CD prevents colonization by toxigenic strains not yet established
- Human trials underway

1. Gerding DN, Johnson S. *Clin Infect Dis*. 2010;51:1306-1313.
2. Sambol SP, et al. *J Infect Dis*. 2002;186:1781-1789; with permission.

Non-toxigenic *C. difficile* prevented CDI in 87%–97% of hamsters



Prevention of Fatal CDI with Toxigenic CD (J9)
Prior Colonization of Hamsters with Nontox CD (M3)



? Alternative CDI Therapies

Therapy	Comments
Teicoplanin	May have a superior cure rate to vancomycin
Doxycycline/linezolid	May be protective against CDI
Tigecycline	Promising in treating severe/refractory CDI
LFF571	Investigational new drug; undergoing further human trials
CB-183 315 (Cubist)	Novel lipopeptide structurally related to daptomycin
Nitazoxanide	Inhibitor of pyruvate ferredoxin.; may be useful in salvage therapy
Amixicile	Novel inhibitor of pyruvate ferredoxin oxidoreductase - Promising in a murine model

BEST CDI Management Strategy

Control Measures-"The CD Bundle"

1. **Identify disease and implement appropriate prevention measures**
   a) Contact Precaution – Extended to entire duration of hospital stay
   b) Hand washing with soap and water
   c) Increased case finding methodologies
   d) Early identification
      a) RNs could order tests without MD order
   e) Informatics tools (alerts)
   f) Informatics tools (flags)
   g) Enhanced environmental cleaning
      i. Sodium hypochlorite (Bleach) or H2O2/acetic/peroxyacetic acid
      ii. Cubical curtain changes
      iii. Common equipment
2. **Target antibiotic restriction**

Muto CA, et al. *Clin Infect Dis*. 2007;45:1266-73.

Case Conclusion

- The patient was treated with enteral vancomycin × 14 days followed by a 6 week enteral vancomycin taper
- Patient had no more recurrences!!

Continuing Professional Development
Reflect | Plan | Do | Evaluate

Center for Independent Healthcare Education is committed to supporting pharmacists in their Continuing Professional Development (CPD) and lifelong learning. Please use this form to incorporate the learning from this educational activity into your everyday practice.

Continuing Professional Development: a self-directed, ongoing, systematic and outcomes-focused approach to learning and professional development that assists individuals in developing and maintaining continuing competence, enhancing their professional practice, and supporting achievement of their career goals.

CPD Value Statement:

"Pharmacists who adopt a CPD approach accept the responsibility to fully engage in and document their learning through reflecting on their practice, assessing and identifying professional learning needs and opportunities, developing and implementing a personal learning plan, and evaluating their learning outcomes with the goal of enhancing the knowledge, skills, attitudes and values required for their pharmacy practice."

REFLECT

Consider my current knowledge and skills, and self-assess my professional development needs and goals related to serious bacterial infections.

PLAN

Develop a "Personal Learning Plan" to achieve intended outcomes, based on what and how I want or need to learn.

Develop objectives that are specific for you, measurable, achievable, relevant to the learning/ practice topic, and define the time frame to achieve them.

DO

Implement my learning plan utilizing an appropriate range of learning activities and methods.

List learning activities that you will engage in to meet your goals.
List resources (e.g. materials, other people) that you might use to help achieve your goal.

EVALUATE

Consider the outcomes and effectiveness of each learning activity and my overall plan, and what (if anything) I want or need to do next.

Monitor progress regularly toward achievement of your goal.

Please remember to complete and return the "Activity Evaluation and Credit Application Form" to program staff

Upcoming Educational Activity

Online Learning Activity

For healthcare professionals who were unable to participate in the presentation, an online learning activity based on the live program will be available.

www.vemcomeded.com

Also Available::

Bacterial Infections in Patients with Cancer: New Challenges, New Opportunities

This continuing medical education activity is designed for physicians, pharmacists, and other healthcare professionals who care for patients with or at-risk of serious bacterial infections, including patients being treated for malignancy and/or with neutropenic fever. This program is divided into 3 episodes that focus on key pathogens: (1) Gram-positive bacteria (e.g., *S. aureus*, MRSA, enterococci), (2) Gram-negative bacteria (e.g., ESBL- and carbapenemase-producing Enterobacteriaceae, *P. aeruginosa*), and (3) *C. difficile*. Current trends in the evolving epidemiology of infection in patients with cancer are discussed. Management approaches focus on effective treatment strategies for infections caused by MDR bacteria.

This activity is based on the CME Ancillary Educational Event held adjunct to ASCO 2014 Annual Meeting.

www.vemcomeded.com

Follow us on Facebook:
www.facebook.com/VemcoMedEd