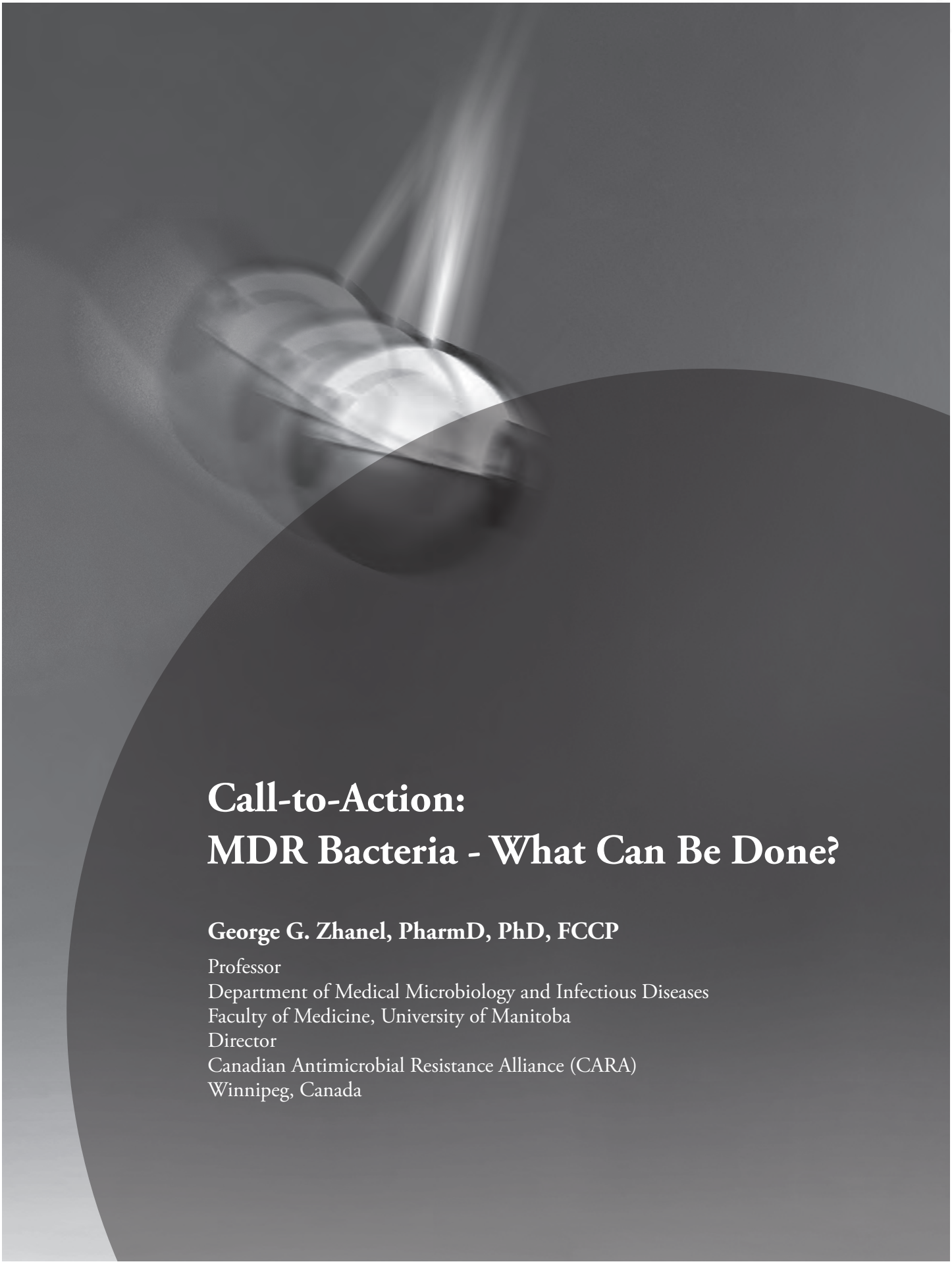

Call-to-Action: MDR Bacteria - What Can Be Done?

George G. Zhanel, PharmD, PhD, FCCP

Professor
Department of Medical Microbiology and Infectious Diseases
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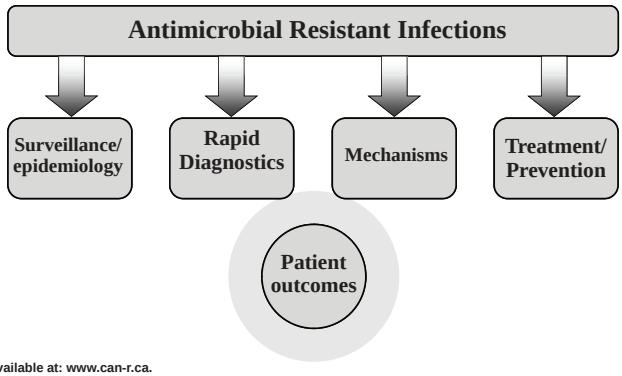
Director
Canadian Antimicrobial Resistance Alliance (CARA)
Winnipeg, Canada

Canadian Antimicrobial Resistance Alliance (CARA)



Available at: www.can-r.ca.

www.can-r.ca

CANWARD 2007-12 Study

George Zhanel, Heather Adam, Mel Baxter, Melissa McCracken, Laura Mataseje, Michael R Mulvey, Barbara Weshnoweski, Ravi Vashisht, Nancy Laing, James Karlowsky, Kim Nichol, Andrew Denisuik, Alyssa Golden, Patricia Simner, Franil Tailor, 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

JAC symposium 2012.
DMID symposium 2011.
CJIDMM symposium 2009.
www.can-r.ca

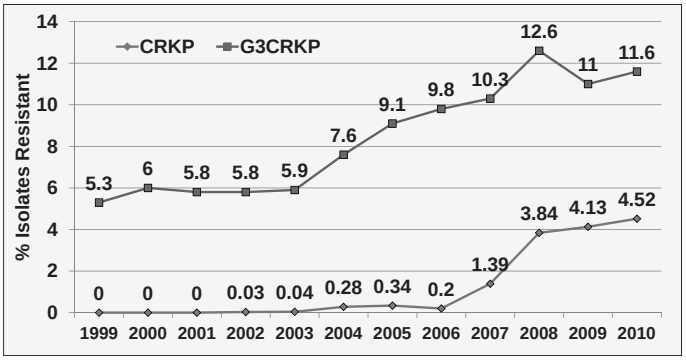
Bacteriology of Top 10 *Pathogens* in Canadian Hospitals (n=27,123) CANWARD 2007-2012

Ranking	Organism	% of Total
1.	*Escherichia coli*	20.1
2.	*Staphylococcus aureus*	20.0
3.	*Pseudomonas aeruginosa*	8.0
4.	*Streptococcus pneumoniae*	6.9
5.	*Klebsiella pneumoniae*	6.1
6.	*Enterococcus species*	6.0
7.	*CoNS/S.epidermidis*	4.4
8.	*Haemophilus influenzae*	3.8
9.	*Enterorobacter cloacae*	2.3
10.	*Streptococcus agalactiae*	1.6
Total	-	79.2

Zhanel GG, et al. *J Antimicrob Chemother.* 2013;68(Suppl1):7-22.

Rising Incidence of MDR Pathogens

Retrospective analysis of ~500,000 *K. pneumoniae* isolates from throughout the US



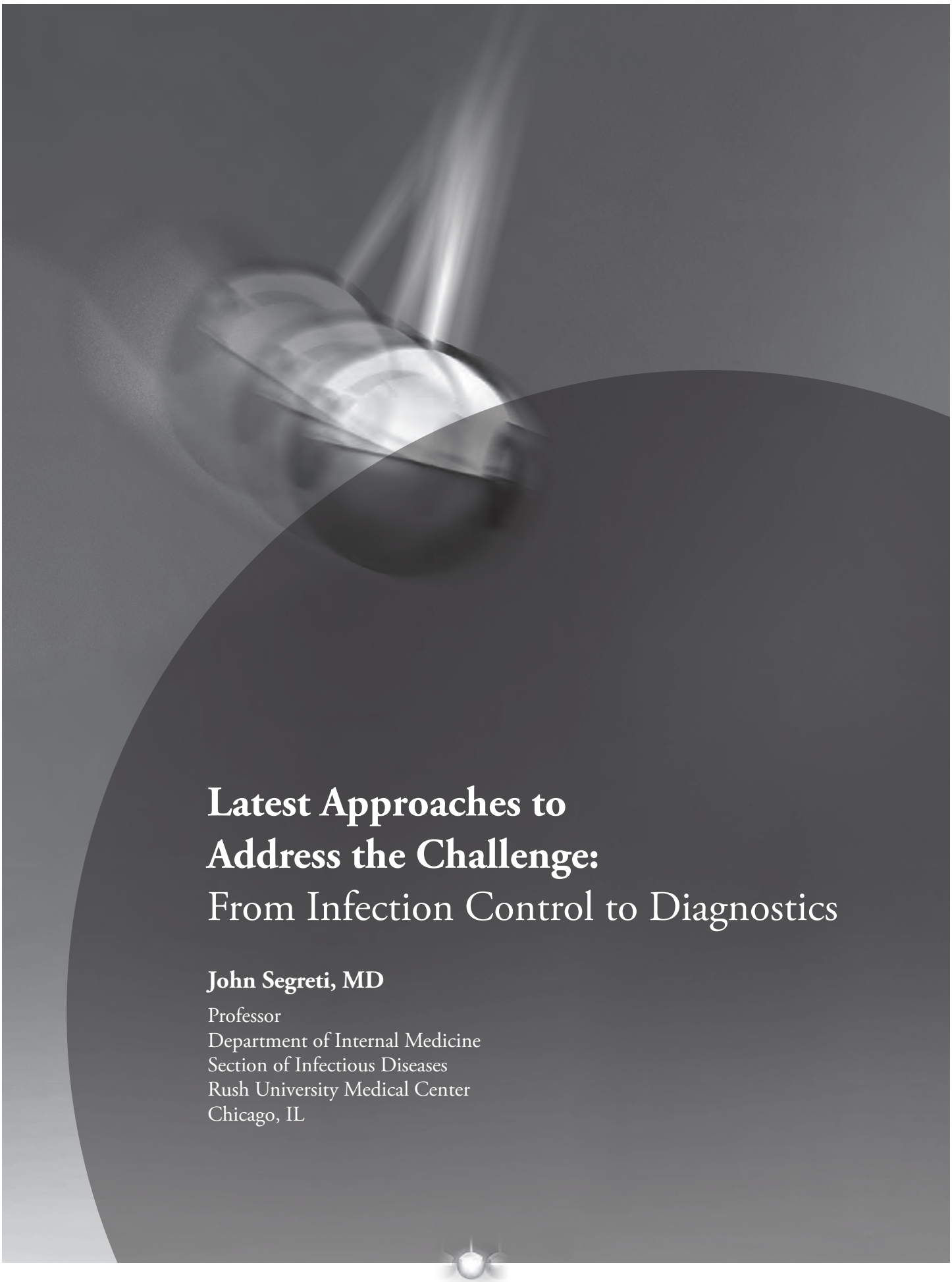
CRKP, carbapenem-resistant *K. pneumoniae*; G3CRKP, third-generation cephalosporin-resistant *K. pneumoniae*
Braykov NP, et al. *Infect Control Hosp Epidemiol.* 2013;34:259-268.

Potential Solutions to Combat MDR Pathogens

1. **Surveillance**
2. **Infection prevention/control**
3. **Rapid diagnostics**
4. **Antimicrobial stewardship**
5. **New antimicrobials**

Spellberg B, et al. *Clin Infect Dis*. 2011;52(Suppl5):397-428.

Notes



Latest Approaches to Address the Challenge:
From Infection Control to Diagnostics

John Segreti, MD

Professor
Department of Internal Medicine
Section of Infectious Diseases
Rush University Medical Center
Chicago, IL

What are the Challenges of MDR Infections?

- Pandemic spread in hospitals and beyond
  - LTACHs
  - Nursing homes
  - Community
- Clinical and economic costs
- Difficult to diagnose in a timely manner
- Lack of effective agents, especially against CRE
- Growing patient pool vulnerable to infections

The Impact of MDR Infections

- Infection with resistant pathogens is associated with negative health outcomes
  - Increased mortality/morbidity
  - Longer length of ICU and hospital stay
  - Higher healthcare costs
- Few new antibiotic classes under development
  - Highlights the need to optimize use of existing strategies while we await new classes of antimicrobials

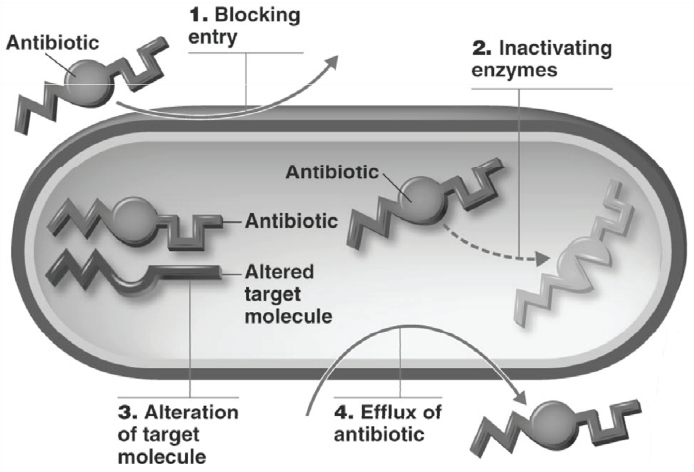
Gaynes R, et al. *Clin Infect Dis.* 2005;41:848-854.
Spellberg B, et al. *Clin Infect Dis.* 2004;38:1279-1286.
Lautenbach E, et al. *Infect Control Hosp Epidemiol.* 2006;27:893-900.
Cosgrove S, et al. *Clin Infect Dis.* 2006;42:S82-S89.

Risk Factors for Resistant Organisms

- Previous antibiotic treatment
- Previous hospital admission
- Nursing home
- Comorbidities – cardiovascular disease, HIV, chronic respiratory disease, kidney disease
- Hemodialysis
- Home wound care (past 30 days)
- Family member with resistant organism

Herrero FS, et al. *Semin Respir Crit Care Med.* 2012;33;220-231.

Resistance to Antibiotics



Control Strategies

- Prevent selection of resistant bacteria
  - Limit use of antibiotics
  - Effectively kill bacteria
- Prevent transmission of resistant bacteria
- Prevent infections

Antimicrobial Stewardship

- A marriage of infection control and antimicrobial management
- Selection of drugs for your formulary based not only on efficacy, but also considering issues surrounding collateral damage
- The primary goal is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, such as toxicity, selection of pathogenic organisms, and emergence of resistance
  - The secondary goal is to reduce costs without sacrificing quality of care
- One strategy is to optimize antimicrobial selection and dosing based on the causative organism, the site of infection, and pharmacokinetics-pharmacodynamics

Dellit TH, et al. *Clin Infect Dis*. 2007;44:159-177.

CMS Measures and Stewardship

- Should be complementary to improve patient outcomes
  - Appropriate use per guidelines
  - Avoid overuse of ABX (e.g. antipseudomonal ABX if no pseudomonas indications)
- Improving Compliance and Stewardship
  - Order sets; Electronic Record (CPOE) to list only appropriate ABX
  - Clearly define CAP vs. HCAP
    - e.g., from ECF, prior hospitalization in 3 months
  - Define indications for anti-Pseudomonas Therapy
    - Structural lung disease (bronchiectasis); COPD with repeated ABX or steroids; any suggestion of *Pseudomonas*

File TM Jr, Gross PA. *Clin Infect Dis.* 2007;44:942-944.
Dellit TH, et al. *Clin Infect Dis.* 2007;44:159-177.
Shorr A, Owens R. *Am J Health-Syst Pharm.* 2009;66(Suppl 4):S8-14.

De-escalation

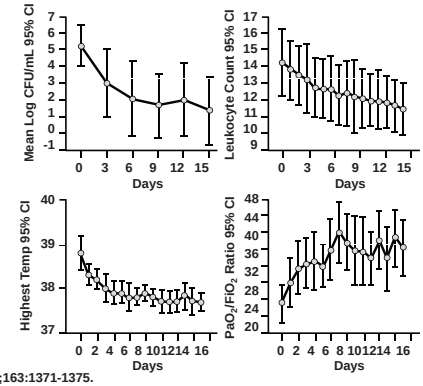
- Initial broad-spectrum therapy followed by narrowing or discontinuation of antimicrobials after obtaining susceptibility results and observing the patient's clinical course[1]
- Balances the need to provide broad-spectrum treatment with the need to limit antimicrobial exposure, in order to minimize the emergence of resistance[2]
- Endorsed recently in the IDSA/SHEA antimicrobial stewardship guidelines[3]

1. Park DR, et al. *Respir Care.* 2005;50:932-952.
2. Kollef MH. *Drugs.* 2003;63:2157-2168.
3. Dellit TH, et al. *Clin Infect Dis.* 2007;44:159-177.

Resolution of Infectious Parameters After Antimicrobial Therapy in Patients With Ventilator-associated Pneumonia

- **DESIGN**
  - N=27
  - Prospective cohort study
  - Ventilated patients with VAP
- **PRIMARY OBJECTIVE**
  - Define time to resolution of VAP symptoms after initiation of antibiotics
    - Symptoms:
      - Temp
      - PaO_2/FIO_2
      - Leukocyte count

MAJOR RESULTS:

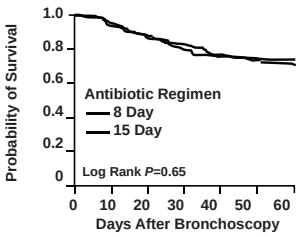


Dennesen P, et al. *Am J Respir Crit Care Med.* 2001;163:1371-1375.

Comparison of 8 vs. 15 Days of Antibiotic Therapy for Ventilator-associated Pneumonia in Adults

- **DESIGN**
  - N=401
  - Prospective, randomized, double-blind
  - Ventilated patients with VAP
- **PRIMARY OBJECTIVE**
  - To determine if 8 days is as effective as 15 days of antibiotic therapy
- **OUTCOMES**
  - Patients who received a short course had neither excess mortality nor excess pulmonary infection recurrence

Kaplan-Meier Estimates of the Probability of Survival



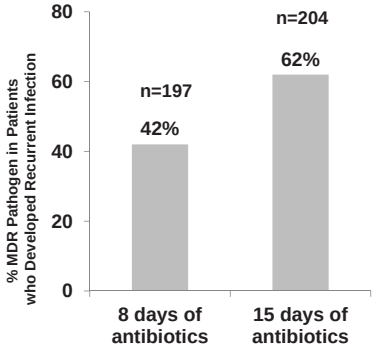
No. at Risk							
8 d ABX	197	187	172	158	151	148	147
15 d ABX	204	194	179	167	157	151	147

Probability of survival is for the 60 days after ventilator-associated pneumonia onset as a function of the duration of antibiotic administration.

Chastre J, et al. *JAMA*. 2003;290:2588-2598.

Comparison of 8 vs. 15 Days of Antibiotic Therapy for Ventilator-associated Pneumonia in Adults

- **OUTCOMES**
  - No significant differences in:
    - Number of days alive without mechanical ventilation or organ failure
    - New antibiotic therapy during the study period
    - Duration of ICU stay
    - Mortality rate at day 60
  - Resistant pathogens emerged more frequently in patients with recurrent pulmonary infection who had received antibiotics for 15 days



P=0.04

Chastre J, et al. *JAMA*. 2003;290:2588-2598.

Meta-analysis on Procalcitonin to Guide Antibiotic Use

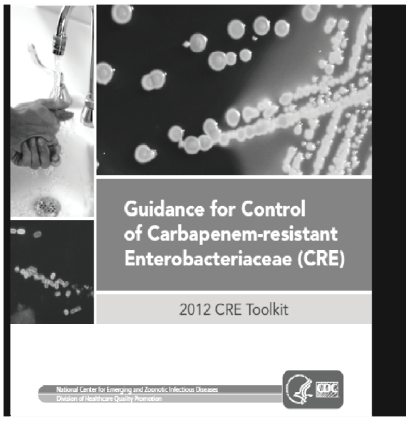
- Identified clinical trials in which patients with ARI were assigned to receive antibiotics based on a procalcitonin algorithm or usual care
- Patient data from 4221 adults with ARIs in 14 trials were analyzed
- Procalcitonin guidance was not associated with increased mortality or treatment failure in any clinical setting or ARI diagnosis.
- Total antibiotic exposure per patient was significantly reduced from 8 [5–12] to 4 [0–8] days; adjusted difference in days, −3.47 [95% CI, −3.78 to −3.17]) and across all clinical settings and ARI diagnoses.
- Further high-quality trials are needed in critical care patients.

Schuetz P, et al. *Clin Infect Dis*. 2012;55(5):651–62.

Prevent Transmission

- Use appropriate infection control precautions
- Universal gloving?
- Active surveillance for colonization?
- Decolonization?
- Environmental cleaning
- WASH YOUR HANDS!!!!

CDC: 2012 CRE Toolkit



Available at: http://www.cdc.gov/hai/organisms/cre/cre-toolkit/

Automated Hand Hygiene Monitoring

- Direct observation of hand hygiene by trained observers is considered the gold standard for determining hand hygiene compliance rates among HCWs, but
  - Direct observations are time-consuming and costly
  - Provides information about a very low percentage of all hand hygiene opportunities
  - Possible Hawthorne effect
  - Significant variability from ward-to-ward, hospital-to-hospital, etc.

Automated Hand Hygiene Monitoring

- Devices that record each time a product dispenser is accessed and by whom
- Record vastly greater numbers of hand hygiene events than direct observers
- Data can be analyzed

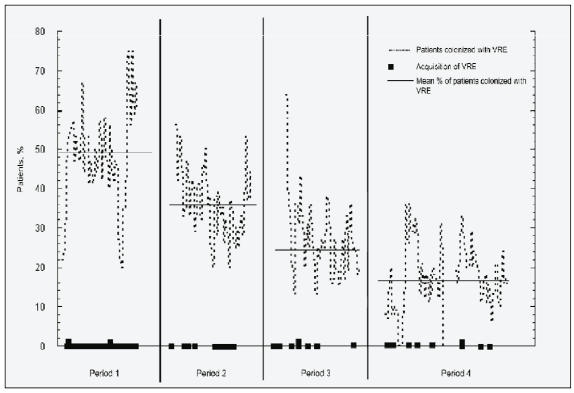
Automated Hand Hygiene Monitoring

- Systems are expensive to install and maintain
- Most studies of electronic monitoring systems have significant limitations
  - Short study periods, implementation on only 1 or 2 wards
  - Failure of some studies to establish the sensitivity and specificity of electronically derived compliance rates as determined by direct observations of hand hygiene
  - Limited data on the impact of the systems on healthcare-associated infection rates
  - Lack of cost-benefit or return on investment analysis

Improve Environmental Cleaning

- Contaminated surfaces in hospitals play an important role in the transmission of MRSA, VRE, *Clostridium difficile*, *Acinetobacter* spp., and norovirus
- Improved surface cleaning and disinfection can reduce transmission of these pathogens

Improve Environmental Cleaning



Hayden M, et al. *Clin Infect Dis*. 2006;42:1552–60.

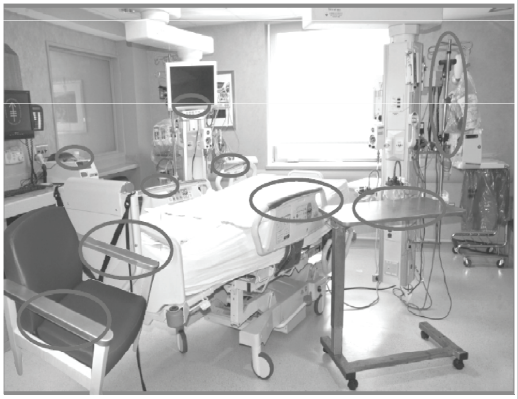
Improve Environmental Cleaning

- Several studies have demonstrated that less than 50% of room surfaces are clean after routine cleaning
- Typically used compounds are not active against spore forming pathogens such as *C. difficile* and norovirus
- Several manufacturers have developed room disinfection units that can decontaminate environmental surfaces and objects
- These systems use ultraviolet light (UV), hydrogen peroxide or peracetic acid
- These technologies do not replace standard cleaning and disinfection of surfaces
- These methods can only be used for terminal decontamination because the room must be emptied of people

Weber DJ, et al. *Curr Opin Infect Dis*. 2013;26:338–344.

Self-disinfecting Surfaces

Self-disinfecting surfaces created by impregnating or coating surfaces with heavy metals such as silver or copper.



Schmidt MG, et al. *J Clin Microbiol*. 2012;50:2217-23.

Eradicate Infection

- Source Control
- Start appropriate antibiotics
- Optimize PK/PD
- Improve laboratory diagnosis

IDSA: Guidelines on the Diagnosis of Infectious Diseases

IDSA GUIDELINES

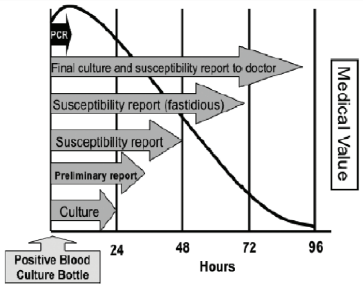
A Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases: 2013 Recommendations by the Infectious Diseases Society of America (IDSA) and the American Society for Microbiology (ASM)[a]

Ellen Jo Baron,[1,2] J. Michael Miller,[3] Melvin P. Weinstein,[4] Sandra S. Richter,[5] Peter H. Gilligan,[6] Richard B. Thomson Jr.,[7] Paul Bourbeau,[8] Karen C. Carroll,[9] Sue C. Kehl,[10] W. Michael Dunne,[11] Barbara Robinson-Dunn,[12] Joseph D. Schwartzman,[13] Kimberle C. Chapin,[14] James W. Snyder,[15] Betty A. Forbes,[16] Robin Patel,[17] Jon E. Rosenblatt,[17] and Bobbi S. Pritt[17]

Baron EJ, et al. *Clin Infect Dis.* 2013;57(4):e22-e121.

Improve Identification and Susceptibility Testing

Tests that provide accurate organism identification and antimicrobial susceptibility increase the effectiveness of antimicrobial stewardship programs



Goff DA, et al. *Pharmacotherapy*. 2012;32:677–687.

Prevent Infection

- Avoid IV catheters, urinary catheters and ET tubes whenever possible
- Remove catheters as soon as possible
- Use appropriate skin prep and peri-operative antibiotic prophylaxis for patients undergoing surgical procedures
- Adopt evidence-based bundles

2013 Measures: Value-Based Purchasing 20 Measures for FFY 2013

Experience of Care Measures Encompassing 8 Key Topics
- **Communication with nurses**
- **Communication with doctors**
- **Responsiveness of staff**
- **Pain management**
- **Communication**
- **Cleanliness and quietness**
- **Discharge information**
- **Overall rating of hospital**

12 Clinical Process Measures
- **Acute Myocardial Infection**
- **Heart Failure**
- **Pneumonia**
  - **Blood cultures**
  - **Approved Antimicrobials**
- **SCIP (SCIP 1,2,3 and 4 considered HAI)**

FFY, Federal Fiscal Year.
Medicare Program; Hospital Inpatient Value-Based Purchasing Program. Available at: https://www.federalregister.gov/articles/2011/05/06/2011-10568/medicare-program-hospital-inpatient-value-based-purchasing-program. Accessed August 25, 2013.

General Strategies to Prevent HAIs

- Perform surveillance
- Provide feedback
- Educate healthcare personnel on HAIs
- Ensure compliance with hand hygiene
- Ensure compliance with appropriate disinfection, sterilization and maintenance of patient equipment

Intervention to Decrease Catheter-Related Bloodstream Infections

- 108 ICUs in Michigan
- Intervention
  - Hand hygiene
  - Full barrier precautions
  - Chlorhexidine skin prep
  - Avoid femoral site
  - Remove unnecessary catheters
- Mean infection rate fell from 7.7/1000 catheter-days to 1.4/1000 catheter-days
- Change was durable and continued 16 to 18 months after intervention

Provonost P, et al. *N Engl J Med*. 2006;355:2725-32.

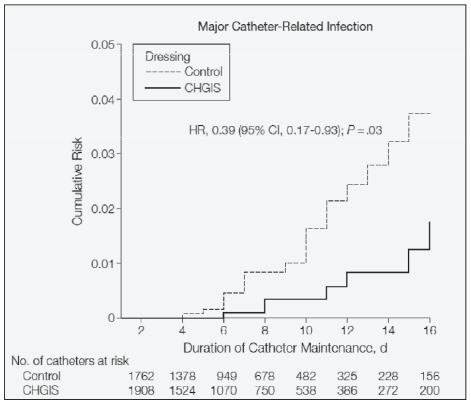
Maintenance Bundle

- Daily inspection of the insertion site
- Site care if the dressing was found to be wet, soiled, or had not been changed for 7 days
- Documentation of ongoing need for the catheter
- Proper application of a CHG-impregnated sponge at the insertion site
- Performance of hand hygiene before handling the intravenous system
- Application of an alcohol scrub of the infusion port for 15 seconds prior to each line access

CLABSI rate decreased from 5.7 to 1.1 infections per 1000 central line-days (RR 0.19, 95% CI 0.06–0.63, p=0.004)

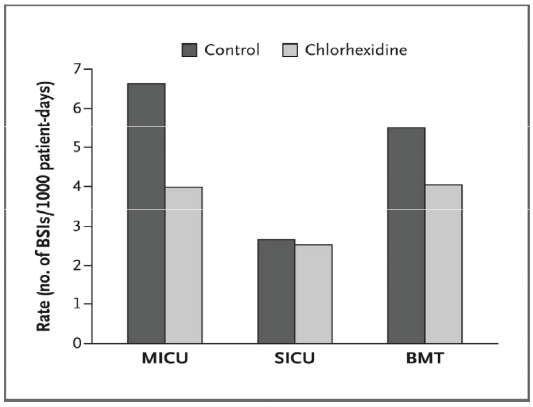
Guerin K, et al. *Am J Infect Control*. 2010;38:430-3.

Chlorhexidine-impregnated Sponge



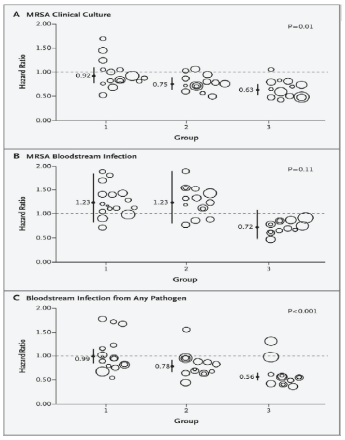
Timsit JF, et al. *JAMA*. 2009;301:1231-1241.

Rates of Primary Bloodstream Infections According to the Type of Hospital Unit



Climo MW, et al. *N Engl J Med*. 2013;368:533-542.

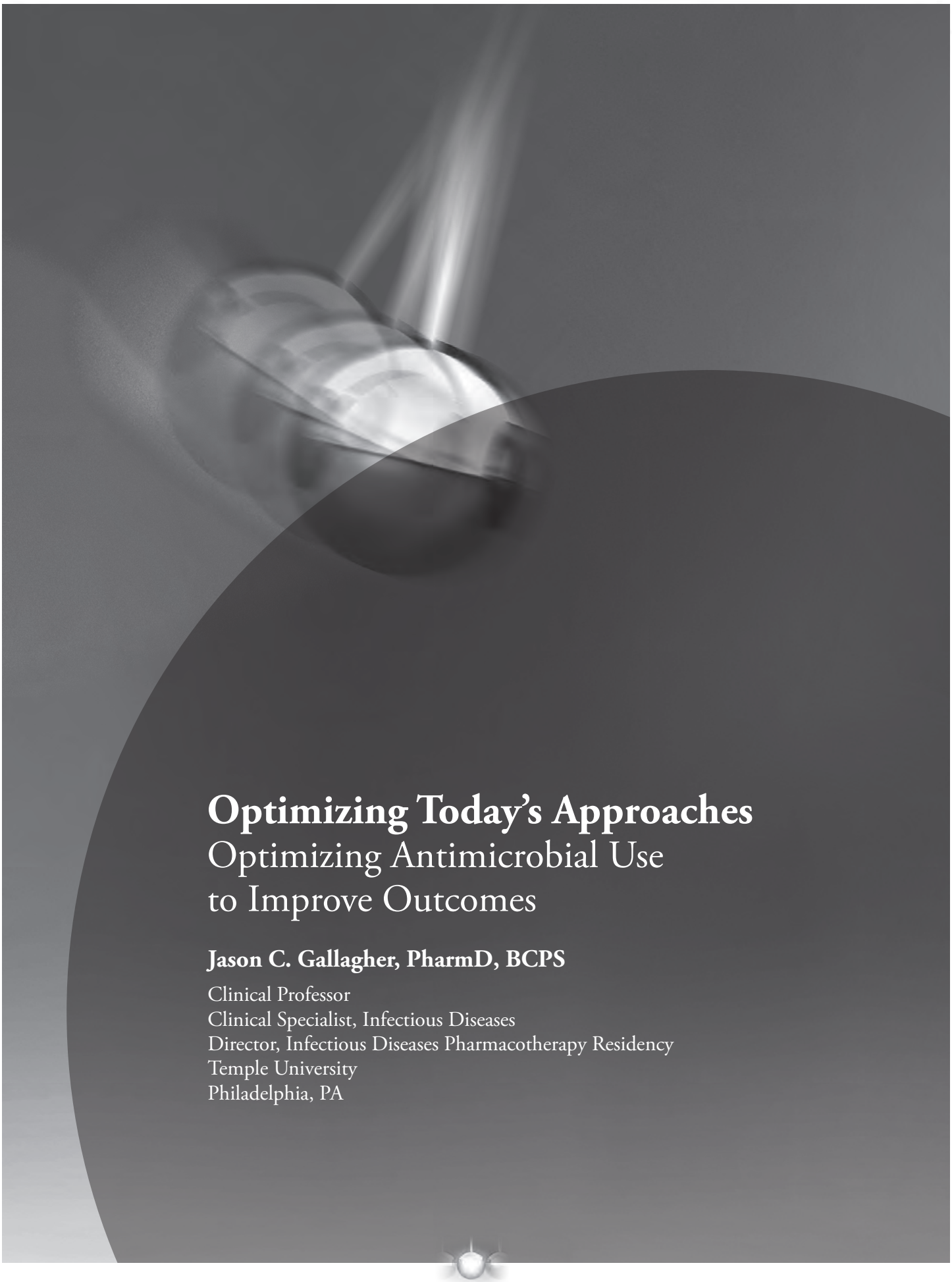
Effect of Trial Interventions on Outcomes



Huang SS, et al. *N Engl J Med*. 2013;368:2255-2265.

Conclusions

- New antimicrobials are needed
- How soon they will be available is uncertain
- In the meantime,
  - efforts to prevent selection and spread of resistant bacteria must take priority and
  - we need to use current agents as efficiently as possible



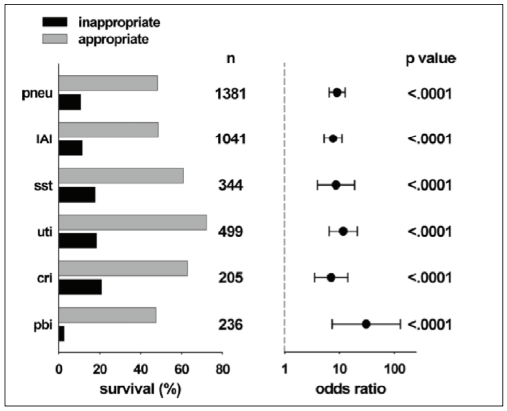
Optimizing Today's Approaches

Optimizing Antimicrobial Use to Improve Outcomes

Jason C. Gallagher, PharmD, BCPS

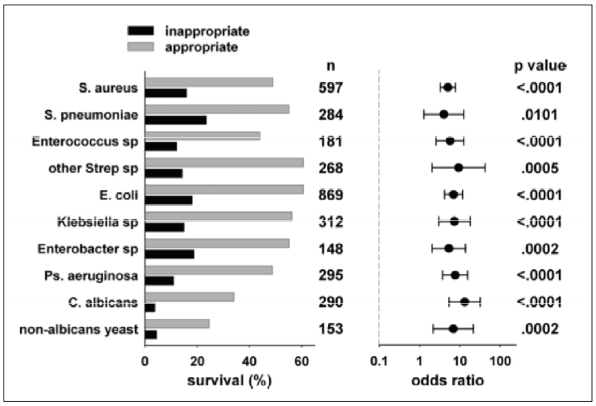
Clinical Professor
Clinical Specialist, Infectious Diseases
Director, Infectious Diseases Pharmacotherapy Residency
Temple University
Philadelphia, PA

Inappropriate Antibiotics Are Bad
Septic Shock



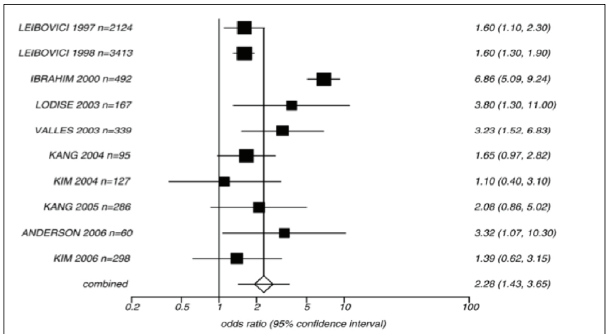
Kumar A, et al. *Chest*. 2009;136:1237-48.

Inappropriate Antibiotics Are Bad
Septic Shock



Kumar A, et al. *Chest*. 2009;136:1237-48.

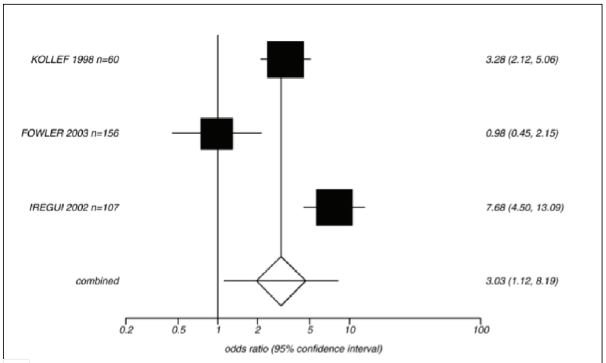
Inappropriate Antibiotics Are Bad
Bloodstream Infections



Adjusted mortality data for patients with BSI treated with inappropriate antimicrobial therapy (n = 7401).

Kuti EL, et al. *J Crit Care*. 2008;23:91-100.

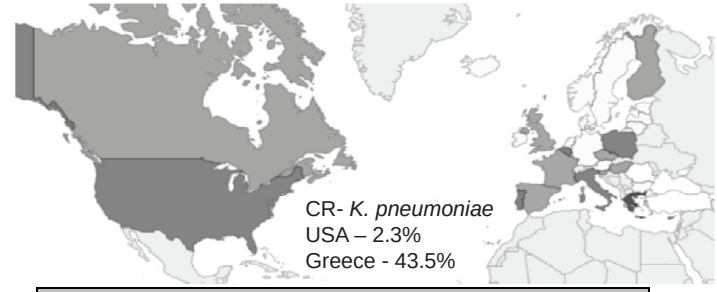
Inappropriate Antibiotics Are Bad
Ventilator-Associated Pneumonia



Adjusted mortality data for VAP patients treated with inappropriate antimicrobial therapy (n = 323).

Kuti EL, et al. *J Crit Care*. 2008;23:91-100.

Carbapenem-Resistant *Enterobacteriaceae*
They're bad too



Outcomes in BSIs	ESBL-*K. pneumoniae*	CR-*K. pneumoniae*	P-value
Micro cure	98/106 (92.5%)	27/44 (61.2%)	<0.001
30-day mortality	32/108 (29.6%)	20/44 (45.5%)	0.06

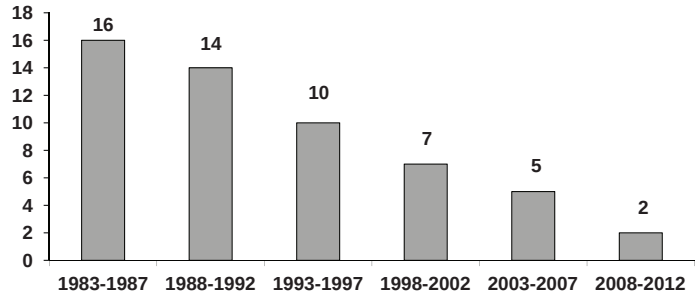
Rose C. Presented at SCCM's 42nd Critical Care Congress 2013 San Juan, Puerto Rico.
Available at: http://www.cddep.org/resistancemap/bug-drug/CRKP.

In my institution, carbapenem-resistant Enterobacteriaceae are…

1. Commonly isolated (>10% of *Klebsiella*)
2. Occasionally isolated (3%–10%)
3. Rarely isolated (>0%–3%)
4. We have never isolated CRE (we win)

It's Not Getting Better

New Systemic Antibacterial Agents Approved by FDA

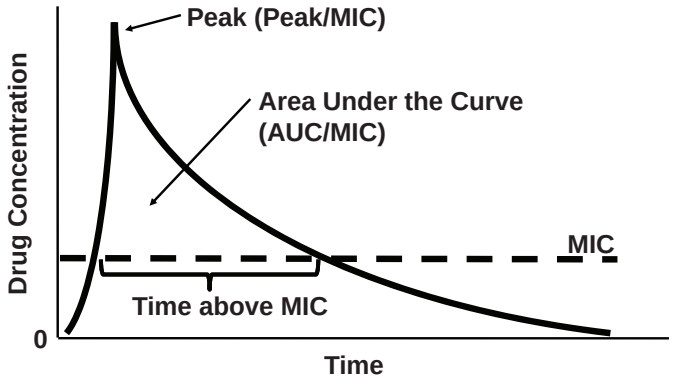


Boucher HW, et al. *Clin Infect Dis*. 2013;56:1685-1694.

What Can We Do About This With What We Have Available?

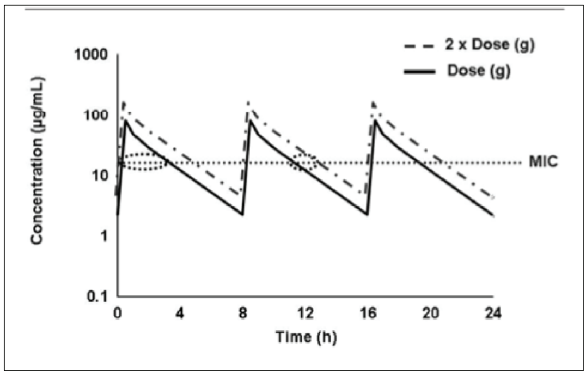
- **Extended-infusion beta-lactams**
  - Why?
  - Where have they shown a benefit?
- **Individualized PK/PD**
  - Don't we do this already?
  - Does it help?
- **Colistin**
  - Can we improve its use?

Pharmacodynamics
Parameters Associated with Efficacy



Mandell GL, et al. *Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases*. 4th ed. 1990.

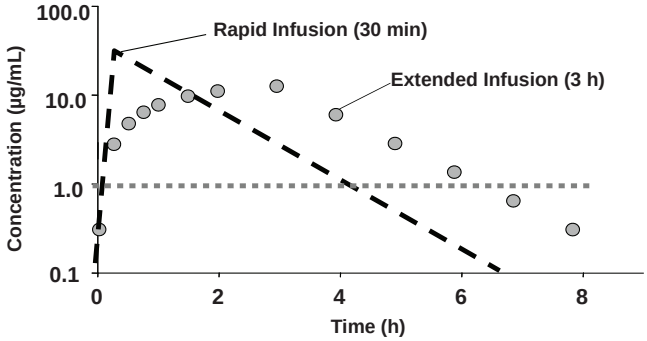
Increasing Frequency Increases T>MIC
Increasing Doses, Not So Much



Nicolau DP. *Crit Care*. 2008;12(Suppl 4):S2.

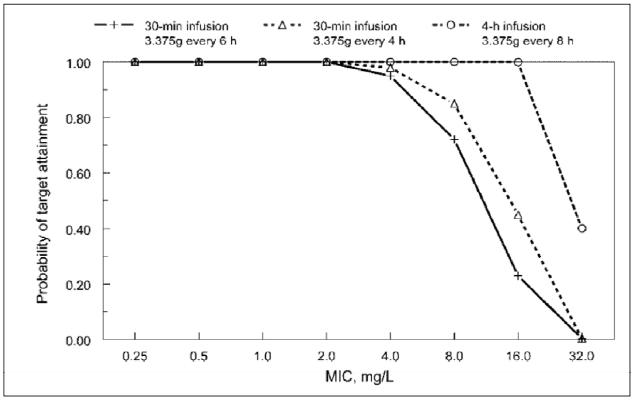
Extended Infusions Increase T>MIC

Meropenem 500 mg administered as a 0.5-hour or 3-hour infusion



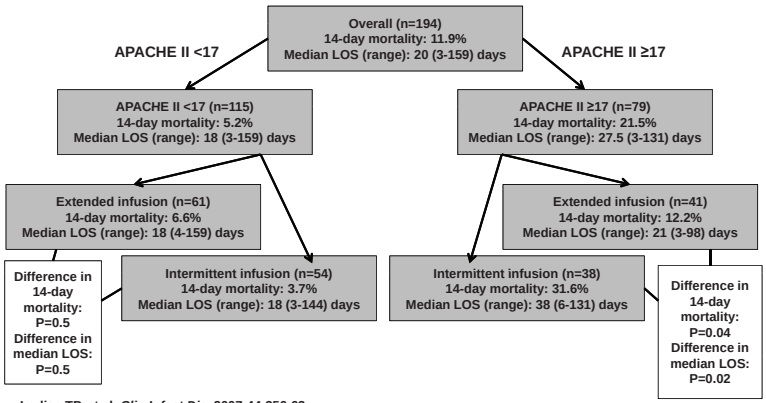
Nicolau DP. *Crit Care*. 2008;12(Suppl 4):S2.

Extended-Infusion Pip/Tazo Increases T>MIC for Higher MICs



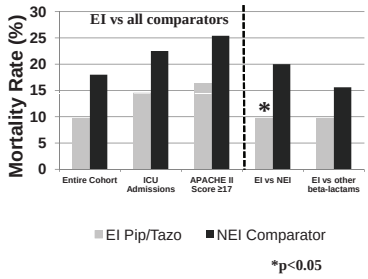
Lodise TP, et al. *Clin Infect Dis*. 2007;44:356-63.

Extended-Infusion Pip/Tazo Decreases Mortality in *Pseudomonas* Infections



Lodise TP, et al. *Clin Infect Dis.* 2007;44:356-63.

Extended-Infusion Pip/Tazo Decreases Mortality in *Pseudomonas* infections



*p<0.05

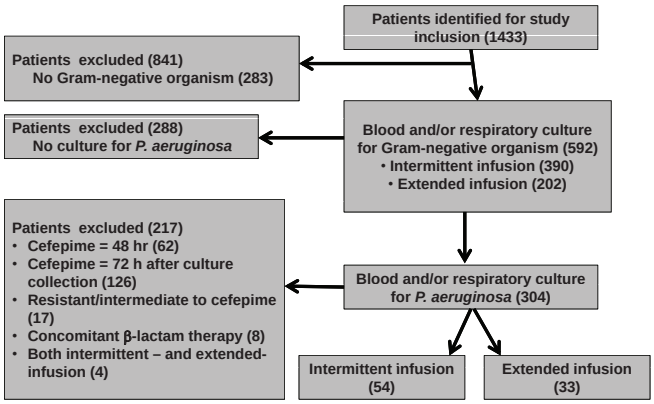
Multivariate Analysis for Extended Infusion Pip-tazo

Variable	Odds Ratio (95% CI)	P value
Mortality		
EI vs comparator abx	0.43 (0.18 – 1.01)	0.053
EI vs NEI pip-tazo	0.22 (0.07 – 0.76)	0.02
EI vs other NEI β-lactams	0.25 (0.04 – 1.64)	0.15
Time to death (days)		
EI vs comparator abx	2.77 (0.85 – 4.7)	<0.01

Evaluation of extended infusion (EI) piperacillin/tazobactam among 14 hospitals
186 patients received EI pip/tazo
173 patients received comparators

EI, extended infusion pip/tazo; NEI, non-extended infusion pip/tazo
Yost RJ, et al. *Pharmacotherapy*. 2011;31:767-775.

Extended-Infusion Cefepime Also Decreases Mortality



Bauer KA, et al. *Antimicrob Agents Chemother*. 2013;57:2907.

Extended-Infusion Cefepime

Clinical or Economic Outcome	Infusion Treatment		P value
	Intermittent (n=54)	Extended (n=33)	
Mortality, n (%)	11 (20)	1 (3)	0.03
LOS (days)			
Hospital	14.5	11 (7-20)	0.36
Infection related	12 (6-21)	10 (6-16)	0.45
ICU	18.5 (5.5-32.5)	8 (4-20)	0.04
Duration (days) of mechanical ventilation	14.5 (5-30)	10.5 (8-18)	0.42
Cost (US$), median (IQ range)			
Total hospital costs	51,231 (17,558-107,031)	28,048 (13,866-68,991)	0.13
Infection-related hospital costs	15,322 (8,343-27,337)	13,736 (10,800-23,312)	0.78

Bauer KA, et al. *Antimicrob Agents Chemother.* 2013;57:2907.

Extended-Infusion Cefepime

Exact Logistic Regression Model for the Occurrence of Mortality

Variable	OR (95% CI)	P Value
Infusion type	0.06 (0.001 – 0.64)	0.01
ICU admission at time of culture collection	8.88 (1.45 – 100.85)	0.01
APACHE II score	1.13 (1.03 – 1.27)	0.01

Bauer KA, et al. *Antimicrob Agents Chemother.* 2013;57:2907.

Continuous-Infusion Meropenem

Clinical Cure Rates of Ventilator-Associated Pneumonia

Rate	Continuous Infusion, n (%)	Intermittent infusion, n (%)	OR (95% CI)	P Value
All cases	38 (90.47)	28 (59.57)	6.44 (1.97 – 21.05)	<0.001
Microorganism				
P. aeruginosa	11 (84.61)	6 (40)	8.25 (1.33 – 51.26)	0.02
Others	27 (93.10)	22 (68.75)	6.13 (1.21 – 30.98)	0.02
MIC				
0.25 – 0.49	21 (100)	23 (76.67)	7.09 (0.72 to 56.38)	0.03
≥0.50	17 (80.95)	5 (29.41)	7.84 (2.26 – 46.09)	0.003

Before/after study of meropenem 1 gm IV q8h over 30 min vs. 4 gm/24h continuously

Lorente L, et al. *Ann Pharmacother.* 2006;40:219-223.

Extended-Infusion Doripenem

Outcomes by Duration of Infusion

	All Patients			Critically Ill Patients		
Characteristic	**1 hour (n=106)**	**4 hours (n=94)**	**P value**	**1 hour (n=42)**	**4 hours (n=44)**	**P value**
Clinical success, n(%)	70 (66.0)	68 (72.3)	0.336	20 (47.6)	32 (72.7)	0.017
Length of stay, days*	12 (7-19)	11 (7-18)	0.399	12 (7-19)	11 (7-18)	0.691
Duration of bacteremia, days*	6 (3-8) (n=13)	3 (2-5) (n=19)	0.058	5 (3-8) (n=24)	3 (2-6) (n=38)	0.313
Inpatient mortality, n (%)	13 (12.3)	12 (12.8)	0.915	10 (23.8)	7 (15.9)	0.358
Infection recurrence within 90 days, n (%)	17 (16.0)	17 (18.1)	0.700	8 (19.0)	5 (11.4)	0.320

*Data presented as median (interquartile range)
Hsaiky L, et al. *Ann Pharmacother*. 2013;47:999-1006.

Extended-Infusion Doripenem

Variables Associated with Clinical Failure Among Critically Ill Patients

Characteristic	Unadjusted OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value
Pneumonia	4.7 (1.9 – 11.9)	0.001	7.8 (2.4 – 25.6)	0.001
Standard-infusion doripenem	2.9 (1.2 – 7.2)	0.017	5.5 (1.6 – 18.7)	0.006
Bacteremia	2.3 (0.8 – 6.6)	0.118	7.0 (1.6 – 31.3)	0.011

Hsaiky L, et al. *Ann Pharmacother*. 2013;47:999-1006.

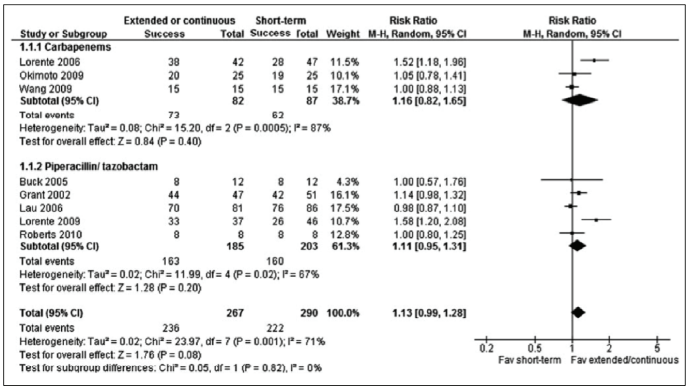
Continuous Infusion Beta-Lactams An RCT!

- 60 patients with severe sepsis randomized to receive continuous or intermittent infusions at clinician-chosen doses
  - Meropenem
  - Piperacillin/tazobactam
  - Ticarcillin/clavulanate
- Blinded, placebo-controlled
- Primary endpoint- free plasma T>MIC

Endpoint	Intervention Group (n=30)	Control (n=30)	P value
Plasma antibiotic concentration >MIC, n (%)	18 (81.8) (n=22)	6 (28.6) (n=21)	.001
Clinical cure (test of cure date), n (%)	23 (76.7)	15 (50.0)	.032
Clinical cure (test of cure date with treatment exclusions), n (%)	21 (70.0)	13 (43.3)	.037
Clinical cure (last day of blinding), n (%)	9 (30.0)	6 (20.0)	.37
Time to clinical resolution (days)	11 (6.75 – 24.25)	16.5 (7 – 28)	.14
ICU survival, n (%)	28 (93.3)	26 (86.7)	.67
Hospital survival, n (%)	27 (90.0)	24 (80.0)	.47

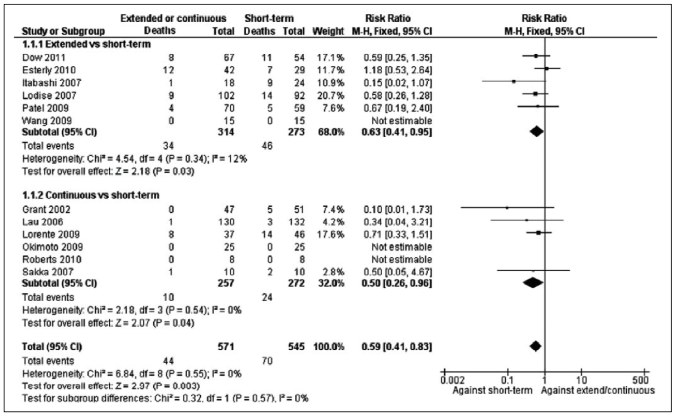
Dulhunty JM, et al. *Clin Infect Dis*. 2013;56:236-44.

Meta-analysis of Infusion Comparisons
Clinical Cure



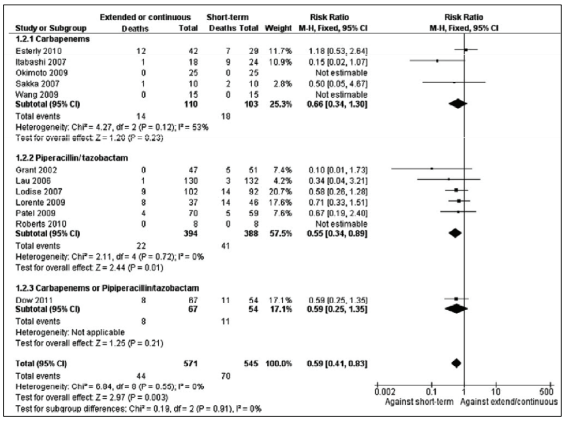
Falagas ME, et al. *Clin Infect Dis*. 2013;56:272-82.

Meta-analysis - Mortality



Falagas ME, et al. *Clin Infect Dis*. 2013;56:272-82.

Meta-analysis - Mortality



Falagas ME, et al. *Clin Infect Dis*. 2013;56:272-82.

Therapeutic Drug Monitoring of Beta-Lactams

- Study of 30-bed ICU over 11 months
- Adjusted based on twice-weekly steady-state troughs (intermittent) or time (continuous)
- PD Goal: 100% free time at 4–5× MIC
- Dose frequency increases if <100% $fT_{>4\text{-}5 \times MIC}$ by 25%–50% *or* changing to maximum dose continuous infusion
- Dose or frequency decreases if <100% $fT_{>10 \times MIC}$

fT, free or unbound antibiotic concentration
Roberts JA, et al. *Int J Antimicrob Agents*. 2010;36:332-339.

Therapeutic Drug Monitoring of Beta-Lactams

Indication	Patients	Dose maintained	Dose increased	Dose decreased
Total, n	236	61 (25.8%)	119 (50.4%)	56 (23.7%)
Primary or secondary bacteremia	8%	11%	72%	17%
Hospital-acquired pneumonia	38%	16%	60%	25%
Community-acquired pneumonia	20%	45%	32%	23%
Meningitis	7%	41%	47%	12%
Wound prophylaxis post-trauma or post-operative	4%	10%	90%	0%
Skin and soft-tissue infection	7%	31%	50%	19%
Abdominal sepsis	12%	25%	36%	39%
Neutropenic sepsis	2%	75%	25%	0%
Urosepsis	3%	14%	29%	57%

Overall, 74.2% of initial doses did not reach targeted endpoints
No association between subtherapeutic initial concentrations and mortality

Roberts JA, et al. *Int J Antimicrob Agents*. 2010;36:332-339.

PK/PD Optimization on the Patient-Level in HAP

- Hypothesis: Adjusting doses of antibiotics based on concentrations and MICs would improve outcomes
- Design: Cohort of patients with HAP
  - 205 with MIC and PK data
  - 433 missing MIC or PK data
- Outcomes assessed: clinical cure, microbiological eradication

Scaglione F, et al. *Eur Respir J*. 2009;34:394-400.

PK/PD Optimization on the Patient-Level in HAP

Drug Class	Drugs	Index	Sampling Time(s)
Beta-lactams	Ceftazidime Cefotaxime	≥70% T>MIC C_{max}:MIC ≥4:1	0.5 and 5.6 hrs after infusion
Fluoroquinolones	Ciprofloxacin Levofloxacin	Peak:MIC ≥10:1	0.5 hr after infusion
Aminoglycosides	Amikacin	Peak:MIC ≥8:1	0.5 hr after infusion

Scaglione F, et al. *Eur Respir J.* 2009;34:394-400.

PK/PD Optimization on the Patient-Level in HAP

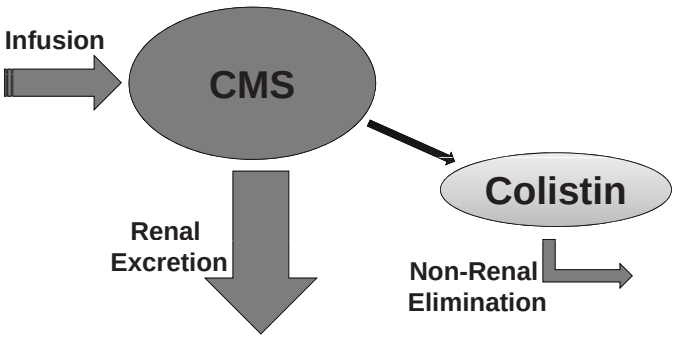
	Evaluated Patients	Controls	P Value
Patients, n	205	433	
Cure, n	168	293	
Failure	37 (18.04)	140 (32.33)	<0.001
Mortality or AMA	21 (10.24)	102 (23.55)	<0.001
Length of stay, days	12.35 ± 3.62	14.86 ± 3.94	0.0076
Duration of mechanical ventilation, days	4.28 ± 1.3	5.39 ± 1.8	0.09

Made adjustments in 81/205 patients (39.5%)

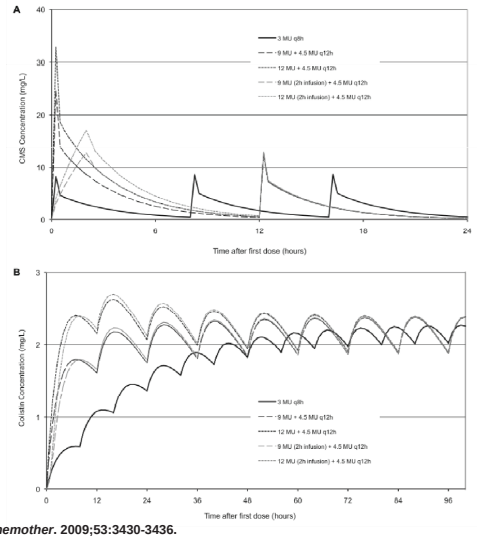
Dose adjustment by PK/PD associated with clinical cure (OR 2.24, 95% CI, 1.51-3.74) and microbiologic clearance (OR 3.09, 95% CI, 1.12-8.03)

AMA, patients left hospital against medical advice
Scaglione F, et al. *Eur Respir J.* 2009;34:394-400.

Colistin and Colistimethate Sodium



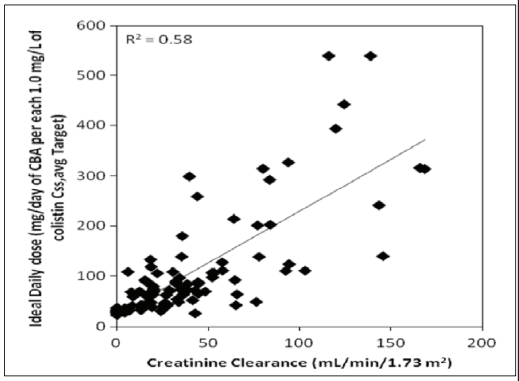
Can We Improve Polymyxin Use?



Plachouras D, et al. *Antimicrob Agents Chemother*. 2009;53:3430-3436.

Can We Improve Polymyxin Use?

Relationship between "ideal" maintenance dose of colistin and creatinine clearance in 101 critically ill patients (89 not on renal replacement and 12 on hemodialysis)



Css,avg, average steady-state plasma concentration; CBA, colistin base activity
Garonzik SM, et al. *Antimicrob Agents Chemother.* 2011;55:3284-94.

Colistin Dosing Recommendations

Loading Dose (in mg CBA)

Dose = Colistin $C_{ss,avg}$ target × 2 × wt (kg)

Daily Maintenance Dose (in mg CBA) (24 hours later)

Dose = Colistin $C_{ss,avg}$ target × (1.5 × CrCl + 30)

Intervals recommended:

CrCl ≥10 mL/min – q8-12h

CrCl ≤10 mL/min – q12h

Recommend not to use for CrCl >70 mL/min unless targeting a low $C_{ss,avg}$

Css,avg, average steady-state plasma concentration; CBA, colistin base activity
Garonzik SM, et al. *Antimicrob Agents Chemother.* 2011;55:3284-94.

High-Dose, Extended-Interval Colistin in Practice

- Observational cohort of 28 ICU cases with GNR sepsis receiving colistin >72 hours
- Dose given: 9 MU IV loading dose, maintenance dose of 4.5 MU IV q12h
- Patients: APACHE II 18±6; septic shock 12/28, severe sepsis 16/28; 18 BSIs, 10 VAP
- Clinical cure: 23/28 episodes (82.1%)
- Nephrotoxicity: 5/28 episodes (17.8%)

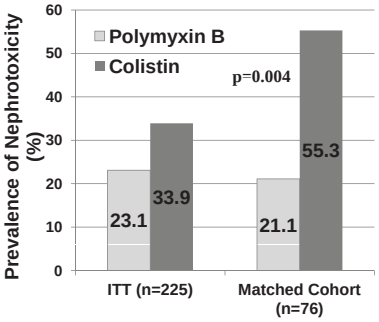
Dalfino L, et al. *Clin Infect Dis*. 2012;54:1720-1726.

Colistin Nephrotoxicity How Toxic is It?

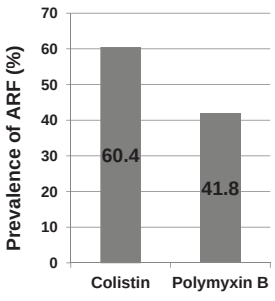
Study (Year)	Cohort	Evaluable Study Size	Nephrotoxicity
Garnacho-Montero (2003)	VAP (ICU)	21	23.8%
Michalopoulos et al (2005)	ICU	43	18.6%
Hachem et al (2007)	Cancer	31	23%
Hartzell et al (2009)	All	66	41%
Garonzik et al (2009)	ICU	89	48%
Cheng et al (2010)	*Pseudomonas*; 65% ICU	84	14%
Doshi et al (2011)	ICU	49	31%
Pogue et al (2011)	All; 75% ICU	126	43%
Collins et al (2013)	All; 79% ICU	174	48%
Durante-Mangoni et al (2013)	*Acinetobacter*; 61% ICU	101 (COL) 101 (COL+RIF)	28.7% (COL) 23.7% (COL+RIF)

Should We Be Using Polymyxin B?

Higher Prevalence of Nephrotoxicity with Colistin[1]



Higher Incidence of Acute Kidney Injury with Colistin[2]



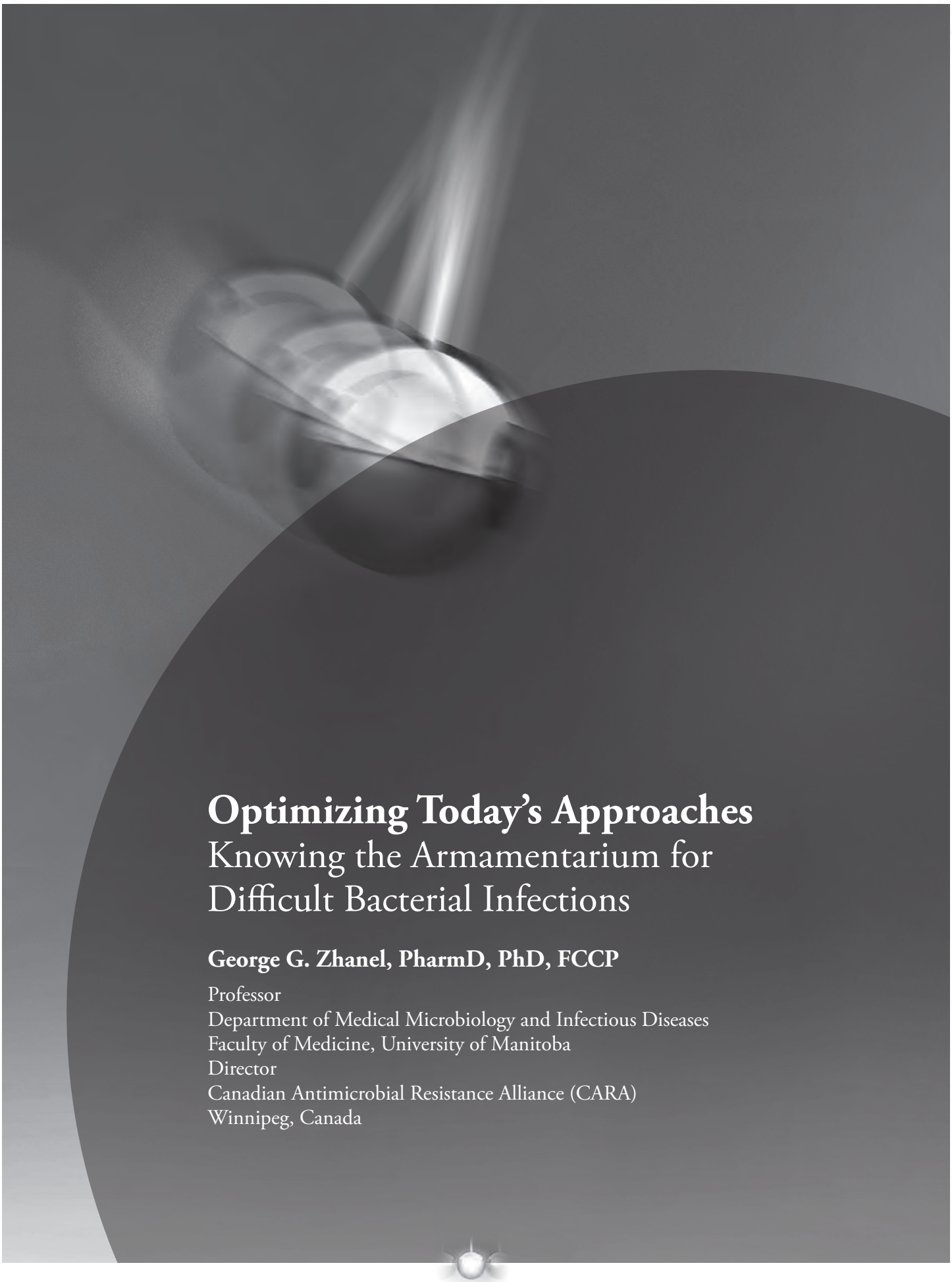
ARF, acute renal failure
1. Phe K, et al. Poster presented at ICAAC 2013. Presentation No. K-716.
2. Akajagbor D, et al. *Clin Infect Dis*. 2013;[Epub ahead of print].

Other Areas of Interest

- Combination therapy for MDR GNRs
  - Colistin/polymyxin B combinations
  - Carbapenem combinations
  - What to do with rifampin
- Combination therapy with daptomycin
  - MRSA (ceftaroline, antistaphylococcal penicillins)
  - VRE (ampicillin)
- Combination therapy of ceftriaxone + ampicillin for VRE (*E. faecalis*)
- New agents

Summary

- PK/PD optimization (in many forms) has a benefit
  - Extended and continuous infusions
  - Patient-level TDM
- Colistin dosing seems to be coming into focus
- We know less than we don't know about treating MDR pathogens, but we'll have to learn it



Optimizing Today's Approaches
Knowing the Armamentarium for Difficult Bacterial Infections

George G. Zhanel, PharmD, PhD, FCCP

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Department of Medical Microbiology and Infectious Diseases
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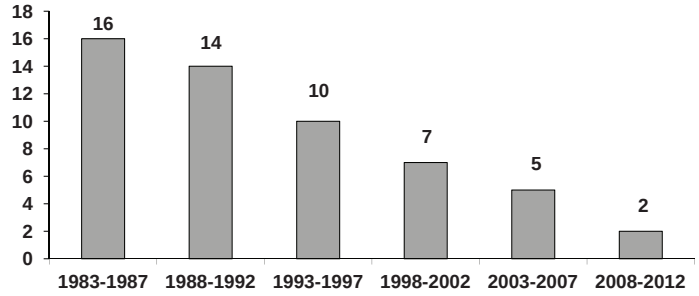
New Systemic Antibacterial Agents Approved by FDA



Boucher HW, et al. *Clin Infect Dis*. 2013;56:1685-1694.

Objectives

1. Review investigational agents vs. MDR Gram-positive pathogens
2. Review investigational agents vs. MDR Gram-negative pathogens

Canadian Antimicrobial Resistance Alliance (CARA; www.can-r.ca)

George Zhanel, Heather Adam, Mel Baxter, Melissa McCracken, Laura Mataseje, Michael R Mulvey, Barbara Weshnoweski, Ravi Vashisht, Nancy Laing, James Karlowsky, Kim Nichol, Andrew Denisuik, Alyssa Golden, Patricia Simner, 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

Investigational Agents vs. MDR Gram-positive Pathogens

- **Dalbavancin**
- **Oritavancin**
- **Oxazolidinones (eg. tedizolid, radezolid)**
- **Solithromycin**
- **Eravacycline (TP-434)**

- **High-dose daptomycin**
- **AFN-1252**
- **CF-301**

Data presented at ICAAC 2012 and 2013.

Dalbavancin

- **IV lipoglycopeptide**
- **Active versus:**
  - *Staphylococcus* spp. (MRSA, VISA)
  - *Streptococcus* spp.
- **$t_{½}$ ~200 hours**
- **Concentration-dependent killing**

- **Phase III**
  - aBSSSI 1000 mg day 1, 500 mg day 8

aBSSSI, acute bacterial skin and skin structure infection.
Zhanel GG, et al. *Drugs*. 2010;70 (7):859-886.

Oritavancin

- **IV lipoglycopeptide**
- **Active versus:**
  - *Staphylococcus* spp. (MRSA, VISA)
  - *Streptococcus* spp.
  - Enterococcus spp. (VRE-*vanA*)
- **$t_{½}$ ~390 hours**
- **Rapid, concentration-dependent killing**

- **Phase III**
  - aBSSSI 1200 mg day 1

aBSSSI, acute bacterial skin and skin structure infection.
Zhanel GG, et al. *Drugs*. 2010;70 (7):859-886.

Tedizolid

- **IV/PO oxazolidinone**
- **More active (~8 fold) than linezolid versus:**
  - *Staphylococcus* spp. (MRSA, VISA, VRSA)
  - *Streptococcus* spp.
  - Enterococcus spp. (VRE-*vanA*)
- **F ~90%, $t_{½}$ ~9 hours, OD dosing**
- **Phase III**
  - aBSSSI 200mg OD 5-7 days
  - reduced MAO-A and MAO-B inhibition
  - reduced myelosuppression

F, bioavailability; aBSSSI, acute bacterial skin and skin structure infection; MAO, monoamine oxidase.

Golden A, et al. Poster to be presented at ICAAC 2013 (Presentation No. E-143).
Kanafani ZA, Corey GR. *Expert Opin Invest Drugs.* 2012;21(4):515-522.

Solithromycin

- **IV/PO fluoroketolide**
- **More active than macrolides versus:**
  - *Streptococcus* spp.
    - macrolide-R strains
- **Good PK = OD dosing**
- **Phase III**
  - CABP 800 mg day 1, 400 mg × 4 days
  - Gonorrhea 1200 mg SD

Still JG, et al. *Antimicrob Agents Chemother.* 2011;55:1997-2003.

Eravacycline (TP-434)

- **IV/PO broad-spectrum fluorocycline**
- **Active versus:**
  - **Gram-positive cocci:**
    - *Staphylococcus* spp. (MRSA, VISA)
    - *Streptococcus* spp.
    - *Enterococcus* spp. (VRE-*vanA*)
  - **Gram-negative bacilli:**
    - ESBL/MDR producing enterics
    - *Acinetobacter* spp.
- **Phase II**
  - cIAI (vs. ertapenem), cUTI, aBSSSI, pneumonia(?)

cUTI, complicated urinary tract infection; aBSSSI, acute bacterial skin and skin structure infection

Investigational Agents vs. MDR Gram-negative Pathogens

- **Ceftazidime-avibactam**
- **Ceftaroline-avibactam**
- **Ceftolozane/tazobactam**
- **Imipenem/MK-7655**
- **Plazomicin**
- **Eravacycline (TP-434)**

- **Fosfomycin**
- **Aztreonam-avibactam**
- **ACHN-975**
- **RPX-7009**
- **FPI-1465**

Data presented at ICAAC 2012 and 2013.

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
- ~4 fold more active vs. *Pseudomonas aeruginosa*

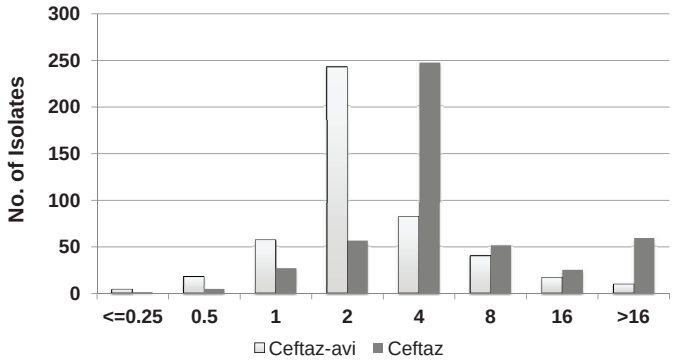
Zhanel GG, et al. *Drugs*. 2013; 73:159-177.

Activity of Ceftazidime-avibactam vs. Enterobactaeriaceae

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

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

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



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

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

Ceftazidime-avibactam

- Currently in Phase III
- Clinical trials:
  - **Complicated Intraabdominal Infections:** Ceftazidime-avibactam 2000 mg/500 mg + metronidazole 500mg, each Q8H vs meropenem
  - **Complicated Urinary Tract Infections:** Ceftazidime-avibactam 500 mg/125 mg Q8H vs imipenem

Boucher HW, et al. *Clin Infect Dis*. 2013;56:1685-1694.
Zhanel GG, et al. *Drugs*. 2013;73:159-177.

Ceftaroline-avibactam

Avibactam is a non-β-lactam, β-lactamase inhibitor

Inhibits Ambler class A, C and some D β-lactamases
- ESBL, AmpC, KPC

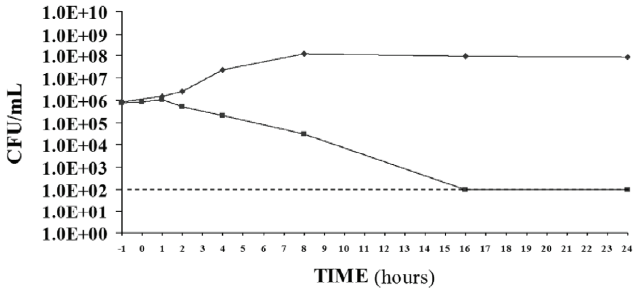
Ceftaroline kills MRSA, hVISA, VISA and VRSA

Avibactam broadens activity vs. Enterobacteriaceae

Karlowsky JA, et al. *Antimicrob Agents Chemother*. 2013 in press.
Zhanel GG, et al. *Drugs*. 2009; 69 (7): 809-831.

In vitro Pharmacodynamic Modeling of Ceftaroline vs VISA NRS4

Ceftaroline dosed at 600 mg IV q12h [fC_{max}, 16 mg/L; $t_{1/2}$, 2.6 h]



Zhanel GG, et al. *J Antimicrob Chemother*. 2011;66(6):1301-1305.

Activity of Ceftaroline-avibactam vs. Enterobactaeriaceae

Genotype	Ceftaroline $MIC_{50/90}$	Ceftaroline-avibactam $MIC_{50/90}$ (fold >)
All *E. coli* (n = 2162)	0.12/1	≤0.03/0.06 (16)
ESBL *E. coli* (n = 114)	>16/>16	≤0.03/0.06 (>256)
AmpC *E. coli* (n = 57)	4/16	0.06/0.12 (128)
All *K. pneumoniae* (n =702)	>16/>16	0.06/0.12 (>128)
ESBL *K. pneumoniae* (n = 25)	2/32	0.06/0.5 (64)

Karlowsky JA, et al. *Antimicrob Agents Chemother*. 2013 in press.

Ceftaroline-avibactam

- Currently in Phase II
- Clinical trials:
  - **Complicated Intraabdominal Infections:** Ceftaroline/avibactam + metronidazole vs. doripenem
  - **Complicated Urinary Tract Infections:** Ceftaroline-avibactam 600 mg/600 mg Q8-12H vs. doripenem

Boucher HW, et al. *Clin Infect Dis*. 2013;56:1685-1694.

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)

Boucher HW, et al. *Clin Infect Dis*. 2013;56:1685-1694.

Activity of Ceftolozane/tazobactam vs. Enterobactaeriaceae

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

Zhanel GG, et al. Poster presentation at ICAAC 2013 (Presentation No. E-1689).

Activity of Ceftolozane/tazobactam *vs.* *Pseudomonas aeruginosa* (n=2435)

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

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

Walkty A, et al. *Antimicrob Agents Chemother*. 2013 (in press).

Ceftolozane/tazobactam

- Currently in Phase III
- Clinical trials:
  - **Complicated Intraabdominal Infections:** Ceftolozane/tazobactam 1000 mg/500 mg + metronidazole 500mg each Q8H vs meropenem
  - **Complicated Urinary Tract Infections:** Ceftolozane/tazobactam 1000 mg/500 mg Q8H vs levofloxacin
  - **Nosocomial and ventilatory-associated bacterial pneumonia study?**

Boucher HW, et al. *Clin Infect Dis*. 2013;56:1685-1694.

Imipenem/MK-7655

MK-7655 β-lactamase inhibitor with a similar structure to avibactam

Inhibits Ambler class A, C and some D β-lactamases
-ESBL, AmpC, KPC

Imipenem/cilastatin is a broad-spectrum anti-pseudomonal carbapenem

MK-7655 broadens activity vs. Enterobacteriaceae

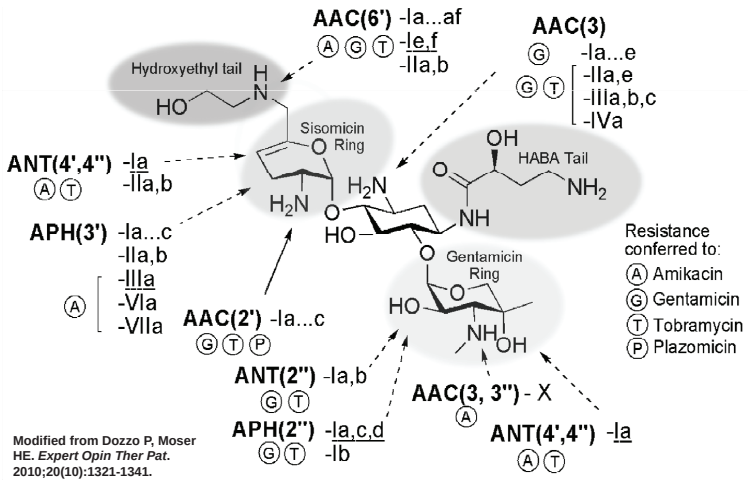
Boucher HW, et al. *Clin Infect Dis*. 2013;56:1685-1694.
Zhanel GG, et al. *Drugs*. 2007; 67(7):1027-1052.

Imipenem/MK-7655

- Currently in Phase II
- Clinical trials:
  - **Complicated Intraabdominal Infections:** Imipenem/cilastatin + MK-7655 vs. Imipenem/cilastatin alone
  - **Complicated Urinary Tract Infections:** Imipenem/cilastatin + MK-7655 vs. Imipenem/cilastatin alone

Boucher HW, et al. *Clin Infect Dis*. 2013;56:1685-1694.

Structure/Activity of Plazomicin



Modified from Dozzo P, Moser HE. *Expert Opin Ther Pat.* 2010;20(10):1321-1341.

Plazomicin Activity vs. MDR Enterobacteriaceae

Organism	Agent	Range	MIC_{90} (µg/ml)
E. coli (n=3050) (10% ESBLs)	ACHN-490	≤0.06 - >16	1
	Gentamicin	≤0.25 - >64	32
	Amikacin	≤0.5 - >64	4
	Ciprofloxacin	≤0.12 - >4	>4
	Imipenem	≤0.12 - 8	0.25
Klebsiella spp. (n=1155) (32% KPCs)	ACHN-490	0.12 - >16	1
	Gentamicin	≤0.25 - >64	64
	Amikacin	≤0.5 - >64	32
	Ciprofloxacin	≤0.12 - >4	>4
	Imipenem	≤0.12 - >16	16
Enterobacter spp. (n=204)	ACHN-490	<0.06 - 8	1
	Gentamicin	≤0.25 - >64	16
	Amikacin	≤0.5 - 64	4
	Ciprofloxacin	≤0.12 - >4	>4
	Imipenem	≤0.12 - 16	1

Susceptible
Intermediate
Resistant

Landman D, et al. *J Antimicrob Chemother.* 2010;65:2123-2127.

Plazomicin

- Plazomicin is a next-generation aminoglycoside synthetically derived from sisomicin
- Retains activity against both Gram-negative (MDR) and Gram-positive bacterial strains expressing all clinically relevant aminoglycoside-modifying enzymes
- Is not active versus organisms harbouring rRNA methyl-transferases

Zhanel GG, et al. *Expert Rev Anti Infect Ther.* 2012;10(4):459–473.

Plazomicin

- 15 mg/kg IV: C_{max} was 113 µg/mL, $AUC_{0\text{-}24}$ 239h·µg/mL, $t_{½}$ (hr) 3.0 hr and V_{ss} 0.24 L/kg
- Animal and human studies to date have not reported nephrotoxicity or ototoxicity
- Phase II cUTI: plazomicin 15 mg/kg IV QD × 5 days vs. levofloxacin 750 mg IV × 5 days reported in 2012

Zhanel GG, et al. *Expert Rev Anti Infect Ther*. 2012;10(4):459–473.

Conclusions:

- **We have several new antibacterial agents in the pipeline**
- **However we also must focus on:**
  - **Surveillance**
  - **Infection prevention/control**
  - **Rapid diagnostics**
  - **Antimicrobial stewardship**