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

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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
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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
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.

Challenges and Opportunities in Managing Serious Bacterial Infections: A Role for Pathogen-Directed Therapy
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.
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.
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
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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

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

Morbidity and Mortality of MDR Organisms

<table>
<thead>
<tr>
<th>Organism</th>
<th>Infections included</th>
<th>Est. # of cases</th>
<th>Est. annual # deaths</th>
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<tbody>
<tr>
<td>MRSA</td>
<td>Invasive</td>
<td>80,000</td>
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<td>1,300</td>
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<td>All infections</td>
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IDSA Call-to-Action: Bad Bugs, No Drugs

As resistance increases . . . number of new antimicrobials diminishes

VRE, vancomycin-resistant enterococci; FQRP, fluoroquinolone-resistant Pseudomonas.

HAZARD LEVEL

URGENT

Clostridium difficile, Carbapenem-resistant Enterobacteriaceae (CRE), Drug-resistant Neisseria gonorrhoeae (sulfonamide resistance)

HAZARD LEVEL

SERIOUS

Multidrug-resistant Acinetobacter, Drug-resistant Enterococcus faecalis, Drug-resistant Enterobacteriaceae (ESBLs), Vancomycin-resistant Enterococcus (VRE), Methicillin-resistant Staphylococcus aureus (MRSA), Drug-resistant Streptococcus pneumoniae, Drug-resistant Mycobacterium, Drug-resistant Tuberculosis (MDR and XDR)

HAZARD LEVEL

CONCERNING

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

Increasing Drug Resistance

P. aeruginosa

A. baumannii

Inadequate Antimicrobial Therapy Associated with Increased Mortality


MDR Pseudomonas-Impact


Extensively Drug Resistant (XDR) *Pseudomonas aeruginosa* Containing *blaVIM* and *blaIMP* and Elements of *Salmonella* Genomic Island 2: A New Genetic Resistance Determinant in Northeast Ohio

- Frederico Perez,1,2,6 Andrea M. Hujs,1,2,6 Steven H. Marshall1, Amy J. Ray,2,6 Philip N. Rathe,2,6 Nannrada Suvantrat,3 Donald Dumford III1, Patrick O'Shea2, T. Nicholas J. Domitrovic2, Robert A. Salata2,6, Kalyan D. Chavda2, Liang Chen1, Barry N. Kreiswirth2,6, Alejandro J. Vila,3,6 Susanne Haussler1, Michael R. Jacobs,2,6, and Robert A. Bonomo1,2,6

Mortality Associated With MRSA: Two Meta-analyses

![Graph showing mortality comparison between MRSA and MSSA](image)


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


FOUR CORE ACTIONS

PREVENTING INFECTIONS, PREVENTING SPREAD.

TRACKING RESISTANCE PATTERNS.

IMPROVING USE OF ANTIBIOTICS.

DEVELOPING NEW ANTIBIOTICS AND DIAGNOSTIC TESTS.

Practice Case 1
Gram-Positive Infections
Optimized Approaches in Managing Gram-Positive Infections

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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


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**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.

**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

![Graph showing mortality associated with MRSA and MSSA across two time periods (1980-2000 and 1990-2000).]


MRSA: Decreasing Incidence

• Decreasing Trend (from CDC; 2013)

![Graph showing decreasing trend in severe MRSA infections from 2005 to 2011.]

• Why
  – Better awareness, isolation, treatment


MRSA: Diagnostic Testing

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

![Graph showing rapid diagnostic process with timelines for culture, susceptibility reporting, and treatment.]

Effect of Antimicrobial Timing on Survival

<table>
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<th>Time from Hypotension Onset (Hours)</th>
<th>Survival Fraction</th>
<th>Cumulative Effective Antimicrobial Initiation</th>
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<tr>
<td>0-0.49</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>0.5-0.99</td>
<td>0.9</td>
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<td>1.0-1.99</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>2.0-2.99</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>3.0-3.99</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>4.0-4.99</td>
<td>0.5</td>
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</tr>
<tr>
<td>5.0-5.99</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>6.0-6.99</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>7.0-7.99</td>
<td>0.2</td>
<td>0.2</td>
</tr>
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<td>8.0-8.99</td>
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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 antimicrobial²


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

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 pneumonia¹
  - Cavitary pneumonia
  - Neutropenia
  - Hemoptysis

Antimicrobials for MRSA pneumonia¹
  - Appropriate: vancomycin, linezolid
  - Approved for HAP/VAP: telavancin
  - Not approved: ceftaroline
  - Unclear: clindamycin, trimethoprim/sulfa

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


MRSA: Vancomycin or Linezolid for Pneumonia?


MRSA: Vancomycin or Linezolid for Pneumonia?

- Guidelines: either
- Meta-analysis

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


MRSA: Vancomycin or Linezolid for Pneumonia?

- Multi-center observational evaluation in VAP
- No difference in mortality
- No difference nephrotoxicity, anemia, thrombocytopenia

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

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


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*


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

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 14–24) % of Patients

- Oritavancin: 82.2%
- Vancomycin: 83.5%
- S. aureus: 81.4%
- MRSA: 80.6%

Clinical Success (Day 26–30) % of Patients

- Dalbavancin: 84.4%
- Vanco/Linezolid: 89.5%
- S. aureus: 85.1%
- MRSA: 90%

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 % of Patients

- Tedizolid: 88.7%
- Linezolid: 88.5%
- S. aureus: 84.3%
- MRSA: 81.3%
- MSSA: 92%
- 7-14 days after the end of therapy

Vancomycin-Resistant Enterococci (VRE): Impact

- Most prevalent in E. faecium
- Significant burden of infection3
  - Common nosocomial pathogen
  - Intra-abdominal, urinary tract infections, bacteremia
- Infection control and antimicrobial stewardship both needed to control2
  - 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 infection1

Parenteral Therapy for Infections Due to VRE


CABP: Unmet Needs

- Increasing resistance
  - Macrolide resistant S. pneumoniae: now > 40% in US
  - 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 QD1

- 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 (86.1%) vs. ceftriaxone (74.2%) (95% CI, 2.8 to 17.1)

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

<table>
<thead>
<tr>
<th>Serotype (no. tested)</th>
<th>Percentage of non-susceptible rates and MIC\textsubscript{50%} values (2011-2012 collection):</th>
<th>Ceftriaxone (MIC for non-susceptible)</th>
<th>Cefaroline (MIC for non-susceptible)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CLSI (≥2 µg/ml)</td>
<td>EUCAST (≥1 µg/ml)</td>
<td>MIC\textsubscript{50%}</td>
</tr>
<tr>
<td>19A (165)</td>
<td>49.4%</td>
<td>78.0%</td>
<td>1/2</td>
</tr>
<tr>
<td>19F (35)</td>
<td>14.3</td>
<td>22.9</td>
<td>≤0.06/0</td>
</tr>
<tr>
<td>35B (92)</td>
<td>4.3%</td>
<td>8.0</td>
<td>1/1</td>
</tr>
<tr>
<td>All (1,190)</td>
<td>8.7</td>
<td>21.0</td>
<td>≤0.06/1</td>
</tr>
</tbody>
</table>

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.


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


CABP: Possible Future Agents

<table>
<thead>
<tr>
<th></th>
<th>S. pneumoniae</th>
<th>Haemophilus</th>
<th>Atypicals</th>
<th>MRSA (300)</th>
<th>GNR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftobiprole (β-lactam; Basilea)</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Deltaflouxacin (Fluoroquinolone; Melinta)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tedizolid (oxazolidinone; Cubist)</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Omadacycline (tetracycline; Paratek)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Eravacycline (tetracycline; Tetraphase)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>GSK1322322 (peptide deformylase inhibitor; GSK)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>BC-3781 (pleuromutilin; Nabriva)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Solithromycin (fluoroketolide; Cempra)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
</tbody>
</table>

Challenges and Opportunities in Managing Serious Bacterial Infections: A Role for Pathogen-Directed Therapy
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


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: 39.1°C; WBC 18,500/mm³
- Vancomycin 1 g q12h and piperacillin-tazobactam 4.5 g q6h begun empirically
- BAL performed in ICU

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* >10⁵ 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 longer respiratory support than other organisms even when treated adequately

MV, mechanical ventilation; VAP, ventilator-associated pneumonia.

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

<table>
<thead>
<tr>
<th>Agent</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>S</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>R</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>R</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>R</td>
</tr>
<tr>
<td>Ceftriazone</td>
<td>R</td>
</tr>
<tr>
<td>Cefepime</td>
<td>R</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>R</td>
</tr>
<tr>
<td>Colistin</td>
<td>S</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>I/R</td>
</tr>
<tr>
<td>Imipenem</td>
<td>R</td>
</tr>
<tr>
<td>Meropenem</td>
<td>R</td>
</tr>
<tr>
<td>Doripenem</td>
<td>R</td>
</tr>
<tr>
<td>Piperacillin-Tazobactam</td>
<td>R</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>S</td>
</tr>
</tbody>
</table>
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


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 Ceferpine

Antipseudomonal fluoroquinolones:
Ciprofloxacin Levofloxacin

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

Monobactams
Aztreonam

Phosphonic acids
Fosfomycin

Polymyxins
Colistin Polymyxin B


BAD BUGS, NO DRUGS
As Antibiotic Discovery Stagnates ...
A Public Health Crisis Brews

IDSA
Infectious Diseases Society of America
July 2004

First understand your local problem with MDR/XDR!

GNB:
Resistant Isolates in the US per CDC

<table>
<thead>
<tr>
<th>Organism</th>
<th>No. of resistant isolates/100,000 population</th>
<th>3-class resistance†</th>
<th>4-class resistance‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>560,145</td>
<td>0.73</td>
<td>0.37</td>
</tr>
<tr>
<td><em>Acinetobacter baumannii</em></td>
<td>1,038,672</td>
<td>0.92</td>
<td>0.58</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>1,000,658</td>
<td>0.85</td>
<td>0.50</td>
</tr>
</tbody>
</table>

† Antimicrobial classes were penicillins, cephalosporins, aminoglycosides, fluoroquinolones, and carbapenems for *P. aeruginosa* and *A. baumannii*. Antimicrobial classes were penicillins, cephalosporins, aminoglycosides, fluoroquinolones, carbapenems, and β-lactams for *K. pneumoniae*.

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

GNB: Resistant Isolates in the US per CDC

<table>
<thead>
<tr>
<th>Organism</th>
<th>Ventilator-associated pneumonia</th>
<th>Central line-associated bloodstream infection</th>
<th>Catheter-associated urinary tract infection</th>
<th>Surgical site infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomonas aeruginosa (n = 1,391)</td>
<td>232 (56)</td>
<td>111 (56)</td>
<td>292 (43)</td>
<td>31 (5)</td>
</tr>
<tr>
<td>Acinetobacter baumannii (n = 49)</td>
<td>590 (49)</td>
<td>372 (31)</td>
<td>180 (36)</td>
<td>51 (4)</td>
</tr>
<tr>
<td>Klebsiella pneumoniae (n = 1,379)</td>
<td>89 (13)</td>
<td>237 (30)</td>
<td>290 (46)</td>
<td>44 (6)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa (n = 49)</td>
<td>34 (40)</td>
<td>84 (40)</td>
<td>36 (40)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>A. baumannii (n = 49)</td>
<td>744 (90)</td>
<td>173 (35)</td>
<td>50 (13)</td>
<td>13 (3)</td>
</tr>
<tr>
<td>E. coli (n = 143)</td>
<td>51 (34)</td>
<td>90 (60)</td>
<td>85 (57)</td>
<td>19 (9)</td>
</tr>
</tbody>
</table>

* Isolates reported to the National Healthcare Safety Network (NHSN), 2009–2010.


Pseudomonas Resistance in HAI

![Graph showing resistance rates for various antibiotics across different infections]

* Isolates reported to the National Healthcare Safety Network (NHSN), 2009–2010.


Pseudomonas Resistance to Carbapenems

![Map showing resistance rates across EU 2011]

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population (n)</th>
<th>Inappropriate IAT</th>
<th>Appropriate IAT</th>
<th>Mortality risk (OR or RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kollef et al. 1999†</td>
<td>ICU admission (2000)</td>
<td>52.1</td>
<td>12.2</td>
<td>4.26</td>
</tr>
<tr>
<td>Kollef et al. 1999†</td>
<td>ICU admission with documented infection (655)</td>
<td>52.1</td>
<td>23.5</td>
<td>2.22</td>
</tr>
<tr>
<td>Peralta et al. 2007‡</td>
<td>E. coli bacteremia (663)</td>
<td>11.3</td>
<td>4.2</td>
<td>2.26</td>
</tr>
<tr>
<td>Kutl et al. 2008‡</td>
<td>VAP (813)</td>
<td>NR</td>
<td>NR</td>
<td>2.34</td>
</tr>
<tr>
<td>Kutl et al. 2008‡</td>
<td>Bloodstream infection (11,483)</td>
<td>NR</td>
<td>NR</td>
<td>2.33</td>
</tr>
<tr>
<td>Micek et al. 2010*</td>
<td>GNB sepsis (760)</td>
<td>51.7</td>
<td>36.4</td>
<td>2.30</td>
</tr>
<tr>
<td>Muscedere et al. 2012‡</td>
<td>VAP (350)</td>
<td>48.7</td>
<td>19.5</td>
<td>3.05</td>
</tr>
</tbody>
</table>


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

- Inadequate antimicrobial treatment
- Adequate antimicrobial treatment

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).
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

![Graph showing early vs delayed therapy](image)

NP/VAP: nosocomial pneumonia/ventilator-associated pneumonia.

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


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

<table>
<thead>
<tr>
<th>Drugs</th>
<th>None</th>
<th>Cipro</th>
<th>Gentamicin</th>
<th>Amikacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pip-Tazo</td>
<td>80%</td>
<td>82%</td>
<td>81%</td>
<td>96%</td>
</tr>
<tr>
<td>Cefepime</td>
<td>81%</td>
<td>83%</td>
<td>82%</td>
<td>96%</td>
</tr>
<tr>
<td>Meropenem</td>
<td>82%</td>
<td>83%</td>
<td>83%</td>
<td>96%</td>
</tr>
</tbody>
</table>


Selection: Patient Risk

Gram-negative bacteremia with severe sepsis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Community-Acquired</th>
<th>HCA-Community</th>
<th>HCA-Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefepime</td>
<td>6.9</td>
<td>12.9</td>
<td>26.3</td>
</tr>
<tr>
<td>Imipenem or Meropenem</td>
<td>1.2</td>
<td>5.3</td>
<td>14.3</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>13.9</td>
<td>17</td>
<td>27.6</td>
</tr>
</tbody>
</table>

HCA, healthcare-associated.

The Impact of Combination Antibiotic Therapy: Hospital-Acquired Infection

<table>
<thead>
<tr>
<th>Drug</th>
<th>Alone</th>
<th>Plus Ciprofloxacin</th>
<th>Plus Gentamicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefepime</td>
<td>23.6</td>
<td>19.6</td>
<td>15.5</td>
</tr>
<tr>
<td>Imipenem or Meropenem</td>
<td>15.8</td>
<td>11.2</td>
<td>8.8</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>26.3</td>
<td>18</td>
<td>12.9</td>
</tr>
</tbody>
</table>

Antimicrobial Agents for the Treatment of MDR Gram-Negative Infections

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


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

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

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Ceftazidime MIC&lt;sub&gt;90&lt;/sub&gt;</th>
<th>Ceftazidime-avibactam MIC&lt;sub&gt;90&lt;/sub&gt; (fold &gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESBL E. coli (n = 161)</td>
<td>16/64</td>
<td>0.12/0.25 (256)</td>
</tr>
<tr>
<td>ESBL K. pneumoniae (n = 29)</td>
<td>64/&gt;64</td>
<td>0.5/1 (&gt;64)</td>
</tr>
<tr>
<td>AmpC E. coli (n = 94)</td>
<td>16/64</td>
<td>0.12/0.5 (128)</td>
</tr>
<tr>
<td>ESBL and AmpC E. coli (n = 8)</td>
<td>32/&gt;64</td>
<td>0.12/0.12 (&gt;512)</td>
</tr>
</tbody>
</table>

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

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

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

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)

<table>
<thead>
<tr>
<th>Genotype/Phenotype</th>
<th>Ceftolozane-Tazobactam MIC&lt;sub&gt;90&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>All E. coli (n = 1146)</td>
<td>≤0.12/0.25</td>
</tr>
<tr>
<td>ESBL E. coli (n = 84)</td>
<td>0.25/1</td>
</tr>
<tr>
<td>All K. pneumoniae (n = 395)</td>
<td>≤0.12/0.5</td>
</tr>
<tr>
<td>ESBL K. pneumoniae (n = 15)</td>
<td>0.5/2</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Agent</th>
<th>All Isolates MIC&lt;sub&gt;50/90&lt;/sub&gt;</th>
<th>MDR (158) MIC&lt;sub&gt;50/90&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime</td>
<td>4/32</td>
<td>&gt;32/32</td>
</tr>
<tr>
<td>Ceftolozane/ Tazobactam</td>
<td>0.5/1</td>
<td>2/16</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0.25/4</td>
<td>4/&gt;16</td>
</tr>
<tr>
<td>Colistin</td>
<td>1/2</td>
<td>1/2</td>
</tr>
<tr>
<td>Meropenem</td>
<td>0.5/6</td>
<td>8/&gt;32</td>
</tr>
<tr>
<td>Piperacillin/ Tazobactam</td>
<td>4/32</td>
<td>128/512</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>≤0.5/2</td>
<td>4/64</td>
</tr>
</tbody>
</table>

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


---

### 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

<table>
<thead>
<tr>
<th></th>
<th>Doripenem</th>
<th>Imipenem</th>
<th>Diff (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MITT</td>
<td>ME</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical cure rate</td>
<td>n</td>
<td>N %</td>
<td>n</td>
<td>N %</td>
</tr>
<tr>
<td>MITT</td>
<td>36</td>
<td>79 45.6</td>
<td>50</td>
<td>88 56.8</td>
</tr>
<tr>
<td>ME</td>
<td>28</td>
<td>57 49.1</td>
<td>36</td>
<td>59 66.1</td>
</tr>
<tr>
<td>Creatinine clearance* (MITT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 150 mL/min</td>
<td>8</td>
<td>18 44.4</td>
<td>20</td>
<td>28 71.4</td>
</tr>
<tr>
<td>&gt;80 - ≤150</td>
<td>31</td>
<td>15 48.4</td>
<td>37</td>
<td>19 51.4</td>
</tr>
<tr>
<td>&gt;50 - &lt;80</td>
<td>23</td>
<td>12 52.2</td>
<td>18</td>
<td>9 50.0</td>
</tr>
<tr>
<td>&gt;30 - ≤50</td>
<td>5</td>
<td>0 0</td>
<td>2</td>
<td>1 50.0</td>
</tr>
<tr>
<td>≤30</td>
<td>2</td>
<td>1 50.0</td>
<td>3</td>
<td>1 33.3</td>
</tr>
<tr>
<td>All cause 28-day mortality</td>
<td>MITT</td>
<td>ME</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MITT</td>
<td>17</td>
<td>79 21.5</td>
<td>13</td>
<td>88 14.8</td>
</tr>
</tbody>
</table>

MITT = Microbiological ITT, ME = Microbiologically Evaluable

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

CPIS for *Pseudomonas aeruginosa* MITT

![Graph showing CPIS for Pseudomonas aeruginosa](image)

**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
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
- Half of the colectomy cases were associated with CD death

Severe CDI in Pittsburgh

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 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)

Pathogenesis

Asymptomatic *C. difficile* colonization

CT Findings

Diffuse colonic wall thickening

Stop Delivering the Seed or Use Less Fertilizer

CD Epidemiology

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

* C. difficile spores have been recovered from:
  - Hospital toilets/commodes
  - Metal bedpans
  - 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

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

<table>
<thead>
<tr>
<th>Agent</th>
<th>Response Rate*</th>
<th>Relapse Rate</th>
<th>Time to Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole</td>
<td>94%–95%</td>
<td>5%–16%</td>
<td>2.4–3.2 days</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>94%–100%</td>
<td>15%–16%</td>
<td>2.6–3.1 days</td>
</tr>
</tbody>
</table>

*Successful treatment of the initial episode of CDI

**Metronidazole - 500 mg PO TID for 10–14 d**

- **Historical first-line agent**
  - Advantages
    - Comparable to vancomycin
    - Preferred according to guidelines
    - Low cost
  - Disadvantages
    - High relapse or reinfection rate
    - Less effective than vancomycin 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

---

### 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

**Clinical Cure in Mild Disease (n=81)**

- Age > 60 (1 point)
- Temp >38.3°C (1 point)
- Albumin <2.5 (1 point)
- Pseudomembranous colitis (2 points)

**Clinical Cure in Severe Disease (n=69)**

- WBC > 15K (1 point)
- ICU care (2 points)

**P = NS**

**P = 0.02**


---

### CDI - Response to Treatment in Controlled Trials

**Metronidazole**

- 20% Recurrence
- 13% Failure

**Vancomycin**

- 19% Recurrence
- 4% Failure


---


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

![Graph showing clinical success rates for different treatments]


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)


Fidaxomicin

- Approved by FDA on May 27, 2011
- Indication and dosing:
  - Treatment of CDI in adults (≥18 years of age)
  - Recommended dose - 200 mg PO BID for 10 days
- Advantageous characteristics:
  - 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:
  - $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

Alternative CDI Therapies: Nitazoxanide
(Not FDA-Approved for CDI Treatment)

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

Time to resolution of symptoms


Severe and Severely Severe CDI

Severe CDI
- Peripheral white cell count ≥15,000 cells/µL or
- Increase in serum creatinine ≥1.5 times above baseline

Severe Complicated CDI
- 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.
- MIC₉₀ for C. difficile is 0.5–1. µg/mL.
  - All doses achieve 100 to 1000 × this level.

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

Immediate surgical evaluation/consultation
- Colectomy may be life-saving
- Total abdominal colectomy with end ileostomy is procedure of choice
- Diverting ileostomy with vancomycin washout


Alternative Adjunctive Therapies for Severe CDI

(Not FDA-Approved for CDI Treatment)

- Tigecycline1-3
  - 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


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 concomitant 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
- 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

Treatment of Multiple Recurrences
(Mostly Uncontrolled Observational Studies with Limited Numbers)

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

Multiple Recurrent CDI: A Retrospective Study*

<table>
<thead>
<tr>
<th>Vancomycin</th>
<th>Recurrence, n (%)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium dose (1 &lt;2 g/day)</td>
<td>14</td>
<td>10 (71)</td>
</tr>
<tr>
<td>Low dose (1 ≤ 1 g/day)</td>
<td>48</td>
<td>26 (54)</td>
</tr>
<tr>
<td>High dose (≥ 2 g/day)</td>
<td>21</td>
<td>9 (43)</td>
</tr>
<tr>
<td>Tapering dose</td>
<td>29</td>
<td>9 (31)</td>
</tr>
<tr>
<td>Pulse dosing</td>
<td>7</td>
<td>1 (14)</td>
</tr>
<tr>
<td>Other †</td>
<td>6</td>
<td>2 (33)</td>
</tr>
<tr>
<td>All</td>
<td>125</td>
<td>57 (46)</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Recurrence, n (%)</td>
<td></td>
</tr>
<tr>
<td>Low dose (≤ 1 g/day)</td>
<td>29</td>
<td>13 (45)</td>
</tr>
<tr>
<td>Medium dose (1.5 g/day)</td>
<td>5</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Other ‡</td>
<td>4</td>
<td>1 (25)</td>
</tr>
<tr>
<td>All</td>
<td>38</td>
<td>16 (42)</td>
</tr>
</tbody>
</table>

* 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.

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

**PUT DOWN THAT Coffee**

- Preparation of donor specimen
  - Fresh (<6 hours)
  - ~30 g or ~2 cm³ 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


---

**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.**


---

**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**

<table>
<thead>
<tr>
<th>Company</th>
<th>Product Name (Type)</th>
<th>Patient Response</th>
<th>Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanofi Pasteur</td>
<td>C. difficile vaccine Cdiffense</td>
<td>Phase II 445 volunteers age 40 – 75 4-fold ↑ in toxins A and B detectable antibodies. Peak responses at day 60</td>
<td>Phase III 15,000 volunteers, age ≥ 50 randomize in a 2:1 ratio to vaccine or placebo group*</td>
</tr>
<tr>
<td>Pfizer</td>
<td>C. difficile vaccine (PF-06425090)</td>
<td>Pending</td>
<td>Phase II</td>
</tr>
<tr>
<td>Rebiotix</td>
<td>RBX2660 (microbiota suspension), “fake poop” ready-to-use enema format</td>
<td>40 patients at 13 US centers</td>
<td>Phase II</td>
</tr>
<tr>
<td>Merck/Medarex</td>
<td>MK-3415A (acetaxumab + bezlotoxumab)</td>
<td>6.9% vs 25% recurrent CDI</td>
<td>Phase III</td>
</tr>
<tr>
<td>ViroPharma</td>
<td>VP 20621, spores of a non-toxigenic C. difficile strain (NTCD)</td>
<td>168 patients randomized and dosed following antibiotic treatment for CDI. VP20621 reduced the incidence of CDI recurrence by a 59 % vs. placebo. CDI recurrence rate was 2% (2/86) in the treatment group colonized with VP20621</td>
<td>Phase II</td>
</tr>
</tbody>
</table>

*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.


**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.

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

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


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

<table>
<thead>
<tr>
<th>Clindamycin</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
<th>Day 8</th>
<th>Day..</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non tox CD</td>
<td>M3</td>
<td></td>
<td></td>
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<tr>
<td>Tox CD</td>
<td>J9</td>
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</tbody>
</table>

? Alternative CDI Therapies

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


Case Conclusion

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

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**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.”

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**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.

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**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.

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**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.

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