Sunday, September 7, 2014

6:00 PM – 8:00 PM

Marriott Marquis
Washington, DC

EDUCATIONAL OVERVIEW

The pandemic of multidrug-resistant (MDR) bacteria and their continuing spread is well recognized and considered a global health crisis. In addition to the rising prevalence of MDR pathogens, a growing at-risk patient population has compounded the burden caused by these infections. In particular, infections caused by MRSA, vancomycin-resistant enterococci, *Pseudomonas aeruginosa*, ESBL-producing and carbapenem-resistant Enterobacteriaceae, and *C. difficile* continue to present challenges when utilizing current antimicrobials.

Addressing the MDR crisis requires a multifaceted approach, including having a thorough understanding of resistance mechanisms, local epidemiology, rapid diagnostics, and infection control. When an MDR infection is suspected, clinicians must consider patient-, pathogen-, and drug-related factors when selecting an optimal regimen. Newer and emerging agents can offer effective options to address these difficult infections, though their use must be done in an appropriate manner. Clinicians depend on ID specialists for guidance when managing MDR infections and, thus, they must be skilled and competent in the latest research and evidence-based strategies.

Through a debate format, this activity explores the spectrum of available and emerging agents for the treatment of MDR infections and the ways in which clinicians can apply evidence-based treatment approaches in order to reduce the morbidity and mortality of these infections.

TARGET AUDIENCE

This continuing medical education activity is planned to meet the need of healthcare providers in a variety of practice settings, including large and small health systems, outpatient clinics, managed-care organizations, long-term care facilities, and academia. This activity is especially beneficial for ID physicians and pharmacists who are on the frontline of managing patients with serious bacterial infections in their institutions.

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
- Optimize the use of available antimicrobial agents to treat multidrug-resistant bacterial infections by considering patient and pathogen factors
- Assess the utility of new and emerging therapeutic options as part of pathogen-directed therapy when treating serious bacterial infections

FACULTY

George G. Zhanel, PharmD, PhD, FCCP
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Department of Medical Microbiology and Infectious Diseases
College of Medicine, Faculty of Health Sciences, University of Manitoba
Director, Canadian Antimicrobial Resistance Alliance (CARA)
Winnipeg, Canada

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Professor, Internal Medicine
Master Teacher; Chair, Infectious Disease Section
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Rootstown, OH

Erik R. Dubberke, MD, MSPH
Associate Professor of Medicine
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Washington University School of Medicine
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Richard H. Drew, PharmD, MS, FCCP
Professor and Vice Chair of Research and Scholarship
Campbell University College of Pharmacy and Health Sciences
Associate Professor of Medicine (Infectious Diseases)
Duke University School of Medicine
Durham, NC

EDUCATIONAL PROGRAM (6:00 – 8:00 PM)

6:00 – 6:10 PM **Call-to-Action: Introduction**

6:10 – 7:40 PM **ROUND 1: MRSA and VRE Infections**
Challenges - Richard H. Drew, PharmD
Opportunities - Thomas M. File, Jr., MD

ROUND 2: ESBL-producing and Carbapenem-Resistant Enterobacteriaceae
Challenges - George G. Zhanel, PharmD, PhD
Opportunities - Richard H. Drew, PharmD

ROUND 3: *Pseudomonas aeruginosa*
Challenges - Thomas M. File, Jr., MD
Opportunities - Erik R. Dubberke, MD

ROUND 4: *Clostridium difficile*
Challenges - Erik R. Dubberke, MD
Opportunities - George G. Zhanel, PharmD, PhD

7:40 – 8:00 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: 0473-9999-14-005-L01-P

Activity type: Knowledge-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

George G. Zhanel, PharmD, PhD, FCCP
Thomas M. File, Jr., MD, MS, MACP, FIDSA, FCCP
Erik R. Dubberke, MD, MSPH
Richard H. Drew, PharmD, MS, FCCP
Paul DeLisle
Marco Cicero, PhD
Maja Drenovac, PharmD, CCMEP

Disclosure of Financial Interest

George G. Zhanel, PharmD, PhD (Faculty/Planner) has relevant financial relationships with commercial interests as follows:

- Grant Recipient/Research Support: AstraZeneca, Cubist Pharmaceuticals, The Medicines Company, Merck & Co., Pfizer, Triton, Tetraphase

Dr. Zhanel intends to discuss the off-label uses of the following: Investigational uses of ceftolozane/tazobactam, ceftazidime/avibactam, imipenem, MK7655, eravacycline, oritavancin, tedizolid, dalbavancin, surotomycin, and fecal transplant.

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.

Erik R. Dubberke, MD (Faculty/Planner) has relevant financial relationships with the following commercial interests:

- Advisory Board: Cubist Pharmaceuticals
- Consultant: Merck & Co., Rebiotix, Sanofi-Pasteur
- Grant Recipient/Research Support: Merck & Co., Cubist Pharmaceuticals, Sanofi-Pasteur, Microdermis

Dr. Dubberke intends to discuss the off-label use of following: Investigational treatment for Pseudomonas aeruginosa.

Richard H. Drew, PharmD (Faculty/Planner) has relevant financial relationships with commercial interests as follows:

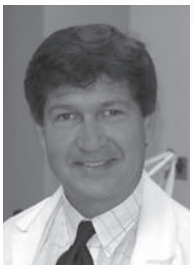
- Publication royalties: UpToDate
- Development team: CustomID

Dr. Drew intends to discuss the off-label uses of the following: Phase I-III agents for treatment of moderate-severe infections, novel dosing strategies of approved agents. Investigational and non-approved uses will be identified as such.

Content review confirmed that the content was developed in a fair, balanced manner free from commercial bias. Disclosure of a relationship is not intended to suggest or condone commercial bias in any presentation, but it is made to provide participants with information that might be of potential importance to their evaluation of a presentation.

Commercial Support

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



George G. Zhanel, PharmD, PhD, FCCP
Professor
Department of Medical Microbiology and Infectious Diseases
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Director, Canadian Antimicrobial Resistance Alliance (CARA)
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Dr. George Zhanel is a microbiologist and pharmacologist who received his PhD in the Department of Medical Microbiology/Infectious Diseases at the Faculty of Medicine, University of Manitoba and a Doctor of Clinical Pharmacy at the University of Minnesota. He is presently Professor in the Department of Medical Microbiology/Infectious Diseases, Faculty of Health Sciences at the University of Manitoba; and Director of the Canadian Antimicrobial Resistance Alliance (CARA). Dr. Zhanel is the founding and Chief Editor of the Canadian Antimicrobial Resistance Alliance (CARA) website (www.can-r.ca).

Dr. Zhanel has published over 800 papers, chapters and abstracts in the area of antimicrobial resistance. He has presented over 1000 lectures as an invited speaker at international, national, and local meetings speaking on the topic of antimicrobial resistance in Canada, United States, Central America, Western and Eastern Europe, Australia, Africa, the Middle East and Asia. Dr. Zhanel has received or been nominated for 40 teaching awards and is a member of the Who's Who in Medical Sciences Education (WWMSE).

As Director of CARA, Dr. Zhanel's antimicrobial resistance interests include understanding the prevalence and epidemiology of antimicrobial resistant infections, describing the clinical relevance of resistant infections, and identifying and developing rapid diagnostic methods to rapidly diagnose resistant infections. Dr. Zhanel's research interests also include investigating the molecular mechanisms of resistance, assessing activity of investigational antimicrobials as well as discovering novel antimicrobials with activity against resistant pathogens, and studying pharmacodynamic modeling and Monte Carlo analyses to provide optimal treatment of antimicrobial resistant infections. Dr. Zhanel's research also includes assessing the medical and economic outcomes of antimicrobial resistant infections as well as studying the relationships between antimicrobial use and the development of antimicrobial resistant infections.

FACULTY

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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 M. File, Jr. is Chair of the Infectious Disease Division and Director of HIV Research at Summa Health System in Akron, Ohio, and Professor of Internal Medicine, Master Teacher, and Chair of the Infectious Disease Section at the 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 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 the current President of the National Foundation for Infectious Diseases and is a member of many other professional societies, including the American Society for Microbiology, the American Thoracic Society (ATS), and the American Society of Hospital Epidemiologists. He is the 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, and evaluation of new antimicrobial agents. A frequent lecturer both nationally and internationally, Dr. File has published more than 200 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, 2nd Ed* (2007, 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.). In addition, he is Editor-in-Chief of *Infectious Diseases in Clinical Practice*. Dr. File is listed in Best Doctors in America (1996 to present) and Marquis Who's Who in America, 65th Ed. 2011.

Erik R. Dubberke, MD, MSPH
Associate Professor of Medicine
Director, Section of Transplant Infectious Diseases
Washington University School of Medicine
St. Louis, MO

Dr. Erik Dubberke, MD, MSPH is an Associate Professor of Medicine, Infectious Diseases Division, and the Director of the Section of Transplant Infectious Diseases at the Washington University School of Medicine in St. Louis, MO.

Dr. Dubberke earned his Medical Degree from the University of Illinois at Chicago, Rockford Campus. He then went on to complete his medicine internship and residency at Washington University School of Medicine and Barnes-Jewish Hospital in St. Louis. He subsequently stayed at Washington University and Barnes-Jewish Hospital to complete his Infectious Diseases fellowship. His interests include transplant infectious diseases, infections in oncology patients, *C. difficile* infection, and healthcare epidemiology.

Dr. Dubberke's research focuses on healthcare epidemiology in transplant and oncology patients, specifically fungal infections, bloodstream infections and *C. difficile* infection. He has studied risk factors, diagnosis, prevention, and outcomes of *C. difficile* infection at Barnes-Jewish Hospital as well as other hospitals that are members of BJC Healthcare. He hopes to determine the influence that antibiotic prescribing patterns and patient-related factors can have on the risk of developing *C. difficile* infection in multiple healthcare settings.

Dr. Dubberke's experience includes didactic lectures and training in infectious diseases and epidemiology, conducting healthcare epidemiology-based research, collaborating with the Centers for Disease Control on study design, developing infection surveillance and prevention guidelines, and professional duties as a hospital epidemiologist. Accomplishments in the field of public health include writing guidelines for the prevention of infections in the healthcare setting and multiple publications of original research.

FACULTY

Richard H. Drew, PharmD, MS, FCCP
Professor and Vice Chair of Research and Scholarship
Campbell University College of Pharmacy and Health Sciences
Associate Professor of Medicine (Infectious Diseases)
Duke University School of Medicine
Durham, NC

Dr. Richard Drew is Professor of Pharmacy and Vice Chair of Research and Scholarship at the Campbell University School of Pharmacy in Buies Creek, North Carolina. In addition, he is Associate Professor of Medicine, Infectious Diseases and Clinical Pharmacist, Infectious Diseases and Internal Medicine at Duke University Medical Center and School of Medicine in Durham, North Carolina.

After completing a Bachelor of Science in Pharmacy at the University of Rhode Island and a Residency in Hospital Pharmacy at Duke University Medical Center, Dr. Drew went on to earn a Master's of Science in Hospital Pharmacy and a Doctor of Pharmacy at the University of North Carolina at Chapel Hill.

Dr. Drew is the author of numerous articles and several book chapters. He serves as a reviewer for several journals including *Clinical Infectious Diseases, Annals of Pharmacotherapy, American Journal of Health-System Pharmacy*, and *Antimicrobial Agents and Chemotherapy*. His chief areas of research interest are gram-positive infections, respiratory tract infections, and information technology. Dr. Drew's research was acknowledged in 2008 when he received the Dean's Award for Research Excellence, Campbell University School of Pharmacy. An active member of several professional associations, Dr. Drew is past-president of the Society of Infectious Diseases Pharmacists.

MRSA and VRE Infections

CHALLENGES

Richard H. Drew, PharmD, MS, FCCP

Professor and Vice Chair of Research and Scholarship
Campbell University College of Pharmacy and Health Sciences
Associate Professor of Medicine (Infectious Diseases)
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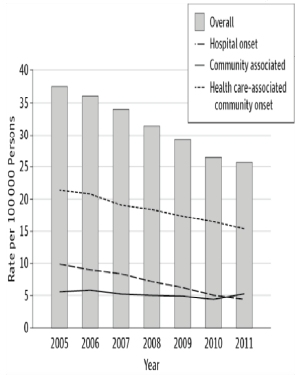
NOTES

MRSA: Incidence and Clinical Impact

- MRSA rates ~50% in many US hospitals
  - HO rates declining in some institutions
  - CA rates steady or increasing
- A leading cause of:
  - Catheter- and device-related infections
  - Skin and skin structure infections
  - Endocarditis
  - Pneumonia (HCAP, VAP)
  - Nosocomial bacteremia
- High attributable mortality/costs
  - 1.9–3.6-fold higher mortality (relative to MSSA)[1]
- Treatment failure rates for invasive infections: 40%–50%



Estimates from US Emerging Infections Program–Active Bacterial Core surveillance (2005-2011)[2]

HO, hospital-onset; CA, community-associated

1.(anon) What Every Health Care Executive Should Know: The Cost of Antibiotic Resistance. Joint Commission Resources Toolkit, 2009 available at: http://www.jointcommission.org/topics/hai_mdro.aspx.
2. Dantes R, et al. *JAMA Intern Med.* 2013;173:1970-8.

Vancomycin-Resistant Enterococci: 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:e75658.**
2. **Rubenstein E, et al. *Crit Care Clin*. 2013;29:841-52.**
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.**

Invasive MRSA: Treatment Controversies

- **Diagnostics**
  - Defining persistent MRSA bacteremia (>7 days vs. 3–4 days)[1,2]
  - Impact of rapid diagnostics on treatment outcomes[6]
- **Drug selection**
  - Role of vancomycin as "drug-of-choice"[1,3,4]
  - Optimal initial therapy for organisms with vancomcyin MIC >1.0 mcg/mL[5]
  - Role of new agents (tedizolid [IV/PO], telavancin, oritavancin, dalbavancin) for invasive/refractory disease
  - Role of novel therapies for treatment failure (carbapenem- and beta-lactam-containing combinations)[7-11]

1.Liu C, et al. *Clin Infect Dis*. 2011;52:e18-33.
2. Kullar R, et al. *Clin Infect Dis*. 2014.doi: 10.1093/cid/ciu583.
3. Kullar R, et al. *Pharmacother*. 2013;33:3-10.
4. Moore CL, et al. *Clin Infect Dis*. 2012;54:51-58.
5. McDaneld PM, et al. *Ann Pharmacother*. 2013;47:1654-65.
6. Trienski TL, et al. *Am J Health-System Pharm*. 2013;70:1908-12.
7. del Río A, et al. *Clin Infect Dis*. 2014. doi: 10.1093/cid/ciu580.
8. Jang HC, et al. *Clin Infect Dis*. 2009;49:395-401.
9. Dhand A, et al. *Clin Infect Dis*. 2011;53:158-163.
10. Moise PA, et al. *Antimicrob Agents Chemother*. 2013; 57:1192-200.
11. Rose WE, et al. *Antimicrob Agents Chemother*. 2012;56:5296-302.

NOTES

Invasive MRSA: Treatment Controversies

- **Drug dosing and administration**
  - Optimal dosing/administration for serious, invasive infections
    - Vancomycin (trough vs. AUC/MIC, continuous infusion)??
    - Daptomycin (6–8 mg/kg/d vs. 10 mg/kg/d)??[1]
- **Role of combination therapy[2]**
  - Rifampin-containing combinations
  - Beta-lactam-containing combinations
  - Continuing role for gentamicin-containing combinations for invasive infections???

1. Falcone M, et al. *Clin Infect Dis*. 2013;57(11):1568-76.
2. Deresinski S. *Clin Infect Dis.* 2009; 49:1072-1079.

VRE: Treatment Controversies

- Optimal drug treatment (linezolid vs. daptomycin vs. ??)[1]
  - Continued role for ampicillin (± gentamicin) for susceptible infections
- Optimal dose for daptomycin therapy[2]
- Role of newer treatment options
- Role/optimal combinations for invasive infections
  - New combinations (ceftriaxone + ampicillin)[4]
  - Optimal therapy for beta-lactam-, high-level aminoglycoside-resistant strains
- Relevance/impact/need to treat VRE bacteriuria[3]

1. Wang DW, et al. *Antimicrob Agents Chemother.* 2013;57:5013-8.
2. Casapao AM, et al. *Antimicrob Agents Chemother.* 2013;57:4190-6.
3. Khair HN, et al. *J Hosp Infect*. 2013;85:183-8.
4. Fernández-Hidalgo N, et al. *Clin Infect Dis*. 2013;56:1261-8.

MRSA/VRE Challenges: Take Home Points

- Varying incidence in institution and community setting
  - HO-MRSA stable/declining, CA-MRSA stable/increasing[1,2,5], VRE rates variable with population
- Multiple organism-, patient-, and treatment-related influences on outcome
- Significant medical and economic consequences of invasive, drug-resistant infections
  - (2013) CDC designates as "…. *serious threats*"[3]
- Need for multiple strategies to prevent and treat[4]
- Significant controversies in management of invasive infections (most notable for MRSA)
  - Optimal drug, combinations, dosing /administration
  - Role/impact of new diagnostics, treatments
  - Definition and management of refractory infections

HO, hospital-onset ; CA, community-associated; VRE, vancomycin-resistant enterococci

1. Dantes R, et al. *JAMA Intern Med.* 2013;173:1970-8.
2. Nguyen DB, et al. *Clin Infect Dis*. 2013;57:1393-1400.
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.
4. Chowers MY, et al. *Infect Control Hosp Epidemiol.* 2009;30:778-781.
5. David MZ, et al. *Clin Infect Dis.* 2014; doi: 10.1093/cid/ciu410.

MRSA and VRE Infections

OPPORTUNITIES

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

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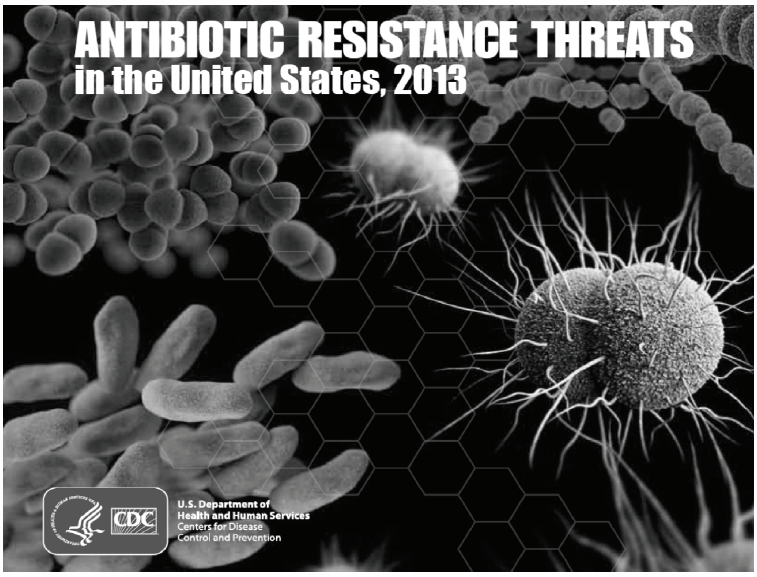


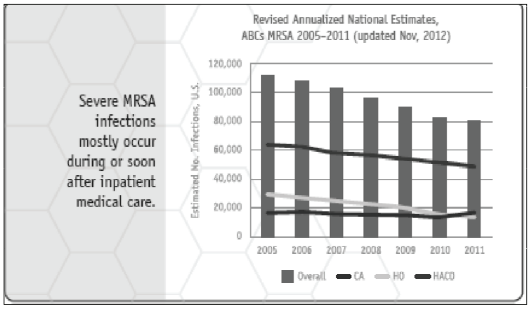
NOTES

MRSA: Opportunities

- Prevalence trend
- New agents
- MRSA pneumonia – antimicrobial agents
- Rapid diagnostics
- Surveillance issues
- Antimicrobial stewardship

MRSA: Decreasing Incidence

- Decreasing Trend (from CDC; 2013)



- Why
  - Better awareness, isolation, treatment

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

NOTES

MRSA: New/Investigational Agents

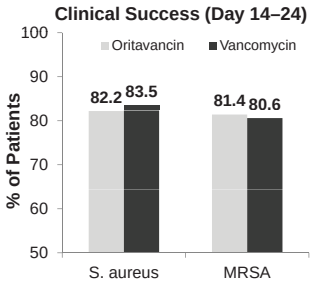
- New Cephalosporins
  - Ceftaroline; ceftobiprole (Europe)
- New Glycopeptides
  - Dalbavancin, Oritavancin
- New Oxazolidinones
  - Tedizolid
- New Fluoroquinolones
  - Delafloxacin and others

MRSA: New/Investigational Agents

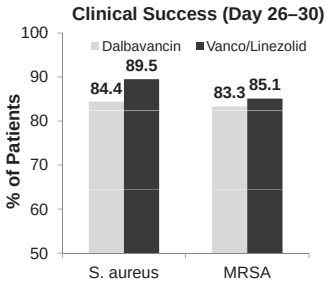
- Others
  - Solithromycin (fluoroketolide)
  - BC-3781 (Pleuromutilin)
  - AFN-12520000
    (Fab I inhibitor targeted for *S. aureus*)
  - Fusidic Acid
  - Topicals

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]



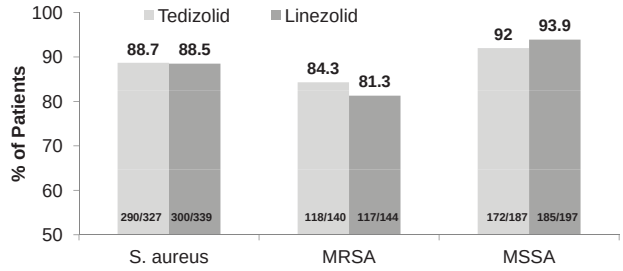
1. Orbactiv™ (oritavancin) for injection Prescribing Information. The Medicines Company, Parsippany, NJ. August, 2014.
2. Dalvance™ (dalbavancin) for injection Prescribing Information. Durata Therapeutics, Chicago, IL. May 2014.

NOTES

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.

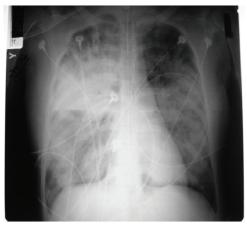
Clinical Response at Post-Therapy Evaluation* by Pathogen

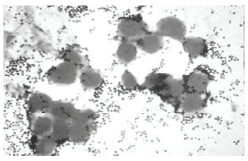


*7-14 days after the end of therapy

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

Case:
30 y/o female presents to ER with fever and respiratory distress; immediate intubation; history of ILI (influenza-like illness)





CXR courtesy of T File MD.

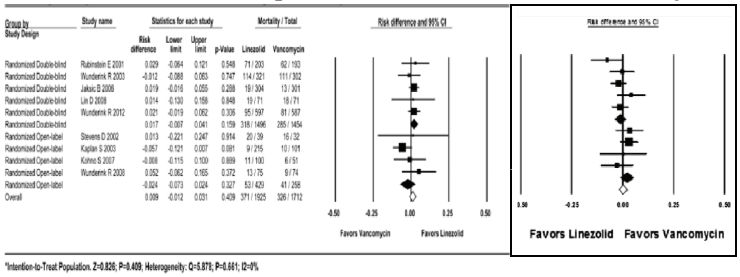
What is your choice of antimicrobial for MRSA?

A. Vancomycin
B. Linezolid

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.

NOTES

MRSA: Vancomycin or Linezolid for Pneumonia?

- Multi-center observational evaluation in VAP

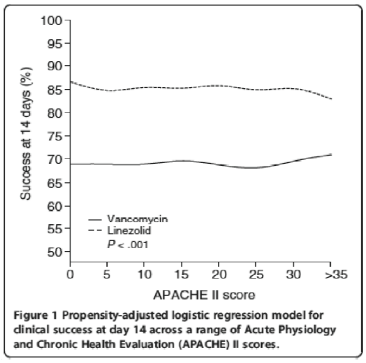
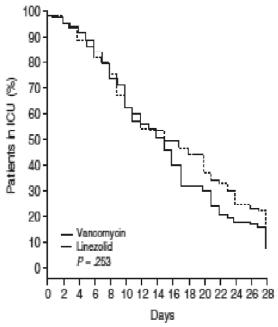


Figure 1 Propensity-adjusted logistic regression model for clinical success at day 14 across a range of Acute Physiology and Chronic Health Evaluation (APACHE) II scores.

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



Mortality

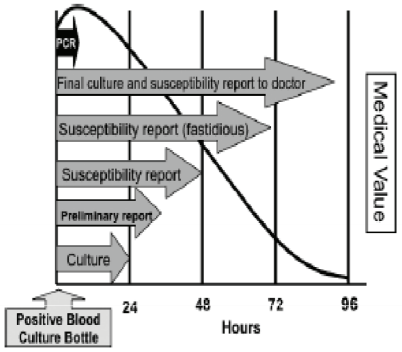
MRSA: Combination Therapy?

- Vancomycin + rifampin
  - Not good for bacteremia
  - Prosthetic body
- Daptomycin plus other 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: Diagnostic testing

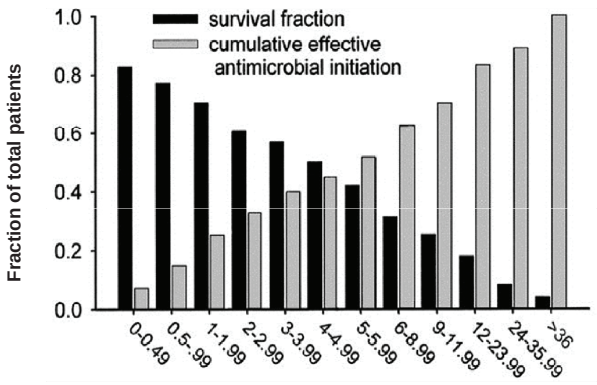
- **Rapid diagnostic tests**
  - **PNA FISH, PCR, MALDI-TOF**



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

NOTES

Effect of Antimicrobial Timing on Survival



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

MRSA: Surveillance

- **Impact of surveillance testing**
  - **Controversial**
  - **Universal vs. targeted decolonization in ICU**

Table 2. Hazard Ratios for Primary and Secondary Trial Outcomes.

Variable	Hazard Ratio (95% CI)			Overall P Value
	Group 1	Group 2	Group 3	
MRSA				
Clinical culture				
As-assigned analysis				
Unadjusted*	0.92 (0.77–1.10)	0.75 (0.63–0.89)	0.63 (0.52–0.75)	0.01
Adjusted	0.92 (0.77–1.10)	0.74 (0.62–0.88)	0.64 (0.53–0.77)	0.02
As-treated analysis, unadjusted	0.93 (0.78–1.11)	0.78 (0.65–0.94)	0.63 (0.52–0.75)	0.01
Randomization to all three groups, unadjusted analysis†	0.93 (0.76–1.13)	0.74 (0.62–0.89)	0.63 (0.52–0.75)	0.02
Randomization strata accounted for, unadjusted analysis	0.93 (0.78–1.11)	0.75 (0.63–0.89)	0.63 (0.52–0.75)	0.01
Mixed medical and surgical ICUs only, unadjusted analysis	0.93 (0.76–1.12)	0.71 (0.59–0.86)	0.57 (0.46–0.71)	0.004
Bloodstream infection				
As-assigned analysis				
Unadjusted	1.23 (0.82–1.85)	1.23 (0.80–1.90)	0.72 (0.48–1.08)	0.11
Adjusted	1.20 (0.80–1.81)	1.19 (0.77–1.84)	0.74 (0.49–1.12)	0.18
As-treated analysis, unadjusted	1.24 (0.82–1.86)	1.34 (0.84–2.15)	0.72 (0.48–1.08)	0.08

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

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.

NOTES

Summary: MRSA Opportunities

- Incidence of MRSA in hospitals is decreasing in general
- Our understanding on the optimal use of current agents is improving
- Several newer agents are available and more investigational agents are on the way
- Rapid diagnostic assays and continued stewardship efforts can improve clinical outcomes

ROUND 2

ESBL-producing and Carbapenem-Resistant Enterobacteriaceae

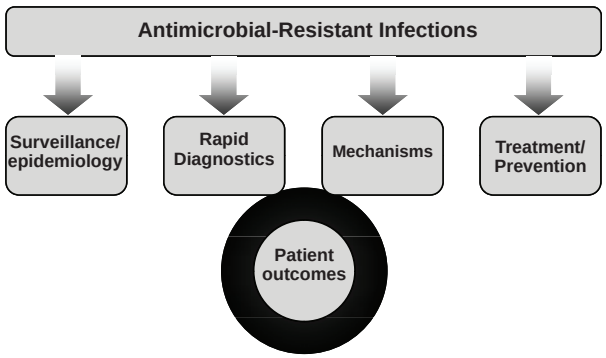
CHALLENGES

George G. Zhanel, PharmD, PhD, FCCP

Professor
Department of Medical Microbiology and Infectious Diseases
College of Medicine, Faculty of Health Sciences, University of Manitoba
Director, Canadian Antimicrobial Resistance Alliance (CARA)
Winnipeg, Canada

NOTES

Canadian Antimicrobial Resistance Alliance (CARA)



www.can-r.ca

Audience Question

I think that ESBL/CRE Enterobacteriaceae is really scary because:

1. *E. coli* is the most common pathogen in my hospital
2. ESBLs are common, clonal and spreading rapidly
3. ESBLs are MDR and also XDR
4. Carbapenemase-producing Enterobacteriaceae are game changers and spreading worldwide
5. Unfortunately all of the above

NOTES

Pathogens Representing a Threat (CDC 2013)

- **Urgent**
  - ***Clostridium difficile* - (CAN-DIFF)**
  - **Carbapenem-resistant Enterobacteriaceae (CRE) – (CANWARD)**
  - **Drug-resistant *Neisseria gonorrhoeae* – (CARING)**

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.

Pathogens Representing a Threat (CDC 2013)

- **Serious**
  - **Extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBLs)**

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.

Challenges

- *E. coli* is the most common pathogen in your hospital
- ESBLs are common, clonal and spreading rapidly
- ESBLs are MDR and also XDR
- Carbapenemase-producing Enterobacteriaceae are game changers and spreading worldwide

MDR, multidrug resistant; XRD, extensively drug resistant.

NOTES

CANWARD 2007-13 Study

George Zhanel, Heather Adam, Mel Baxter, Melissa McCracken, Laura Mataseje, Michael R Mulvey, Barbara Weshnoweski, Ravi Vashisht, Nancy Laing, Sali Biju, James Karlowsky, Kim Nichol, Andrew Denisuik, Alyssa Golden, Philippe Lagacé-Wiens, Andrew Walkty, Frank Schweizer, Jack Johnson, the Canadian Antimicrobial Resistance Alliance (CARA) and Daryl J Hoban

University of Manitoba, Health Sciences Centre, National Microbiology Lab, Winnipeg, Canada and International Health Management Associates (IHMA), Chicago, USA

Zhanel GG, et al. *J Antimicrob Chemother*. 2013;68(Suppl 1):i7-22.
Zhanel GG, et al. Presented at DMID symposium, 2011.
Zhanel GG, et al. *Can J Infect Dis Med Microbiol*. 2009;20(Suppl SA).
www.can-r.ca

Bacteriology of Top 10 Organisms CANWARD 2007–2013 (BLOOD n=14,874)

Ranking	Organism	% of Total
1.	*Escherichia coli*	22.5
2.	*Staphylococcus aureus,* MSSA	13.5
3.	*Klebsiella pneumoniae*	7.4
4.	*Streptococcus pneumoniae*	5.2
5.	*Enterococcus faecalis*	4.2
6.	*Pseudomonas aeruginosa*	3.9
7.	*Staphylococcus aureus,* MRSA	3.9
8.	*Candida albicans*	2.9
9.	*Enterobacter cloacae*	2.3
10.	*Enterococcus faecium*	1.9
Total	**-**	**67.6**

CNS / *S. epidermidis* 7.9

Bacteriology of Top 10 Organisms CANWARD 2007–2013 (URINE, n=4682)

Ranking	Organism	% of Total
1.	*Escherichia coli*	53.3
2.	*Klebsiella pneumoniae*	9.4
3.	*Enterococcus, non-speciated*	8.6
4.	*Enterococcus faecalis*	4.5
5.	*Proteus mirabilis*	4.0
6.	*Pseudomonas aeruginosa*	3.2
7.	*Enterobacter cloacae*	1.9
8.	*Staphylococcus aureus* (MSSA)	1.7
9.	*Klebsiella oxytoca*	1.7
10.	*Streptococcus agalactiae*	1.6
Total	**-**	**89.9**

CNS / *S. epidermidis* 2.1

NOTES

J Antimicrob Chemother 2013; **68** Suppl 1: i57–i65
doi:10.1093/jac/dkt027

Journal of Antimicrobial Chemotherapy

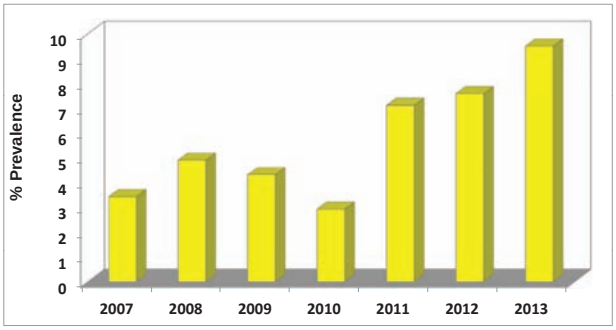
Molecular epidemiology of extended-spectrum β-lactamase-, AmpC β-lactamase- and carbapenemase-producing *Escherichia coli* and *Klebsiella pneumoniae* isolated from Canadian hospitals over a 5 year period: CANWARD 2007–11

Andrew J. Denisuik[1]*, Philippe R. S. Lagacé-Wiens[1,2], Johann D. Pitout[3,4], Michael R. Mulvey[1,5], Patricia J. Simner[6], Franil Tailor[1], James A. Karlowsky[1,7], Daryl J. Hoban[1,7], Heather J. Adam[1,7] and George G. Zhanel[1] on behalf of the Canadian Antimicrobial Resistance Alliance (CARA)†

[1]*Department of Medical Microbiology and Infectious Diseases, University of Manitoba, Winnipeg, Manitoba, Canada R3E 0J9; [2]Department of Microbiology, St Boniface General Hospital/Diagnostic Services of Manitoba, Winnipeg, Manitoba, Canada R2H 2A6; [3]Division of Microbiology, Calgary Laboratory Services, Calgary, Alberta, Canada T2L 2K8; [4]Department of Pathology and Laboratory Medicine, Microbiology, Immunology and Infectious Diseases, University of Calgary, Calgary, Alberta, Canada T2N 4N1; [5]National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, Manitoba, Canada R3E 3R2; [6]Department of Clinical Microbiology, Mayo Clinic, Rochester, Minnesota, USA 55905; [7]Department of Clinical Microbiology, Health Sciences Centre/Diagnostic Services of Manitoba, Winnipeg, Manitoba, Canada R3A 1R9*

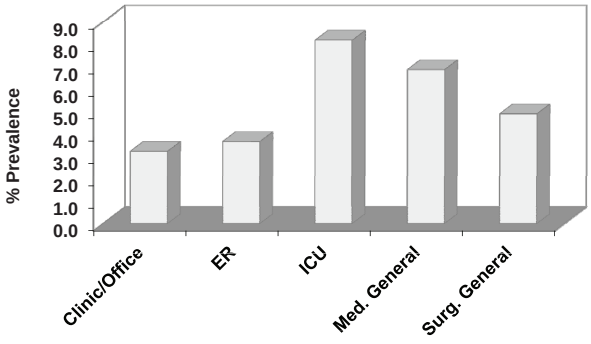
*Corresponding author. Department of Clinical Microbiology, Health Sciences Centre, MS673-820 Sherbrook Street, Winnipeg, Manitoba, Canada R3A 1R9. Tel: +1-204-787-4684; Fax: +1-204-787-4699; E-mail: adenisuik@mymts.net
†Members are listed in the Acknowledgements section.

Increasing Prevalence of ESBL-producing *E. coli* (CANWARD 2007–2013)



Denisuik AJ, et al. Presented at ICAAC 2014, Washington, DC. Abstract #C-778.

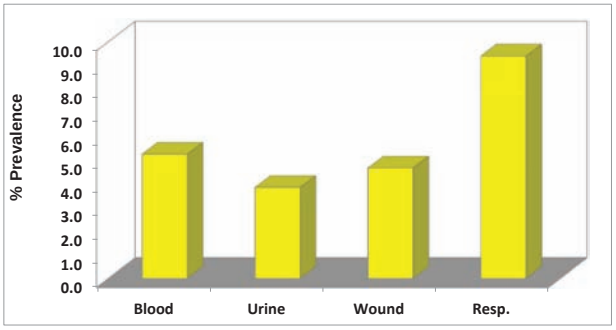
Prevalence of ESBL-producing *E. coli* Isolated from Various Hospital Locations: CANWARD 2007–2013



Denisuik AJ, et al. Presented at ICAAC 2014, Washington, DC. Abstract #C-778.

NOTES

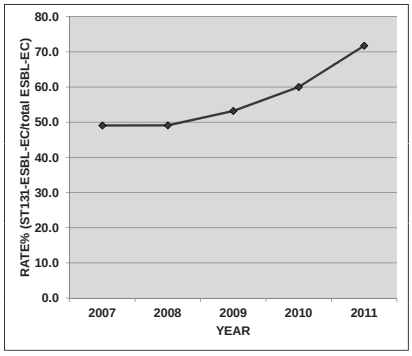
Prevalence of ESBL-producing *E. coli* Isolated from Various Specimen Sources: CANWARD 2007–2013



Denisuik AJ, et al. Presented at ICAAC 2014, Washington, DC. Abstract #C-778.

E. coli O25:H4 ST131 is Spreading Across Canada

The overall prevalence of ST131 ESBL-producing *E. coli* from Canadian hospitals: CANWARD 2007–2011



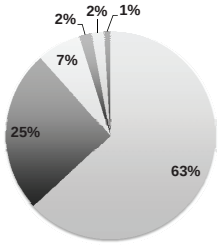
CANWARD Study Year	Total ESBL-*E. coli*	Total ST131 ESBL-*E. coli*	Rate
2007	53	26	49.1
2008	55	27	49.1
2009	47	25	53.2
2010	30	18	60.0
2011	46	33	71.7
P value[a]	0.0368 (0.0179)		

[a]P value comparing ST131 ESBL-EC vs. non-ST131 ESBL-EC: chi-square (one-tailed Fisher's exact test)

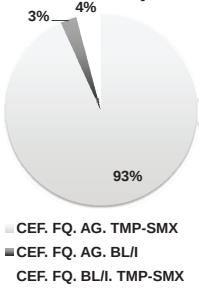
Denisuik AJ, et al. *J Antimicrob Chemother*. 2013;68(Suppl 1):i57-65.

ESBL-producing *E. coli* are MDR or XDR

ESBL *E. coli*: MDR-3 (n=121, 45.0%)



ESBL *E. coli*: MDR-4 (n=83, 30.9%)

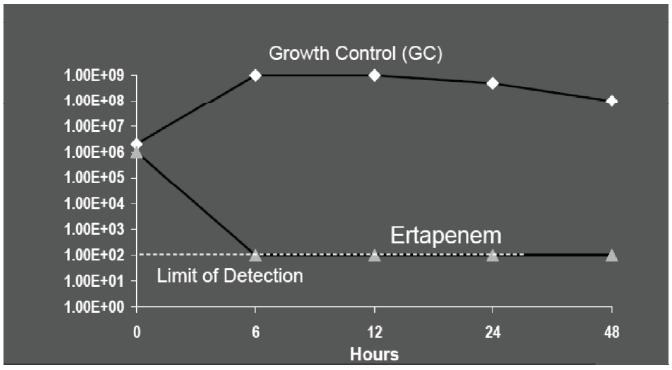


ESBL *E. coli*: XDR (n=8, 3.0%): CEF. FQ. AG. BL/I. TMP-SMX

Denisuik AJ, et al. *J Antimicrob Chemother*. 2013;68(Suppl 1):i57-65.

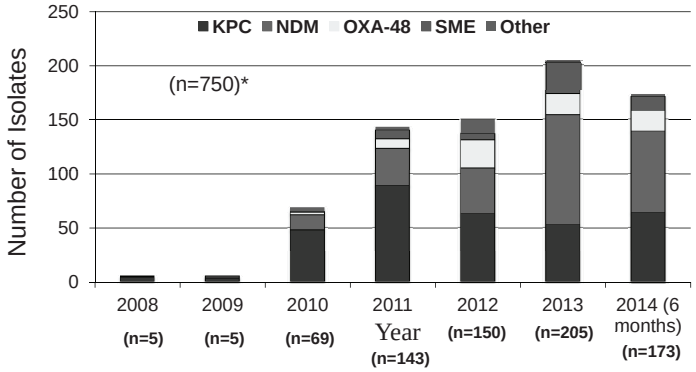
NOTES

Ertapenem Killing of ESBL *E. coli* Simulating *f*T/MIC (1g IV OD, *f*Cmax 14, $t_{1/2}$ 4 hrs) (Strain #64771 CTX-M-15,OXA-1, MIC: Erta 0.25 μg/mL)



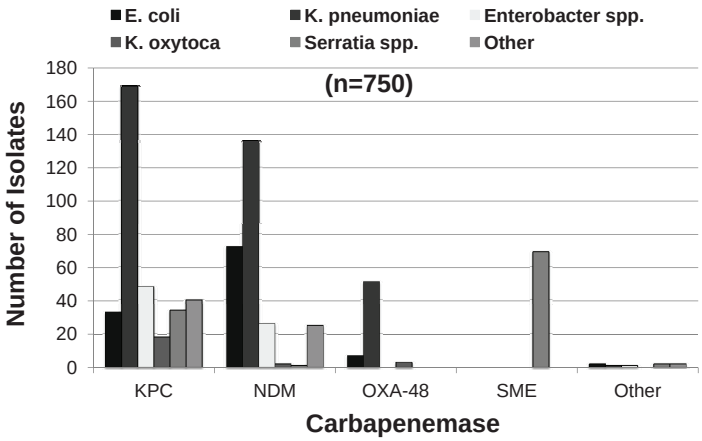
Zhanel GG, et al. *J Antimicrob Chemother.* 2008;61:643-646.

Carbapenemase-Producing Enterobacteriaceae



*One NDM/OXA-48 (2013) and one VIM/KPC (2013) NOT included
Mulvey MR. Public Health Agency of Canada, 2014.

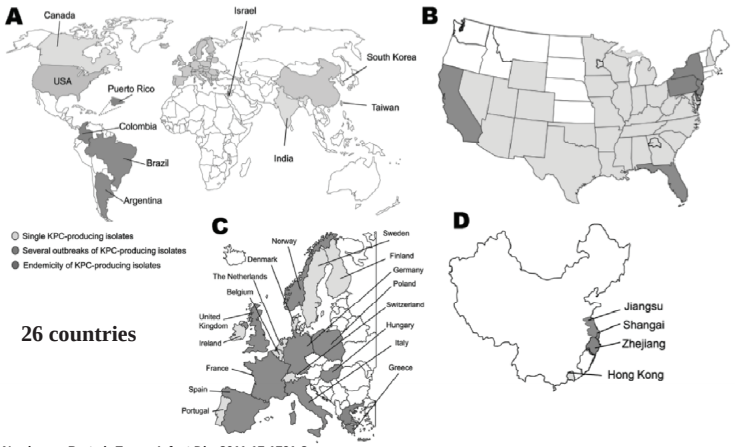
Carbapenemase-Producing Enterobacteriaceae by Species



Mulvey MR. Public Health Agency of Canada, 2014.

NOTES

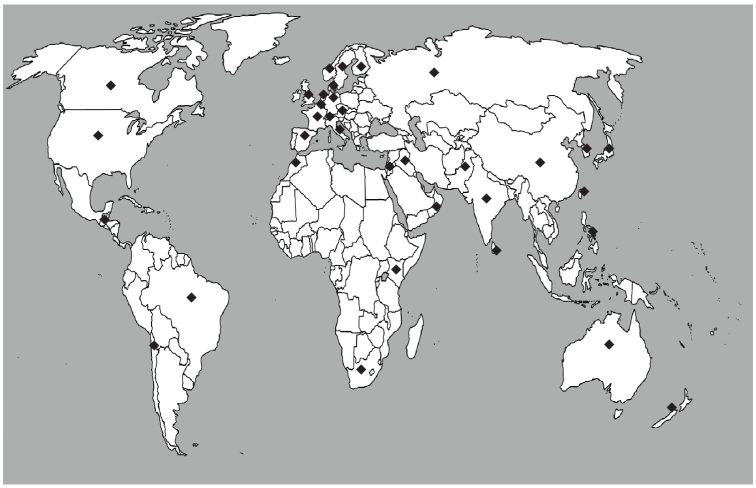
Global Distribution of KPCs



26 countries

Nordmann P, et al. *Emerg Infect Dis*. 2011;17:1791-8.

Global Distribution NDM-1



32 countries; (Kumarasamy et al. *Lancet Infect Dis.* 2010 Sep;10(9):597-602).

Conclusions on Challenges on ESBL-producing and Carbapenem-resistant Enterobacteriaceae

- ESBL's are common, clonal and spreading rapidly
- ESBL are MDR and also XDR
- Carbapenemase-producing Enterobacteriaceae are game changers and spreading worldwide

ROUND 2

ESBL-producing and Carbapenem-Resistant Enterobacteriaceae

OPPORTUNITIES

Richard H. Drew, PharmD, MS, FCCP

Professor and Vice Chair of Research and Scholarship
Campbell University College of Pharmacy and Health Sciences
Associate Professor of Medicine (Infectious Diseases)
Duke University School of Medicine
Durham, NC

NOTES

ESBL/CRE Opportunities: Take Home Points

- Local problem/local solutions
  - Role of local detection / surveillance is KEY
  - "Teamwork" between infection control and antibiotic stewardship
    - Colonization vs. infection
    - Rapid patient identification / communication / investigation / isolation
- Optimal management likely a combination of
  - Optimized dosing regimens of existing agents
  - Rediscovering "old" agents
  - Development of new and investigational agents

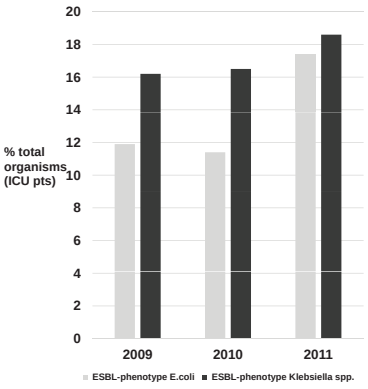
Need for Optimal Antibiotic Dosing

A prospective, multinational pharmacokinetic point-prevalence study (n=361) from 68 hospitals

- Pharmacodynamic targets not consistently achieved
  - 16% did not achieve 50% f $T_{>MIC}$
    - These patients are less likely to have a positive clinical outcome (odds ratio: 0.68, p=0.009).
- Positive clinical outcome associated with increasing target attainment
  - 50% f $T_{>MIC}$ and 100% f $T_{>MIC}$ ratios (odds ratios: 1.02 and 1.56, respectively, p<0.03)
- Targets achieved more frequently with prolonged infusions
  - 20% intermittent bolus did not achieve 50% f $T_{>MIC}$ vs 7% for prolonged infusions

50% f $T_{>MIC}$, 100% f $T_{>MIC}$= free antibiotic concentrations above MIC 50% and 100% of the dosing interval, respectively
Roberts JA, et al. *Clin Infect Dis*. 2014;58(8):1072-83.

ESBL-Producing Organisms: US and Local Perspectives



Sader H, et al. *Diagn Microbiol Infect Dis*. 2014; 78:443-448.

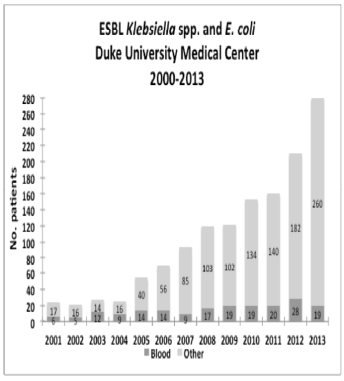
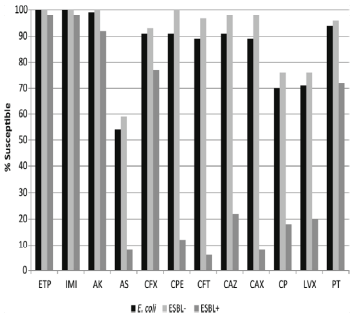


Figure (with permission) courtesy of Kevin Hazen, PhD

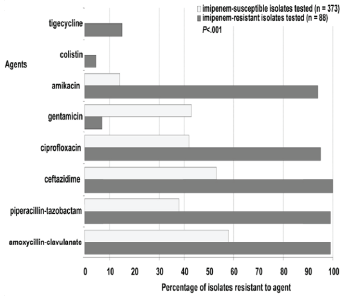
NOTES

ESBL and CRE: Limited Treatment Options

ESBL-positive *E.coli*



Carbapenem-resistant *K. pneumoniae*



all E. coli (n = 516), ESBL-positive (n = 50), and ESBL-negative (n = 466) isolates ETP = ertapenem; IMI = imipenem; AK = amikacin; AS = ampicillin-sulbactam; CFX = cefoxitin; CPE = cefepime; CFT = cefotaxime; CAZ = ceftazidime; CAX = ceftriaxone; CP = ciprofloxacin; LVX = levofloxacin; PT = piperacillin-tazobactam. Hawser SP, et al. *J Infect*. 2014;68:71-6.

Hussein K, et al. *Infect Control Hosp Epidemiol* . 2009;30(7):666-671.

ESBL-producing Pathogens: Limited Treatment Options

- Carbapenems
  - Remain the most reliable class and associated with mortality benefit[1,6]
- Cephamycins (eg, cefoxitin, cefotetan)
- Cefepime
  - TEM and SHV-type ESBLs usually appear susceptible
  - May require higher doses (2gm q8h)[2,3]
  - Inferior to carbapenems[6]
- Fosfomycin (PO only in US)
  - Use generally restricted to urinary tract infections
- Tigecycline[8]
- Piperacillin-tazobactam[4,5]
  - TEM and SHV-type ESBLs usually appear susceptible, but AmpC enzymes, non-ESBL enzymes or additional ESBLs may not inhibited by BLI tazobactam[7]
  - Inoculum effect makes interpretation of in vitro results problematic[7]
  - Role limited primarily to susceptible organisms, UTI
  - May require higher doses for efficacy[5]

1.Paterson DL, et al. *Clin Infect Dis*. 2004;39:31-7.
2. Goethaert K, et al. *Clin Microbiol Infect*. 2006;12:56-62.
3. Chopra T, et al. *Antimicrob Agents Chemother*. 2012;56:3936-42.
4.Gavin PJ, et al. *Antimicrob Agents Chemother*. 2006;50:2244-7.
5. Rodríguez-Baño J, et al. *Clin Infect Dis*. 2012;54:167-74.
6. Lee NY, et al. *Clin Infect Dis*. 2013;56:488-95.
7. Perez F, Bonomo RA. *Clin Infect Dis*. 2012;54:175-7.
8. Kelesidis T, et al. *J Antimicrob Chemother*. 2008;62:895-904.

Carbapenem Resistance in Enterobacteriaceae: Enzymes or Alphabet Soup?

Enzyme	Common genetic platform	Species distribution in Enterobacteriaceae	Geographic distribution
KPC (*Klebsiella pneumoniae* carbapenemase)	*K pneumoniae* sequence type 258, various plasmids types, transposon Tn*4401*x	*K pneumoniae*, *Escherichia coli*, *Enterobacter* species, diverse Enterobacteriaceae	Endemic in the United States, Greece, Israel, Italy, Puerto Rico, China, and South America
NDM (New Delhi metallo-beta-lactamase)	Various plasmid types	*K pneumoniae* and *E coli* predominantly, diverse Enterobacteriaceae	Indian subcontinent and the Balkan region, and around the world
OXA-48 (oxacillinase)	IncI/M-type plasmid	*K pneumoniae* predominantly, diverse Enterobacteriaceae	Southern and Western Europe, Turkey and North Africa; rare in the United States
VIM (Verona integron-encoded metallo-beta-lactamase)	Gene cassettes in class 1 integrons	*K pneumoniae* predominantly	Common in Italy, Greece, and the Far East, sporadic globally
IMP	Gene cassettes in class 1 integrons	*K pneumoniae* predominantly	Common in the Far East and South America, sporadic globally
SME	Chromosome	*Serratia marcescens*	Sporadic in North America and South America

Picture from http://www.leegiobbie.com/Alphabet-Soup----My-Designations.10.htm (accessed 7/31/14)
Table from: Perez F, et al. *Clev Clin J Med*. 2013;80:225-233.

NOTES

CRE Treatment Options

Monotherapy
- Colistin, polymyxin
- Tigecycline
- Aminoglycosides
- Carbapenems
- Fosfomycin
- Doxycycline ?????*

Combination
- Colistin-tigecycline
- Colistin-carbapenem
- Fosfomycin-carbapenem
- Fosfomycin-aminoglycoside
- Carbapenem-aminoglycoside
- Dual carbapenem**
- Tigecycline-gentamicin

*uncomplicated (?asymptomatic) bacteriuria only (Zubair A, et al. *Antimicrob Agents Chemother.* 2014;58:3100–4.)
**ertapenem plus either doripenem or meropenem (Giamarellou H, et al. *Antimicrob Agents Chemother.* 2013;57:2388-90.)
Gaibani P, et al. *J Antimicrob Chemother.* 2014;69:1856-65.
Tascini C, et al. *Antimicrob Agents Chemother.* 2013;57:3990–3.
Tumbarello M, et al. *Clin Infect Dis.* 2012;55:943–50.
Qureshi ZA, et al. *Antimicrob Agents Chemother.* 2012;56:2108–13.

Old Drugs for MDR Gram-negative Pathogens: Fosfomycin and Polymyxins

- **Fosfomycin[1-6]**
  - Susceptibility is highly organism-specific
    - MDR *P. aeruginosa* 511/1693 (30.2%)
    - MDR *A. baumannii* 3/85 (3.5%)
  - Generally restricted to combination therapy
    - Rapid treatment-emergent resistance as monotherapy
  - Not available for IV use in the US
  - Data limited for treatment of serious, non-urinary tract infections
- **Polymyxins (Colistin and Polymyxin B) [7]**
  - Optimal dosing unknown for most patients
    - Less predictable with colistin
  - Nephrotoxicity and neurotoxicity (may be treatment-limiting)
  - Adjunctive use of colistin aerosol for pulmonary infections ???

1. Falagas M, et al. *Int J Antimicrob Agents*. 2009;34:111-120.
2. Pontikis K, et al. *Int J Antimicrob Agents*. 2014;43:52-59.
3. Bulik CC, et al. *Antimicrob. Agents Chemother.* 2011;55:3002–4.
4. Hong JH, et al.. *Antimicrob. Agents Chemother.* 2013;57:2147-53.
5. Giamarellou H, et al. *Antimicrob Agents Chemother.* 2013;57:2388-90.
6. Pontikis K, et al. *Int J Antimicrob Agents.* 2014;43:52-59.
7. Nation R. et al. Clin Infect Dis. 2014:59:88-94.

Carbapenems for CRE????

Observational study (2009 to 2010) in patients (n=205) with CR-*K. pneumoniae* bacteremia

- Treatment
  - Combination of active therapy (n=103), monotherapy (one active drug) (n=72) or no active drug (n=12)
- Outcome
  - Mortality
    - 28-day mortality: 40%.
    - Higher for monotherapy than combo (44.4% versus 27.2%; p=0.018)
    - Lowest (19.3%) with carbapenem-containing combo
  - Predictors of mortality (HR, 95%CI):
    - Ultimately fatal disease (3.25; 1.51 to 7.03; p=0.003)
    - Rapidly fatal underlying diseases (4.20; 2.19 to 8.08; p<0.001)
    - Septic shock (2.15; 1.16 to 3.96; p=0.015)
    - Monotherapy (2.08; 1.23 to 3.51; p=0.006)

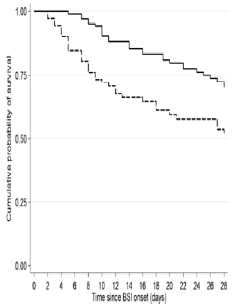


FIG 1 Kaplan-Meier survival estimates of patients with carbapenemase-producing *K. pneumoniae* bloodstream infections according to treatment regimens: combination therapy (continuous line) versus monotherapy (dotted line). P = 0.003 (log rank test).

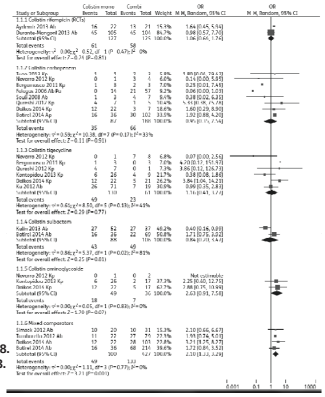
Daikos GL, et al. *Antimicrob. Agents Chemother.* 2014,58:2322-8.

NOTES

CRE: Combo vs Monotherapy

- Lack of controlled trials
  - Selection bias, confounders in observational studies
    - Most involve blood isolates of *K. pneumoniae*
    - Mechanisms for resistance vary among isolates (KPC, MBL, or OXA)
- Monotherapy (gentamicin) may be useful in UTIs
  - CRE asymptomatic bacteriuria may not require therapy [3]
- Considerations for need for combination therapy
  - Prior therapy to predict resistance
  - Risks for treatment failure
  - Ability to tolerate drugs used in combination regimen

All-cause mortality for colistin monotherapy versus combination therapy[1]



1. **Paul M, et al. *J Antimicrob Chemother.* 2014;doi:10.1093/jac/dku168.**
2. **Falagas ME, et al. *Antimicrob Agents Chemother* . 2014;58:654-663.**
3. **Qureshi ZA, et al. *Antimicrob Agents Chemother.* 2014; 58:3100–4.**

CRE: Treatment-Specific Considerations

- Colistin-aminoglycoside combination
  - potential for added nephrotoxicity
- Tigecycline-containing regimen
  - limited utility in bloodstream infections
- Carbapenem-containing regimens
  - best when carbapenem MIC low
  - consider prolonged infusions, higher doses
  - ertapenem use generally restricted to combination carbapenems[1-3]
- Polymyxin-containing combinations
  - optimal dosing unknown (?role for TDM)
  - prepreparation-specific PK and administration issues
  - nephrotoxicity and neurotoxicity
- Aminoglycosides
  - gentamicin may be preferred against KPC- and VIM-producing organisms[4,5]
  - consider high-dose, extended-interval administration to optimize PD

1. **Bulik CC, et al. *Antimicrob. Agents Chemother*. 2011;55:3002–4.**
2. **Hong JH, et al. *Antimicrob. Agents Chemother*. 2013;57:2147-53.**
3. **Giamarellou H, et al. *Antimicrob Agents Chemother*. 2013;57:2388-90.**
4. **Souli M, et al. *Clin Infect Dis*. 2010;50:364–73.**
5. **Castanheira M, et al. *Microb Drug Resist*. 2010;16:61–65.**

MDR Gram-negative Treatment Options: Drugs In Later Phase Clinical Development*

- Beta-lactam/beta-lactamase inhibitors
  - ceftolozane/tazobactam[1]
  - ceftazidime/avibactam[2]
  - ceftaroline/avibactam[5]
  - aztreonam/avibactam
    - active against ESBL, KPC, MBLs
- Carbapenem/beta-lactamase inhibitors
  - imipenem-cilastatin/MK-7655[3]
  - RPX2014 (biapenem)/RPX7009
- Semi-synthetic aminoglycosides
  - plazomicin[4,6]
  - arbekacin

Except as noted, these agents lack *in vitro* activity against MBLs

Indicates *in vitro* activity only
***not intended to be a comprehensive list nor description. Based on www.clinicaltrials.gov (accessed 7/25/14)**

1. Zhanel GG, et al. *Drugs*. 2014;74(1):31-51. 2. Zhanel GG, et al. *Drugs*. 2013;73:159-77. 3. Hirsch E, et al. *Antimicrob. Agents Chemother*. 2012;56:3753-7. 4. Zhanel G et al. *Expert Rev Anti Infect Ther*. 2012;10:459-73. 5. Castanheira M, et al. Antimicrob. Agents Chemother. 2012;56::4779-85. 6. Galani I, et al. *J Chemother*. 2012;24:191–4.

NOTES

ESBL/CRE Opportunities: Summary

- Spread can be minimized through:
  - Local detection and surveillance
  - "Teamwork" between infection control and antibiotic stewardship
- Optimal management through a combination of:
  - Optimized dosing regimens of existing agents
  - Rediscovering "old" agents
  - Use of combination therapy(?)
  - Development of new and investigational agents

HISTORY OF MEDICINE

"Doctor, I have an ear ache."

2000 B.C. - "Here, eat this root."

1000 B.C. - "That root is heathen, say this prayer."

1850 A.D. - "That prayer is superstition, drink this potion."

1940 A.D. - "That potion is snake oil, swallow this pill."

1985 A.D. - "That pill is ineffective, take this antibiotic."

2000 A.D. - "That antibiotic doesn't work. Here, eat this root!"

(modified) author unknown

ROUND 3

Pseudomonas aeruginosa

CHALLENGES

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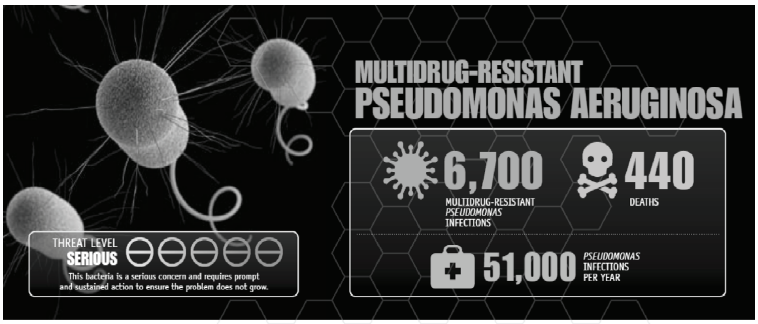
Professor, Internal Medicine
Master Teacher; Chair, Infectious Disease Section
Northeast Ohio Medical University
Rootstown, OH

NOTES

MDR *Pseudomonas* Challenges

- Prevalence
- Resistance mechanisms
- Clinical consequences
- Therapy

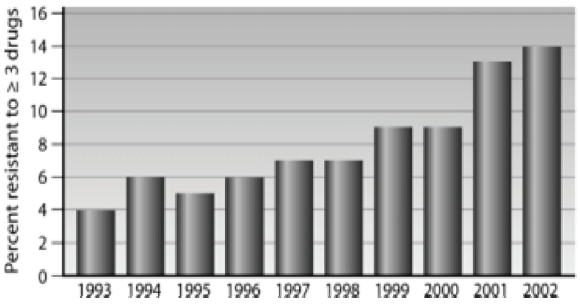


Pseudomonas aeruginosa is a common cause of healthcare-associated infections including pneumonia, bloodstream infections, urinary tract infections, and surgical site infections.

	Percentage of all *Pseudomonas aeruginosa* healthcare-associated infections that are multidrug-resistant	Estimated number of infections	Estimated number of deaths attributed
Multi-drug resistant *Pseudomonas aeruginosa*	13%	6,700	440

U.S. Department of Health and Human Services Centers for Disease Control and Prevention

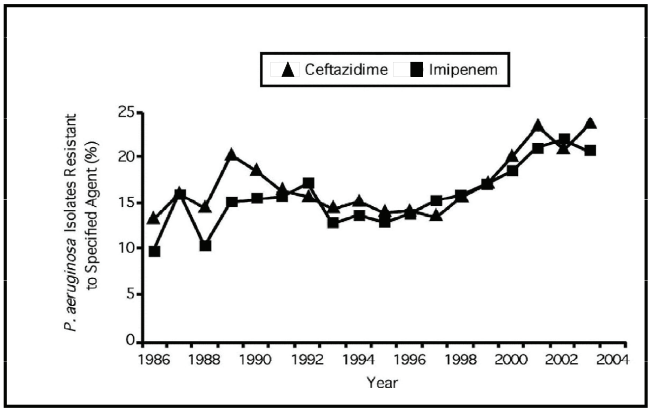
MDR *Pseudomonas*: Prevalence



Lister PD et al. *Clin Microbiol Rev*. 2009;22:582-610.

NOTES

P. aeruginosa Increasing Drug Resistance

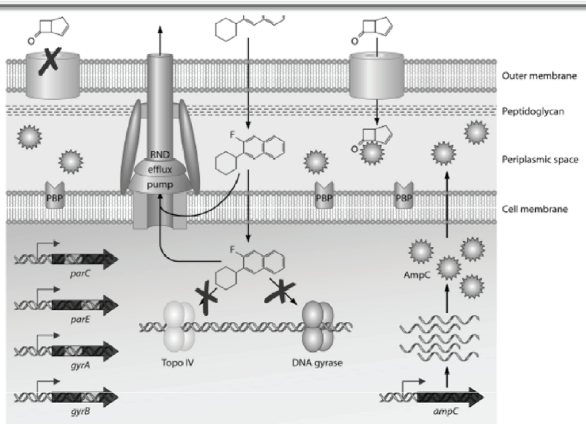


Rahal JJ. *Clin Infect Dis*. 2009;49(Suppl 1):S4-S10.

Pseudomonas Resistance

- Beta-lactams
  - Porin
  - Beta-lactamases
- Fluoroquinolones
  - Chromosomal genes – gyrA/B or parC/E
  - Efflux pumps
- Aminoglycosides
  - AME
- Often multiple mechanisms

Pseudomonas Resistance



Lister PD, et al. *Clin Microbiol Rev*. 2009;22:582-610.

NOTES

Audience Question

Which of the following characteristics is more likely associated with MDR than non-resistant *P. aeruginosa*?

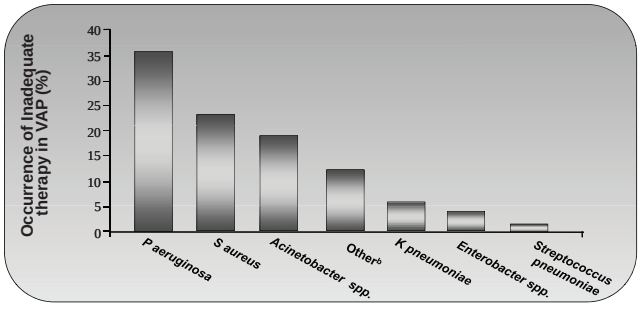
1. Presence of COPD
2. HIV infection
3. Genitourinary source
4. Respiratory source
5. Prior use of anti-pseudomonal antimicrobials

Characteristics of Nosocomial *P. aeruginosa* (Barcelona, 2005–6)

	Non resistant (n=149)	MDR (n=134)
Chronic condition	No significant difference	No significant difference
Mechanical ventilation	6%	23% (p<0.001)
Prior hospitalization (X1)	19%	15.7%
Prior ICU	12%	25.4% (p <0.001
Prior non-antipseudo ABX	40%	19% (p<0.001)
Prior antipseudo ABX	13%	70% (p<0.001)
LOS prior to detection	12.9 d	21.9 d (p<0.001)
Severity score = 4	22%	45%
Mortality	12.8%	24.6% (p=0.02)

Morales E, et al. *BMC Health Serv Res*. 2012;12:122.

Pathogens Associated with Inadequate Therapy[a] in VAP



[a]Definition of inadequate therapy:[1]
i. Microbiologic documentation of infection not being effectively treated at the time of identification
ii. Absence of agents directed at a specific class of microorganisms
iii. Administration of an agent to which the pathogen was resistant

[b]*Haemophilus influenzae*, *Escherichia coli*, *Proteus mirabilis*, *Serratia marcescens*, and *Legionella* spp.

1. Kollef MH. *Clin Infect Dis*. 2000;31(Suppl 4):S131-S138.

NOTES

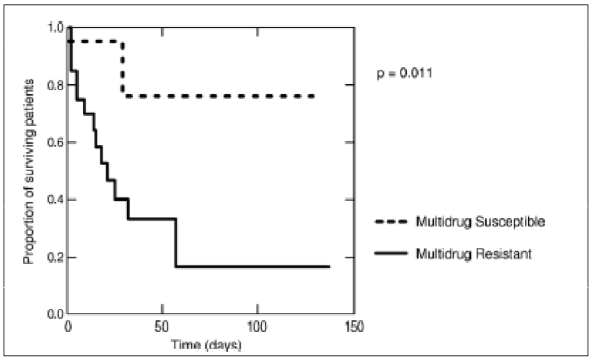
MDR *Pseudomonas* – Impact

Outcome endpoint	% of patients			*P* value[c]
	Overall (n = 109)	MDS[a] (n = 84)	MDR[b] (n = 25)	
30-day mortality	18.3	11.9	40.0	0.003
Hospital (all-cause) mortality	25.7	16.7	56.0	<0.001
Infection-related mortality	19.3	9.5	52.0	<0.001
Inappropriate empirical therapy	14.7	6.0	44.0	<0.001
Mean length of hospital stay associated with bacteremia (days) ± SD	18.7 ± 25.0	16.5 ± 23.6	26.4 ± 28.3	0.120

[a] MDS, multidrug susceptible.
[b] MDR, multidrug resistant.
[c] By comparison of the multidrug-susceptible and multidrug-resistant cohorts.

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

MDR *Pseudomonas* – Impact



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

Pseudomonas: Mortality Risk Factors

Variable	Odds Ratio (P value)
Antimicrobial Resistance	6.8 (0.003)
APACHE II >22	29 (<0.001)
Immunosuppression	5 (0.012)

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

NOTES

MDR *Pseudomonas*: Therapy

- What is optimal therapy?
  - Mono vs. combination therapy
  - Prolonged duration of administration?
  - Use of antimicrobial aerosols for VAP?
  - Duration of antimicrobial therapy

Pseudomonas aeruginosa

OPPORTUNITIES

Erik R. Dubberke, MD, MSPH

Associate Professor of Medicine
Director, Section of Transplant Infectious Diseases
Washington University School of Medicine
St. Louis, MO

NOTES

Audience Question

What do you think provides the most hope for dealing with MDR *Pseudomonas*?

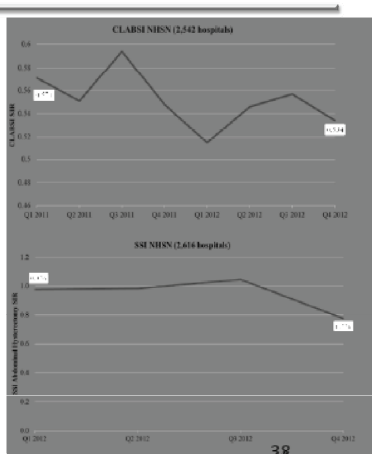
1. Infection prevention and control
2. Rapid diagnostics
3. New antimicrobials
4. Biologics
5. All of the above

Opportunities

- Infection prevention and control
- Rapid diagnostics
- Colistin/polymyxin
- New antimicrobials
- Novel approaches

Infection Prevention and Control

- Reductions in catheter-associated bloodstream infections and surgical site infections
- "Horizontal" approaches to prevent MDRO spread
  - Chlorhexidine bathing



McGann. Roadmap to Eliminate HAI: 2013 Action Plan Conference. Washington DC, Sept 25, 2013.

NOTES

Rapid Diagnostics

- Organism identification
- Susceptibility/resistance mechanisms
- More rapid targeting of antimicrobial therapy
  - Avoid unnecessarily broad antimicrobials
  - Improve coverage if resistance present
- Isolation of patients with MDRO

Diagnostics (Examples)

Available

- MALDI-TOF
  - Rapid organism identification
- PCR
  - Rapid organism identification
  - Rapid identification of specific resistance genes

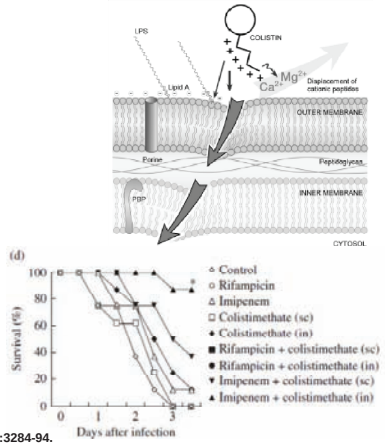
Under development

- Automated microscopy
  - Organism identification in 1 hour
  - Phenotypic susceptibility results in 5 hours

Burnham CA, et al. *J Clin Microbiol.* 2014;114:976-81.

Colistin/Polymyxin

- Optimize dosing
  - Potential for under-dosing if normal renal function
- Combination therapy
  - Ceftazidime
  - Ciprofloxacin
  - Carbapenems
- Enhanced cidal activity in vitro, even if resistant



Aoki N, et al. *J Antimicrob Chemother.* 2009;63:534-42.
Martis N, et al. *J Infect.* 2014;69:1-12.
Garonzik SM, et al. *Antimicrob Agent Chemother.* 2011;55:3284-94.

NOTES

New Antimicrobials

- Ceftolozane/tazobactam
  - Most active agent in vitro (eight others evaluated)
  - $MIC_{50/90}$:
    - All 0.5/2 μg/mL (n=1971)
    - MDR 2/8 μg/mL (n=310)
    - XDR 4/16 μg/mL (n=175)
- Ceftazidime/avibactam
  - Most active agent in vitro
    - 96.9% MIC of <8 μg/mL (n=1967)
  - $MIC_{50/90}$ of meropenem non-susceptible isolates
    - 4/16 μg/mL (87.3% <8 μg/mL) (n=354)
- Imipenem/MK-7655
  - Imipenem-susceptible: MIC 1–2 μg/mL to 0.25–0.5 μg/mL
  - Imipenem-nonsusceptible: MIC 16–64 μg/mL to 1–4 μg/mL

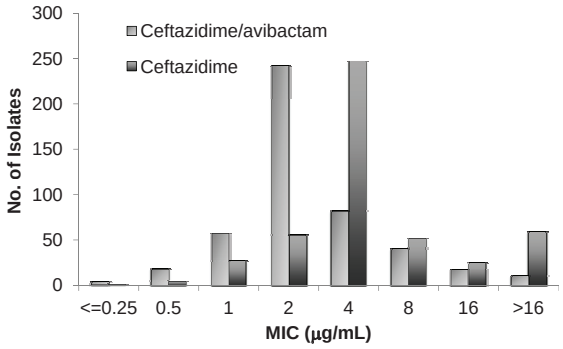
XDR, extensively drug resistant (nonsusceptible to ≥1 agent in all but ≤2 antimicrobial classes)
Farrell DJ, et al. *Antimicrob Agents Chemother.* 2013;57:6305-10.
Sader HS, et al. *Antimicrob Agents Chemother.* 2014;58:1684-92.
Livermore DM, et al. *J Antimicrob Chemother.* 2013;68:2286-90.

Ceftolozane/tazobactam: In vitro Activity Against *P. aeruginosa*

Agent	All Isolates (n=1971) $MIC_{50/90}$	MDR (n=310) $MIC_{50/90}$	XDR (n=175) $MIC_{50/90}$
Ceftolozane/ tazobactam	0.5/2	2/8	4/16
Ceftazidime	2/32	32/>32	32/>32
Cefepime	4/16	16/>16	>16/>16
Meropenem	0.5/8	8/>8	8/>8
Piperacillin/ tazobactam	8/>64	>64/>64	>64/>64
Aztreonam	8/>16	>16/>16	>16/>16
Levofloxacin	0.5/>4	>4/>4	>4/>4
Gentamicin	≤1/8	4/>8	8/>8
Colistin	1/2	1/2	1/2

MDR, multidrug resistant; XDR, extensively drug resistant
Farrell DJ, et al. *Antimicrob Agents Chemother.* 2013;57:6305-10.

Ceftazidime/avibactam in vitro Activity Against *P. aeruginosa* (n=470)



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

NOTES

Novel Approaches

- Active immunization
  - IC43: surface proteins, 2 injections 7 days apart
    - Phase 2 study with mortality benefit (22% vs. 40%)
    - Phase 2/3 study ended prematurely for futility, but will restart because mortality benefit seen on interim analysis
- Passive immunization
  - KB001: human Fab fragment against PcrV
    - Phase 2: prevent pneumonia 32% vs. 60% (p=NS)
  - KBPA-101: monoclonal against LPO-O-polysaccharide of IATS O11
    - Phase 2: 13/13 pneumonia resolution with three doses versus 0/4 with single dose
- Bacteriophages

Vincent JL. *Fut Microbiol*. 2014;9:457-63.
Henry M, et al. *Antimicrob Agents Chemother*. 2013;57:5961-8.

Conclusions

- Healthcare-associated infection rates are declining
  - Fewer infections due to *Pseudomonas*
- Rapid diagnostics may improve antimicrobial prescribing
- Optimize/combination colistin/polymyxin
- Some new antimicrobials/inhibitors in pipeline
- Non-antimicrobial preventatives/therapeutics under development

ROUND 4

Clostridium difficile

CHALLENGES

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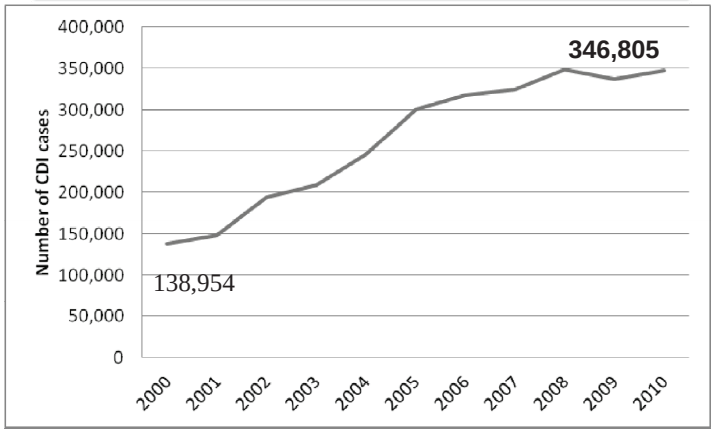
NOTES

Audience Question

At your hospital, *C. difficile* infection (CDI) is seen as:

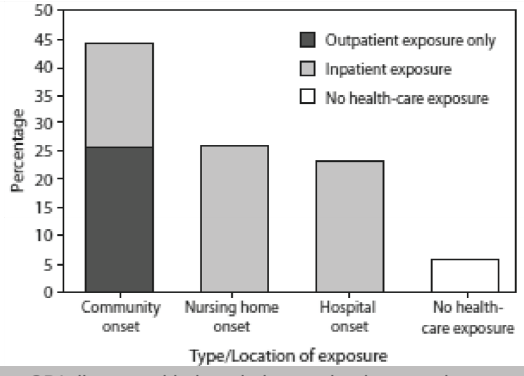
1. No big deal
2. On the radar screen
3. Problematic, but there are other, worse healthcare-associated infections
4. Public enemy #1

CDI Incidence Continues to Increase



Source: AHRQ HCUP data. Available at: http://www.hcup-us.ahrq.gov/reports/statbriefs/sb124.pdf.

CDI Onset in Nursing Homes and the Community



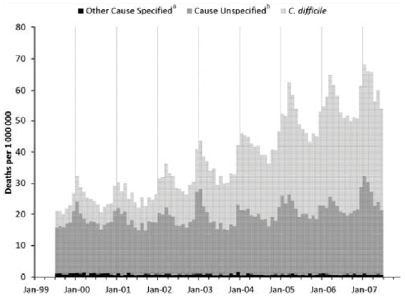
Including CDI diagnosed in hospitals, nursing homes, the community, and recurrent CDI: likely over 700,000 CDI cases in US in 2010

CDC. *MMWR*. 2012;61(09):157-162.

NOTES

Increasing CDI Severity

- **Sherbrooke, Quebec, outbreak, 2003**
  - **16.7% attributable mortality**
- **St. Louis, endemic, 2003**
  - **5.7% attributable mortality**
  - **2.2 times more likely readmitted**
  - **1.6 times more likely discharged to LTCF**



Pépin J, et al. *Can Med Assoc J*. 2005;173:1037-42.
Dubberke ER, et al. *Clin Infect Dis*. 2008;46:497-504.
DubberkeER, et al. *Emerg Infect Dis*. 2008;14:1031-8.
Hall AJ, et al. *Clin Infect Dis*. 2012;55:216-23.

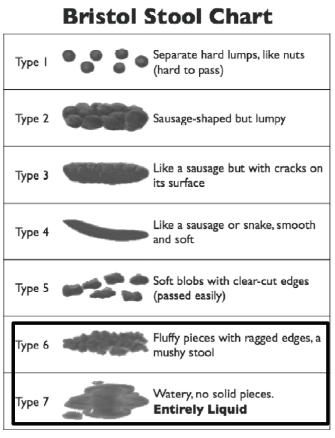
Optimal Method to Diagnose CDI Not Known

- Flaws in Diagnostic Literature
  - Lack of clinical data
  - Detection of *C. difficile*, not diagnosis of CDI
    - Enhanced sensitivity for *C. difficile* detection may decrease specificity for CDI
- Focus on sensitivity and specificity
  - Not negative predictive value and positive predictive value

Peterson LR, et al. *Clin Infect Dis*. 2007;45:1152-60.

Enhanced Sensitivity May Decrease Specificity

- Including clinically significant diarrhea in gold standard:
  - No impact on sensitivity
  - Specificity of NAATs decreased from ~98% to ~89% ($p < 0.01$)
    - Positive predictive value decreased to **~60%** (25% drop)



Dubberke ER, et al. *J Clin Microbiol*. 2011;49:2887-93.

NOTES

CDI Treatment

- Historically two main treatments
  - Metronidazole
  - Oral vancomycin
- Response rates equal until 2000
  - Initial cure in 85% to 95%
  - Recurrence in 15% to 30%
- Metronidazole response rate after 2000: <80%

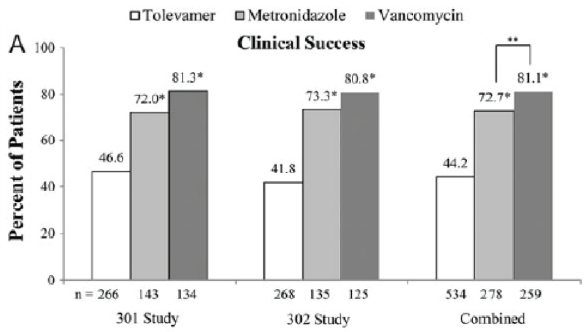
Vancomycin Vs. Metronidazole for Severe CDI

First double blind trial of metronidazole vs. vancomycin

Disease severity	No. of patients cured/ no. of patients treated (%)			
	Mtz group	Vm group	Total	P[a]
Mild	37/41 (90)	39/40 (98)	76/81 (94)	.36
Severe	29/38 (76)	30/31 (97)	59/69 (86)	.02
All	66/79 (84)	69/71 (97)	135/150 (90)	

Zar FA, et al. *Clin Infect Dis*. 2007;45: 302-7.
Lawrence SJ, et al. *Clin Infect Dis*. 2007;45:1648.

Metronidazole Also Inferior For Non-Severe CDI



Vancomycin superior to metronidazole on multivariable analysis, including controlling for clinical severity (p=0.013)

Johnson S, et al. *Clin Infect Dis*. 2014;59:345-354.

NOTES

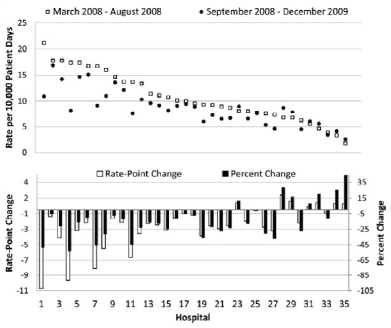
Recurrent CDI

- CDI recurrence is a significant challenge
- Rates of recurrent CDI:
  - 20% after first episode
  - 45% after first recurrence
  - 65% after two or more recurrences

Cohen SH, et al. *Infect Control Hosp Epidemiol.* 2010;31(5):431-455.

Limitations to CDI Prevention in Hospitals

- Preventability of endemic CDI is unknown
- Very limited data outside of outbreak settings
  - Recommendations appear less effective
- Floor effect: ~4–6 cases / 10,000 patient-days



Koll BS, et al. *J Healthc Qual*. 2014;36:35-45.

Conclusions

- CDI incidence and severity have increased
- Optimal diagnostic method not known
- Metronidazole less effective
- New prevention methods needed

ROUND 4

Clostridium difficile

OPPORTUNITIES

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NOTES

Audience Question

Which of the Following are Current/Future Solutions to CDI in Your Hospital?

1. New drugs that target *C. difficile* and not normal colonic flora
2. Monoclonal antibodies (Toxins A and B)
3. Colonic restoration
   - Fecal transplant
   - RePOOPulate
   - Probiotics
4. Vaccines
5. All of the above

Pathogens Representing a Threat (CDC 2013)

- **Urgent**
  - ***Clostridium difficile***
  - **Carbapenem-resistant Enterobacteriaceae (CRE)**
  - **Drug-resistant *Neisseria gonorrhoeae***

Opportunities

- Vancomycin versus metronidazole controversy
- Understanding the importance of the colonic microbiome
- Colonic restoration (fecal transplant)
- Infection control
- Investigational agents

NOTES

IDSA/SHEA *Clostridium difficile* Guidelines 2010

Clinical Definition	Clinical Data	Recomm Treatment	Strength Evidence
Initial episode (mild-moderate)	Leukocytosis (WBC ≤15,000) Scr < 1.5x baseline	**Metronidazole** 500mg TID PO 10-14days	A-I
Initial episode (severe)	Leukocytosis (WBC >15,000) Scr ≥ 1.5x baseline	**Vancomycin** 125mg QID PO 10-14days	B-I

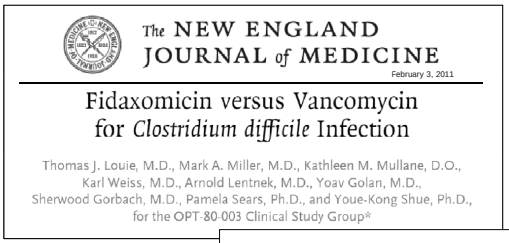
Cohen SH, et al. *Infect Control Hosp Epidemiol.* 2010;31(5):431-455.

Vancomycin vs. Metronidazole for CDI

- Vancomycin is superior to metronidazole for CDI
  - >>> severe
  - >> moderate
  - > mild
- Why
  - Resistance ???
  - PK/PD ???

Wilcox MH. *Clin Infect Dis.* 2014;59(3):355-7.

Landmark Clinical Trial Results Published in International Journals


The NEW ENGLAND JOURNAL of MEDICINE
February 3, 2011

Fidaxomicin versus Vancomycin for *Clostridium difficile* Infection

Thomas J. Louie, M.D., Mark A. Miller, M.D., Kathleen M. Mullane, D.O., Karl Weiss, M.D., Arnold Lentnek, M.D., Yoav Golan, M.D., Sherwood Gorbach, M.D., Pamela Sears, Ph.D., and Youe-Kong Shue, Ph.D., for the OPT-80-003 Clinical Study Group*


THE LANCET Infectious Diseases
8 February 2012

Fidaxomicin versus vancomycin for infection with *Clostridium difficile* in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial

Prof Oliver A Cornely MD, Prof Derrick W Crook MD, Prof Roberto Esposito MD, André Poirier MD, Michael S Somero MD, Prof Karl Weiss MD, Pamela Sears PhD, Prof Sherwood Gorbach MD, for the OPT-80-004 Clinical Study Group

NOTES

Efficacy Outcomes for Clinical Cure and Recurrence Rate Endpoints in Subpopulations at Risk

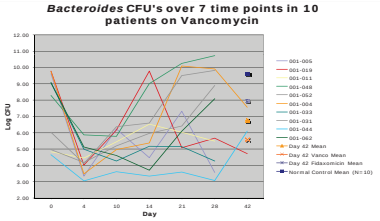
Recurrence Risk Factor	% Clinical Cure			% Recurrence			Reference
	VAN	FIDAX		VAN	FIDAX		
Overall	90.1	91.9	NI	24.6	13.0	p<.05	Mullane DDW '11
Concomitant antibiotics	79.4	90.0	p<.05	29.0	17.0	p<.05	Mullane CID '11
Cancer	74.0	85.1	P=.065	29.6	13.5	P=.018	Cornely JCO '13
Renal failure (CrCl<30)	76.0	73.9	NI	31.6	14.7	P=.09	Mullane AJN '13
Prior CDI	92.0	94.0	NI	35.5	19.7	p<.05	Cornely CID '12
Age>65	93.0	94.0	NI	32.0	14.0	p<.05	Louie AGS '11

NI = Non-inferior

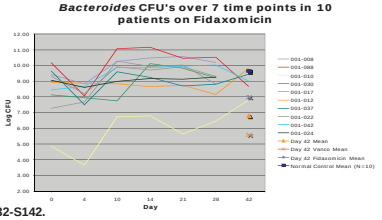
Mullane KM, et al. *Clin Infect Dis*. 2011;53:440-7.
Cornely OA, et al. *J Clin Oncol*. 2013;31:2493-2499.
Cornely OA, et al. *Clin Infect Dis*. 2012;55(Suppl 2):S154-61.
Mullane KM, et al. *Am J Nephrol*. 2013;38:1-11.

Vancomycin Kills Major Components of the Normal Flora Thought to Prevent *C. difficile* Infection

Vancomycin 125mg QID in 10 CDI pts



Fidaxomicin 200mg BID in 10 CDI pts



Louie TJ, et al. *Clin Infect Dis*. 2012;55(Suppl 2):S132-S142.

Fecal Transplantation for CDI

- Random assignment
  - Vancomycin PO 500 mg QID x 14 days
  - Vancomycin PO 500 mg QID x 14 days plus bowel lavage
  - Vancomycin PO 500 mg TID x 4 days, followed by bowel lavage and subsequent infusion of a solution of donor feces through a ND tube

The **primary endpoint** was the resolution of diarrhea associated with *C. difficile* infection without relapse after 10 weeks.

van Nood E, et al. *N Engl J Med*. 2013;368:407-15.

NOTES

Fecal Transplantation for CDI

- 81% (13/16) in infusion group had resolution of CDI after the first infusion
- 31% (4/13) in vancomycin alone had resolution ($p<0.001$)
- 23% (3/13) in vancomycin with bowel lavage
- Increased bowel diversity similar to that in healthy donors, with an increase in *Bacteroides* and *Clostridium* spp. and a decrease in *Proteobacteria* spp.

van Nood E, et al. *N Engl J Med*. 2013;368:407-15.

Clostridium difficile Comes from Diverse Sources

- Sept 2007 – Mar 2011 whole genome sequencing on all symptomatic patients with CDI in healthcare/community settings in Oxfordshire (UK)
- 1250 cases CDI
- 45% were genetically distinct from previous cases

- **Conclusion**:
  - Both symptomatic patients and also genetically diverse sources play a role in the transmission of CDI

Eyre DW, et al. *N Engl J Med*. 2013;369:1195-1205.

Investigational Agents for CDI

- Toxin binders
- Narrow-spectrum agents
  - Surotomycin
  - SMT19969
- Monoclonal antibodies (Toxins A and B)
- Colonic restoration
  - Fecal transplant
  - RePOOPulate
  - Probiotics
- Vaccines
- Phage tail-like particles

NOTES

Conclusions on Opportunities in CDI

- Vancomycin is better than metronidazole
- We now know the importance of the colonic microbiome
- Antimicrobial stewardship and infection control are important
- Investigational agents on the way

Audience Question

Which organism(s) do you consider to be the most challenging?

1. MRSA/VRE
2. ESBL/CRE
3. *P. aeruginosa*
4. *C. difficile*

SUPPLEMENTAL MATERIAL

Old Drugs for MDR Gram-Negative Pathogens: Polymyxins

	Colistin (Polymyxin E)	Polymyxin B
Prodrug (requiring activation)	yes (20-25% to active colistin, high variability)	no
Kinetic highlights		
Clearance (primary route)	CMS (prodrug)-renal; colistin-other	other
Therapeutic serum concentrations		
Timing	slow (need to convert to active drug)	rapid
Obtainable w/ high CrCl	no	yes
Intra-patient variability	high	low
Urinary concentration	high (both as CMS and colistin)	low
Dosing/Administration		
Adult *	5 mg/kg loading dose x 1, then 2.5 mg/kg q8h–q24h (adjusted for renal function)	2.5 mg/kg (25,000 IU/kg) loading dose x 1, then 1.5 mg/kg (15,000 IU/kg) q12h
Pediatric *	5 mg/kg loading dose x 1, then 2.5 mg/kg q8h–q24h (adjusted for renal function)	2.5 mg/kg loading dose x 1, then 1.5 mg/kg (25,000 IU/kg) q12h
Need for loading dose	yes	no
Adjust for renal function	yes	no
Dilutions /infusions	dilute in 100 mL NS, administer over 30 min	dilute in D5W to 1000–1667 IU/mL. Infuse over 60–90 min

IU, international units
*Per package insert. (modified, with permission) courtesy of Christina Sarubbi, PharmD
Nation R, et al. *Clin Infect Dis*. 2014;59:88-94.

Package insert dosing may not provide optimal/adequate drug exposure

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.

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

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Upcoming Educational Activity

Online Learning Activity

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

www.vemcomeded.com

Attending IDWeek?

Please join us for a CME/CPE symposium, ***Challenges and Opportunities in Managing Serious Bacterial Infections: A Role for Pathogen-Directed Therapy***, on Wednesday, October 8, 2014, 8:00 – 10:00 PM at the Pennsylvania Convention Center Room 118ABC.

Register at: 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 Annual Meeting.