Defining the Steps Towards Quality Improvement and Patient Safety

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Prevalence of ICU Infections (EPIC II)

One-day, prospective study
13,796 patients in 1265 ICUs (75 countries)

- Antimicrobial therapy: 71%
- Infection: 51% (of which 70% culture-positive)
- Increased ICU stay associated with
  - Increased rate of infection: 1 day (32%) vs. >7days (70%)
  - Increased rate of MRSA/GNR
- Increased mortality in infected patients
  - ICU: infected (25%) vs. non-infected (11%; *P*<.001)
  - Hospital: infected (33%) vs. non-infected (15%; *P*<.001)

MRSA, methicillin-resistant *Staphylococcus aureus*; GNR, gram-negative rod.
Vincent JL, et al. *JAMA*. 2009;302:2323-2329.

Burden of Hospital-Acquired Infections

Infection Type	Total Infections	Hospital Cost/ Infection	Total Annual Hospital Cost	Deaths/ Year
SSI	290,485	$25,546	$7,421 million	13,088
CLABSI	248,678	$36,441	$9,062 million	30,665
VAP	250,205	$9,969	$2,494 million	35,967
Catheter-associated UTI	561,667	$1,006	$565 million	8,205

SSI, surgical site infection; CLABSI, central line-associated bloodstream infection; VAP, ventilator-associated pneumonia; UTI, urinary tract infection.

Klevens RM, et al. *Public Health Rep.* 2007;122:160-166.
HHS Action Plan to Prevent HAIs. Available at: http://hhs.gov/www.hhophs/initiatives/hai/introduction.html.

HAIs and the Media

Antimicrobial-Resistant Pathogens Associated with HAIs (2006–2007)

Pathogen	CLABSI (%)	CAUTI (%)	VAP (%)
S. aureus	9.9	2.2	24.4
MRSA*	56.8	65.2	54.4
Enterococcus spp.	16.0	14.9	1.3
VRE*	36.4	29.1	32.8
P. aeruginosa	3.1	10.0	16.3
FQ-R*	30.5	33.8	27.8
IMI or MERO-R*	23.0	25.1	26.4
K. pneumoniae	4.9	7.7	7.5
CTX or CTZ-R	27.1	21.2	23.7
A. baumannii	2.2	1.2	8.4
IMI or MERO-R*	29.2	25.6	36.8

Data from National Healthcare Safety Network; * % of total pathogens.

CAUTI, catheter-associated urinary tract infection; CLABSI, central line-associated bloodstream infection; CTX, ceftriaxone; FQ, fluoroquinolone; MERO, meropenem; MRSA, methicillin-resistant *S. aureus*; R, resistant; CTZ, ceftazidime; VAP, ventilator-associated pneumonia; VRE, vancomycin-resistant enterococci.

Hidron AI, et al. *Infect Control Hosp Epidemiol.* 2008;29:996-1011.

Cost of Antimicrobial-Resistant Infections

Antimicrobial-resistant infection	**188 (13.5%)**
Attributable medical costs (per patient)	**$18,588 - $29,069**
Excess hospital duration	**6.4 – 12.7 days**
Societal costs (total)	**$10.7 - $15.0 million**
Attributable mortality	**6.5%**

1391 high-risk inpatients (Chicago teaching hospital)

Roberts RR, et al. *Clin Infect Dis.* 2009;49:1175-1184.

Nonpayment for Performance: Medicare's Reimbursement Rule

- **CMS decided to disallow incremental payments associated with 8 secondary conditions that it sees as preventable complications of medical care.**
- **These conditions, if not present at the time of admission, will no longer be taken into account in calculating payments to hospitals.**

Conditions for Which Medicare Will No Longer Pay More If Acquired during an Inpatient Stay.*

Condition	No. of Medicare Cases in Fiscal Year 2006	Average Medicare Payment for Admissions in Which Condition Was Present
Object left in patient during surgery	764	$61,962
Air embolism	45	$66,007
Blood incompatibility	33	$46,492
Catheter-associated urinary tract infection	11,780	$40,347
Pressure ulcer	122,946	$40,381
Vascular-catheter–associated infection†	Unknown	Unknown
Mediastinitis after coronary-artery bypass grafting	108	$304,747
Fall from bed	2,591	$24,962

* Data are from the *Federal Register*.[2]
† Data are unknown because a unique code for this condition was introduced for fiscal year 2008.

Rosenthal MB. *N Engl J Med.* 2007;357:1573-1575.

Are HAIs Inevitable or Preventable?

Keystone ICU project, 103 ICUs in Michigan

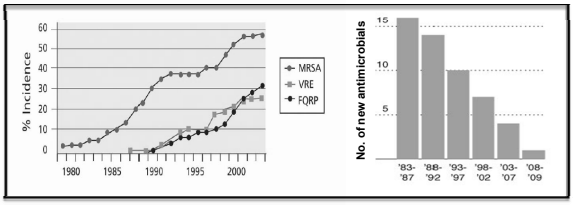
- Introduced 5 evidence-based interventions to reduce catheter-related bloodstream infections (CR-BSIs)
  - Hand-washing
  - Full barrier precautions during CVC insertion
  - Chlorhexidine preparation
  - Avoiding femoral site
  - Removing unnecessary CVCs
- Within 3 months after implementation, median CR-BSI/1000 catheter-days decreased from 2.7 to 0 (P<.002)
- Median rate of CR-BSIs remained at 0/1000 catheter-days during 16–18-month sustainability period

CR-BSI, catheter-related bloodstream infection.
Pronovost P, et al. *N Engl J Med.* 2006;355:2725-2732.
Pronovost PJ, et al. *BMJ.* 2010;340:c309.

IDSA Call-to-Action

Concerns regarding lack of new antimicrobials under development to meet future challenges

As resistance increases . . . …number of new antimicrobials diminishes



VRE, vancomycin-resistant enterococci; FQRP, fluoroquinolone-resistant *Pseudomonas.*
IDSA. Bad Bugs, No Drugs. Available at: www.idsociety.org/badbugsnodrugs.html.

Promoting Value-Based Healthcare to Improve Quality

Institutional challenges
- Rising healthcare costs
- Reduced reimbursement

Response
- Transition from volume-based to value-based healthcare

Requirements
- Improved communication among healthcare personnel
  - Poor coordination leads to wasted resources and adverse reactions

How can hospital pharmacists intervene to improve quality of care for patients with HAIs?

HAIs, hospital-acquired infections.
National Quality Forum. Moving from a volume-based to a value-based healthcare system. Available at: http://www.qualityforum.org/Calendar/2009/10/Webinar__Moving_from_Volume-based_to_a_Value-based_Healthcare_System.aspx.

2009 "Zero Tolerance" Findings

Symposia held at 8 annual meetings of State SHPs
- A total of 1000 pharmacists attended the live program

Program Goals
- Increase overall awareness of the challenges associated with HAIs
- Encourage a multidisciplinary approach to patient care
- Improve the understanding of optimal use of antimicrobial agents
- Tailor therapy to local resistance patterns

Conclusions from post-activity outcomes assessment
- Better communication is still needed between pharmacists and other healthcare providers
- Participants continue to request additional information on the optimal use of antimicrobials
- Continued **lack** of understanding of stewardship principles
  - i.e., the use of antibiograms to guide initial therapy

Taking the Next Step . . .

- **Hospital pharmacists must embrace the role as interventionists to help guide physicians towards appropriate antimicrobial use.**
- **What can pharmacists do to improve collaboration to better manage and prevent HAIs?**
- **What tools are available to optimize treatment approaches for infections caused by:**
  - MRSA
  - ESBL/KPC-producing Enterobacteriaceae
  - MDR *P. aeruginosa/Acinetobacter* spp.
- **How can pharmacists take a proactive approach to improve patient safety and quality of care?**

Strengthening the Pharmacist's Role: The Evolving Face of Resistance

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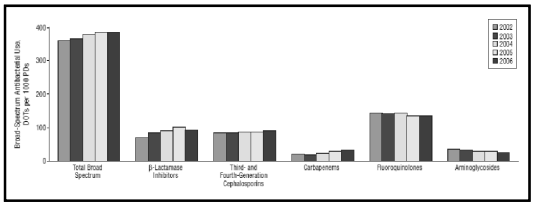
Increased Use of Antimicrobials

22 Academic Health Centers (2002–2006)

- Significant increase in broad-spectrum agents, carbapenems (increased 59%), and piperacillin/tazobactam (increased 84%)



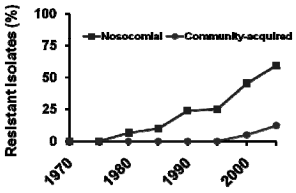
Increased antimicrobial use provides selective pressure for resistance!

Pakyz AL, et al. *Arch Intern Med.* 2008;20:2254-2260.

MRSA

HA- and CA-MRSA Infection: Epidemiology

MRSA prevalence increasing in hospitals and community.[1]



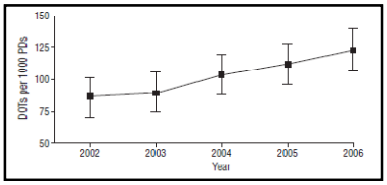
Infection Type	Infections associated with CA-MRSA (N=131)[2]	HA-MRSA (N=937)[2]
Skin/ Soft Tissue	75%	37%
Otitis media/ Externa	7%	1%
Respiratory Tract	6%	22%
BSI	4%	9%
UTI	1%	20%
Other	8%	12%

1. McDonald LC. *Clin Infect Dis*. 2006;42:S65-71.
2. Naimi TS, et al. *JAMA*. 2003;290:2976-2984.

Vancomycin Use Continues to Increase

22 Academic Health Centers (2002–2006)

- Vancomycin use increased 43%
  - Likely due to increased number HA-MRSA and CA-MRSA cases that encourage greater use of vancomycin for empiric treatment

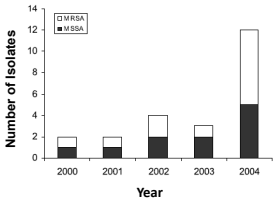


Pakyz AL, et al. *Arch Intern Med*. 2008;20:2254-2260.

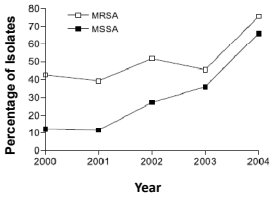
Emerging Resistance Issues: Vancomycin MIC Creep

First documented case of infection by vancomycin-resistant *S. aureus* in US reported in 2002

MRSA and MSSA isolates (number) with vancomycin MIC=2 μg/mL



MRSA and MSSA isolates (%) with vancomycin MIC=1 μg/mL



Wang G, et al. *J Clin Microbiol.* 2006;44:3883-3886.

Vancomycin "MIC Creep": The Counter-Argument

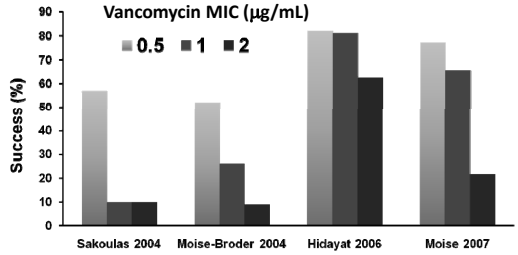
MRSA isolates: 9 US institutions, 2002–2006, N=1800

Year (no. of isolates)	% of Strains for which Vancomycin MIC (μg/mL) was:						
	≤0.375	0.406–0.5	0.563	0.625	0.688	0.75–1.0	>1
2002 (342)	2.6	6.7	8.5	36.8	24.0	18.1	3.2
2003 (365)	1.1	6.6	9.6	45.2	22.5	13.1	1.6
2004 (347)	2.9	6.1	8.9	39.8	19.9	18.7	3.7
2005 (380)	2.4	7.9	10.8	41.6	22.1	11.6	3.7
2006 (366)	1.1	4.1	9.3	44.0	21.0	15.8	3.0
Total (1800)	1.4	6.3	9.4	41.6	21.9	15.8	3.1

Broth microdilution method with precise incremental dilutions

Sader HS, et al. *Antimicrob Agents Chemother.* 2009;53:4127-4132.

Higher Vancomycin MICs Correspond to Poorer Response



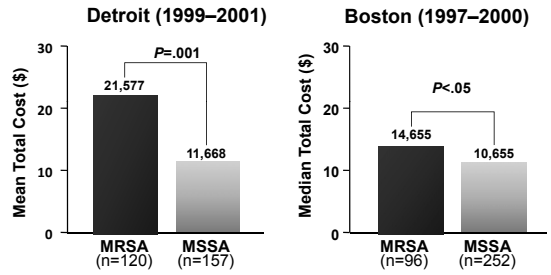
Adapted from Sakoulas G, et al. *J Clin Microbiol.* 2004;42:2398-2402.
Moise-Broder PA, et al. *Clin Infect Dis.* 2005;38:1700-1705.
Hidayat LK, et al. *Arch Intern Med.* 2006;166:2138-2144; Moise PA, et al. *Antimicrob Agents Chemother.* 2007;51:2582-2586.

Vancomycin MIC Interpretive Criteria for *S. aureus*

Old Breakpoints		New Breakpoints	
Susceptible:	≤4 µg/mL	Susceptible:	≤2 µg/mL
Intermediate:	8-16 µg/mL	Intermediate:	4-8 µg/mL
Resistant:	≥32 µg/mL	Resistant:	≥16 µg/mL

CLSI, Clinical and Laboratory Standards Institute. Approved Standard M7-A7. CLSI, Wayne, PA. 2006.

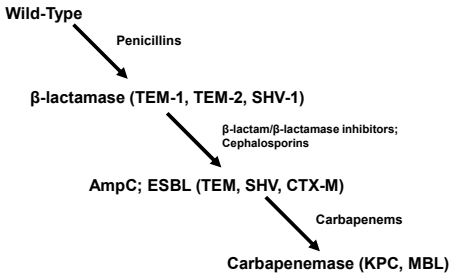
S. aureus Bacteremia: Hospital Costs



Lodise TP, McKinnon PS. *Diagn Microbiol Infect Dis.* 2005;52:113-122.
Cosgrove SE, et al. *Infect Control Hosp Epidemiol.* 2005;26:166-174.

ESBL/KPC-producing Enterobacteriaceae

Evolution of β-Lactamases



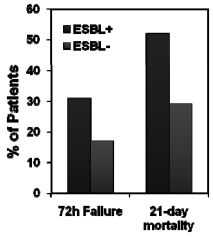
ESBL, extended-spectrum β-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; TEM-1,TEM-2, SHV-1, TEM, SHV, CTX-M, types of β-lactamases.
Adapted from Burgess DS, et al. *Am J Health Syst Pharm.* 2008;65:S4-S15.

KPC Enzymes in US: Growing Threat*

*KPC-producing Enterobacteriaceae are also known as carbapenemase-producing Enterobacteriaceae (CPE).
Srinivasan A, Patel JB. *Infect Control Hosp Epidemiol.* 2008;29:1107-1109.

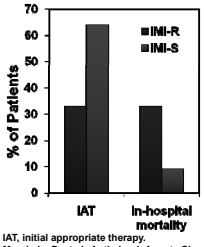
ESBL/KPC-producers and Clinical Outcomes

ESBL-producing *K. pneumoniae* Bloodstream Infections



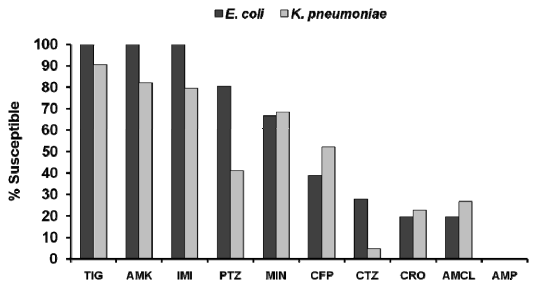
Tumbarello M, et al. *Antimicrob Agents Chemother.* 2006;50:498-504.

Imipenem-resistant (IMI-R) *Enterobacter* Infections



IAT, initial appropriate therapy.
Marchaim D, et al. *Antimicrob Agents Chemother.* 2008;52:1413-1418.

ESBL-producing *E. coli* and *K. pneumoniae* Susceptibility in US, 2004–2006



TIG, tigecycline; AMK, amikacin; IMI, imipenem; PTZ, piperacillin-tazobactam; MIN, minocycline; CFP, cefepime; CRO, ceftazidime; CTX, ceftriaxone; AMCL, amoxicillin-clavulanate; AMP, ampicillin.
Adapted from Hoban DJ, et al. *Diagn Microbiol Infect Dis*. 2007;57:423-428.

K. pneumoniae Carbapenemase: Interspecies Spread in a Single Patient

Case Report

44-year-old woman underwent small bowel transplantation in 2005

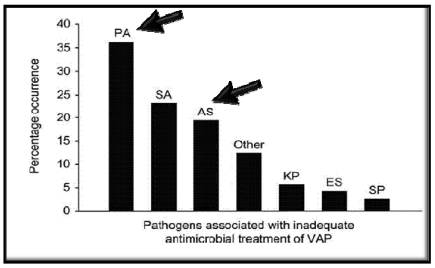
- Prolonged hospital course, multiple episodes of infection and rejection
- Admitted in June 2008 for bacteremia due to *E. coli* and *E. cloacae*
- Over a 5-month period, 5 ertapenem-resistant isolates from 3 species were collected and analyzed (2 *K. pneumoniae*, 2 *E. coli*, 1 *S. marcescens*)
  - 4 isolates showed high MICs to all carbapenems tested
  - Molecular analysis demonstrated transmission from *K. pneumoniae* to *E. coli* and then to *S. marcescens*

	MIC (µg/mL)				
	KP1	EC1	KP2	EC2	SM
Ertapenem	>32	8	>32	>32	>32
Meropenem	>32	.25	>32	>32	>32
Imipenem	>32	.75	>32	>32	>32
Doripenem	>32	1.5	>32	>32	>32
KPC-3 gene	+	-	+	+	+

Sidjabat HE, et al. *Clin Infect Dis*. 2009;49:1736-1738.

P. aeruginosa/Acinetobacter spp.

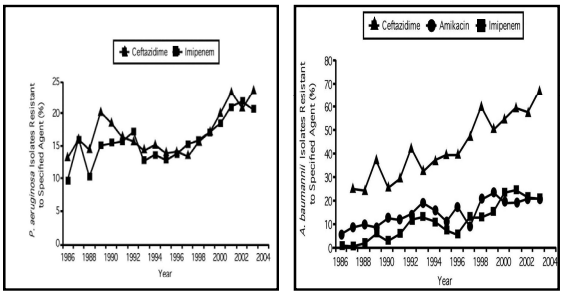
Pathogens Associated with Inadequate VAP Treatment



PA, *P. aeruginosa*; SA, *S. aureus;* AS, *Acinetobacter* spp.; KP, *K. pneumoniae;* ES, *Enterobacter* spp.; SP, *S. pneumoniae.*
Baughman RP. *J Intensive Care Med.* 2009;24:230-241.

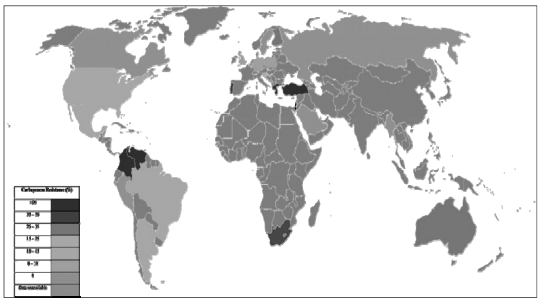
Increasing Drug Resistance

P. aeruginosa ***A. baumannii***



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

Carbapenem Resistance in *A. baumannii*: Worldwide Incidence



Data from the MYSTIC study, 2004.
Perez F, et al. *Antimicrob Agents Chemother.* 2007;51:3471-3484.

Impact of Resistance on Bacteremia Treatment Outcomes

30-day mortality with *A. baumannii*[1]
- IMI-R: 57.5% (n=40)
- IMI-S: 27.5% (n=40)
- *P*=.007

In-hospital mortality with *P. aeruginosa*[2]
- MDR: 21% (n=40)
- Non-MDR: 12% (n=40)
- *P*=.08

IMI, imipenem; MDR, multidrug-resistant.
1. Kwon K, et al. *J Antimicrob Chemother.* 2007;59:525-530.
2. Aloush V, et al. *Antimicrob Agents Chemother.* 2006;50:43-48.

Summary

MRSA
- Prevalence increasing in hospitals and community
- Vancomycin MIC "creep" can hinder the effectiveness of this agent

ESBL/KPC-producers
- Gradual spread throughout US and worldwide
- Effective agents are limited

P. aeruginosa/A. baumannii
- Multidrug resistance common
- Treatment-emergent resistance major concern

Strengthening the Pharmacist's Role: Optimizing Treatment of HAIs

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Managing MRSA Infections

Managing MRSA Infections Treatment Options

Older	Newer	Under Development
Vancomycin	Linezolid	Oritavancin
Clindamycin	Daptomycin	Iclaprim
Rifampin	Tigecycline	Ceftobiprole
Tetracyclines	Telavancin	Ceftaroline
TMP/SMX		

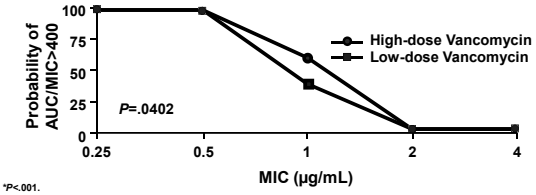
Vancomycin Therapeutic Guidelines: IDSA, ASHP, and SIDP Recommendations

- **Vancomycin displays concentration-independent activity against *S. aureus***
  - Target: AUC/MIC of 400
- **Loading dose: 25–30 mg/kg**
- **Trough serum vancomycin concentrations**
  - Obtained just before 4th dose
  - >10 µg/mL for all patients
  - 15–20 µg/mL for serious infections or if MIC=1 µg/mL
- **Dosage: 15–20 mg/kg q8–12h required for most patients with normal renal function if MIC≤1 µg/mL**
- **If MIC>1 µg/mL, alternative agent recommended**

Rybak MJ, et al. *Clin Infect Dis.* 2009;49:325-327.

Can Higher Doses of Vancomycin Help Achieve AUC/MIC>400 ?

	Mean Trough	Mean AUC
Low Dose (Troughs<15 µg/mL)	9.4 ± 3.2*	318 ± 111*
High Dose (Troughs≥15 µg/mL)	20.4 ± 3.2*	418 ± 152*



*P<.001.
Jeffres MN, et al. *Chest.* 2006;130:947-955.
Mohr JF, Murray BE. *Clin Infect Dis.* 2007;44:1536-1542.

Relationship Between Nephrotoxicity and Higher Vancomycin Dosing

- **Retrospective cohort study compared clinical outcomes and nephrotoxicity in patients with low (<15 µg/mL) vs. high (>15 µg/mL) mean vancomycin trough levels[1]**

	Low Group (n = 39)	High Group (n = 16)	*P* value
Death	**5%**	**19%**	**.1**
Nephrotoxicity*	**10%**	**31%**	**.04**

  - Clinical success and LOS were not significantly different between groups
- **Other studies have also associated higher vancomycin dosing with an increased risk of nephrotoxicity[2,3]**

*Defined as rise in SCr ≥0.5 mg/dL
1. Hermsen ED, et al. Expert Opin Drug Saf. 2010;9:9-14.
2. Lodise TP, et al. Clin Infect Dis. 2009;49:507-514.
3. Lodise TP, et al. Antimicrob Agents Chemother. 2008;52:1330-1336.

Skin and Skin-structure Infection (SSSI)

Non-hospitalized SSSI

- Many antibiotics may work for uncomplicated CA-MRSA infections (randomized trials underway)
- Incision and drainage likely most important
- Pick the cheapest and most convenient (e.g., minocycline, TMP/SMX, or clindamycin) guided by local susceptibilities

Hospitalized SSSI

- Vancomycin, daptomycin, linezolid, telavancin, tigecycline: proven safe and effective

Stevens DL, et al. *Clin Infect Dis.* 2005;41:1373-1406.

Endocarditis and Nosocomial Pneumonia

Endocarditis

- Current standard: vancomycin +/- gentamicin/rifampin (for prosthetic valve)
- Bacteremia/right-sided endocarditis trial: daptomycin non-inferior with less nephrotoxicity

Nosocomial pneumonia

- Linezolid or vancomycin equally recommended
- Studies underway: tigecycline and telavancin

Baddour LM, et al. *Circulation*. 2005;111:e394-e434; Fowler VG Jr, et al. *N Engl J Med*. 2006;355:653-665; ATS/IDSA. *Am J Respir Crit Care Med*. 2005;171:388-416.

Catheter-related Bloodstream Infection

- **Remove infected catheter**
- **Agent**
  - Preferred: vancomycin
  - Alternative: daptomycin or linezolid (if vancomycin MIC>1 µg/mL)
- **Duration**
  - Standard: 4–6 weeks
  - Shorter: 14 days
    - Patient not diabetic or immunosuppressed
    - Infected catheter removed
    - No prosthetic intravascular devices present
    - No evidence of endocarditis or suppurative thrombophlebitis
    - Fever/bacteremia resolved within 72 h of therapy
    - No evidence of metastatic infection

Mermel LA, et al. *Clin Infect Dis*. 2009;45:1-49.

Managing Infections due to ESBL/KPC-producing Bacteria

Infections by ESBL-Producing Bacteria: Treatment Options

Carbapenems
- Preferred agents (almost uniform *in vitro* susceptibility)
- Extensive clinical experience
- Resistance in ESBL-producing bacteria
  - Rare, though multiple mechanisms identified

Tigecycline
- Limited clinical data
- Breakpoints not established for ESBL-producers
- Limited urinary penetration

3rd-generation cephalosporins
- Avoid as monotherapy for confirmed ESBL-producers

Cefepime and pip/tazo
- Controversial; many clinicians would avoid for serious infections

Aminoglycosides and fluoroquinolones
- Higher likelihood of resistance with ESBL-producing Enterobacteriaceae
- Some gentamicin S are R to tobramycin/amikacin

ATS/IDSA. *Am J Respir Crit Care Med.* 2005;171:388-416.
Paterson DL, Bonomo RA. *Clin Microbiol Rev.* 2005;18:657-686.

ESBL-producing *K. pneumoniae* Bacteremia: Treatment

Treatment	All-cause 14-day Mortality
Carbapenem Monotherapy	**1/27** (3.7%)
Quinolone Monotherapy	**4/11** (36.3%)
Cephalosporin Monotherapy	**2/5** (40%)
β-lactam/β-lactamase Inhibitor	**2/4** (50%)
No In Vitro Active Drug	**7/11** (63.6%)

86 episodes

Paterson DL, et al. *Clin Infect Dis.* 2003;39:31-37.

Infections by KPC-producing Bacteria: Treatment Options

Tigecycline
- Not active against *P. aeruginosa*
- Limited clinical data
- Concerns: low serum concentrations, Aes

Colistin
- Optimal dosing unknown
- Limited data for KPC
- Neuro- and nephrotoxicity

Aminoglycosides
- Data primarily with combination therapy
- Nephrotoxicity concern
- Serum concentration monitoring needed

Ampicillin-sulbactam
- β-lactamase inhibitor component active against select strains
  - Not active against KPC-3
- Optimal dose unknown

ATS/IDSA. *Am J Respir Crit Care Med.* 2005;171:388-416.
Paterson DL, Bonomo RA. *Clin Microbiol Rev.* 2005;18:657-686.

Recognition of KPC-producers: Key to Better Outcomes

KPC-producing *K. pneumoniae* Infection

- **Initially reported as imipenem-S (n=13)**
  - 9 treated with imipenem or meropenem
    - Success: 4/9 (44.4%)
- **Initially reported as non-susceptible (n=15)**
  - 10 treated with alternative therapies (gentamicin, tigecycline alone or in combination)
    - Success: 8/10 (80%)
    - Tigecycline success: 5/7

Weisenberg SA, et al. *Diagn Microbiol Infect Dis*. 2009;64:233-235.

Managing Infections due to MDR *P. aeruginosa/Acinetobacter* spp.

P. aeruginosa Infections: Combination Therapy

Meta-analysis

- β-lactam monotherapy vs. β-lactam + aminoglycoside for severe infection
- 64 randomized trials, 7586 patients
  - No difference in mortality or resistance
  - Increased clinical and microbiological failure with combination therapy
  - Increased nephrotoxicity with combination therapy
  - Decreased superinfections with monotherapy

Choice of combination should reflect local resistance patterns

Paul M, et al. *Br Med J*. 2004;328:668.

Combination Antibiogram

University of Chicago Medical Center

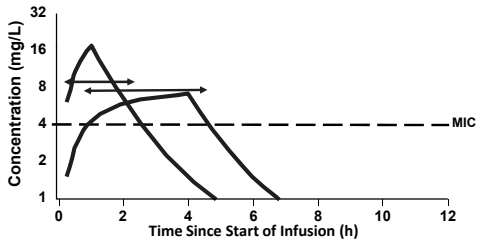
Pathogen	Monotherapy	% Susceptible Gentamicin	Ciprofloxacin	Tobramycin	Amikacin
All Isolates (n=5064)					
Imipenem	84.0	91.0	88.1	93.4	95.0
Ceftazidime	71.5	86.5	82.9	88.5	94.2
Pip-tazo	74.3	87.4	84.2	89.2	93.2
***P. aeruginosa* (n=2115)**					
Imipenem	66.2	82.3	75.7	87.8	91.4
Ceftazidime	70.3	87.9	82.0	93.2	95.0
Pip-tazo	74.7	85.5	82.1	89.6	92.4
***A. baumannii* (n=281)**					
Imipenem	69.8	71.5	69.8	74.4	75.4
Ceftazidime	25.6	35.1	29.5	48.1	62.8
Pip-tazo	19.9	32.7	26.7	45.9	60.1

Pip-tazo, piperacillin-tazobactam.
Christoff J, et al. *Infect Control Hosp Epidemiol.* 2010;31:256-261.

Optimizing β-lactam Therapy: Maximizing %Time>MIC

Prolonged infusion

- Same dose and dosing interval, however, change duration (0.5 h→3–4 h)



OPTAMA: US 2006

640 *E. coli*, 618 *Klebsiella* spp., 606 *P. aeruginosa* (15 US ICUs)

Table 3. Cumulative Fraction of Response (%) of Various Standard Infusion Dosing Regimens Against Three Gram-Negative Bacteria

Antimicrobial	Dosing Regimen	*Escherichia coli* 2002	2004	2006	*Klebsiella* spp. 2002	2004	2006	*Pseudomonas aeruginosa* 2002	2004	2006
Cefepime	1 g every 12 h	99.9	99.1	97.3	99.3	98.5	89.8	80.5	76.8	78.9
	2 g every 12 h	100	99.6	99.1	99.9	99.2	99.6	91.1	89.1	90.0

Table 4. Cumulative Fraction of Response of Various Prolonged Infusion Dosing Regimens Against Three Gram-Negative Bacilli

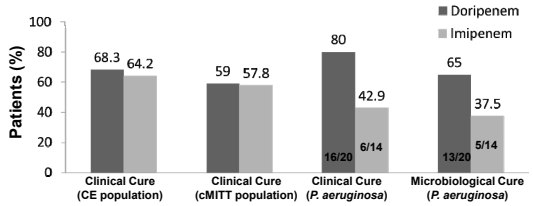
Antibiotic	Regimen	*Escherichia coli* 2002	2004	2006	*Klebsiella* spp. 2002	2004	2006	*Pseudomonas aeruginosa* 2002	2004	2006
Cefepime	2 g every 8 h (3 h PI)	100	99.9	99.5	100	99.8	97.0	96.0	97.7	97.8
Ceftazidime	2 g every 8 h (3 h PI)	99.9	99.9	99.1	99.2	99.8	96.3	97.2	98.2	96.3
Imipenem	1 g every 8 h (3 h PI)	100	100	100	100	99.5	93.4	92.3	93.9	88.6
Meropenem	1 g every 8 h (3 h PI)	100	100	100	100	99.5	91.5	95.0	93.2	91.8
	2 g every 8 h (3 h PI)	100	100	100	100	99.5	95.8	96.8	97.0	96.6
Piperacillin–tazobactam	3.375 mg every 8 h (4 h PI)	98.1	98.4	96.8	96.6	95.8	84.7	85.1	80.5	81.3
	4.5 mg every 6 h (3 h PI)	98.2	98.7	97.6	97.2	96.0	86.6	90.3	84.9	86.6
	2 g every 8 h	100	100	100	100	99.2	90.4	94.5	94.0	92.0
Piperacillin–tazobactam	3.375 g every 6 h	96.7	97	95.9	93.9	93.7	81.1	79.2	74.1	75.7
	4.5 g every 6 h	97.2	97.6	94.9	95.1	94.5	83.0	82.0	77.8	79.1
Tigecycline	100 mg then 50 mg every 12 h	ND	ND	98.2	ND	ND	74.6	ND	ND	ND

MYSTIC = Meropenem Yearly Susceptibility Test Information Collection; ND = no data available.

Crandon JL, et al. *Ann Pharmacother.* 2009;43:220-227.

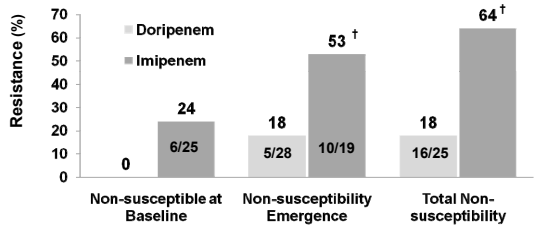
Optimized Dosing for Better Outcomes

- Study design: open-label, randomized 1:1 (n=531)
- Study therapy: doripenem IV 0.5 g q8h (4 h infusion) *or* imipenem IV 0.5 g q6h or 1 g q8h (30–60 min infusion)
- Length of treatment: 7–14 d



CE, clinically evaluable; cMITT, clinically modified intent-to-treat; *P* value not significant for any difference.
Chastre J, et al. *Crit Care Med.* 2008;36:1089-1096.

Baseline and Emergence of Non-susceptible* *P. aeruginosa*



*Doripenem and imipenem non-susceptibility defined as MIC≥8 µg/mL.
Total non-susceptibility (NS)=NS at baseline + NS emergence.
†*P*<.05, microbiologically modified intent-to-treat (mMITT) population.
Chastre J, et al. *Crit Care Med.* 2008;36:1089-1096.

Tigecycline vs. *A. baumannii*

- **Low serum vs. high tissue concentrations**
  - Shouldn't be used for bacteremia?
- **CLSI breakpoints for S/R to be defined**
- **Very little clinical data on use vs. *Acinetobacter***
- **Emergence of resistance during therapy or high resistance rates in certain areas[1,2,3]**

Tigecycline's role in severe *A. baumannii* infections still to be defined

1. Navon-Venzia S, et al. *J Antimicrob Chemother.* 2007;59:772-774.
2. Peleg AY, et al. *Antimicrob Agents Chemother.* 2007;51:2065-2069.
3. Anthony KY, et al. *Clin Infect Dis.* 2008;46:567-570.

Doripenem vs. *A. baumannii*

Doripenem 1 g q8h (4 h infusion) for VAP/nosocomial pneumonia due to *A. baumannii*

	Outcome
Microbiological Eradication	
MIC≤16 µg/mL	**7/7** (100%)
MIC≥32 µg/mL	**4/7** (57%)
Clinical Success	
MIC ≤16 µg/mL	**5/7** (71%)
MIC ≥32 µg/mL	**4/7** (57%)

Nicholson S, et al. Presented at 2009 Annual Meeting of IDSA. Abstract #386.

Colistin plus Rifampin for Treatment of MDR *A. baumannii* Infections

29 critically ill patients with pneumonia (n=19) and bacteremia (n=10)
Colistin 2 million IU q8h (~10 mg/kg/day) plus intravenous rifampin (10 mg/kg q12h)

Characteristic	No. (%), unless noted
APACHE II (mean ± SD)	17.03 ± 3.68
No. receiving mechanical ventilation	22 (75.8)
Duration of Treatment (mean ± SD)	17.7 ± 10.4 days
Length of Hospital Stay (mean ± SD)	33.2 ± 15.8 days
Clinical/Microbiological Response	22 (75.8)
30-day mortality	9 (31)
Nephrotoxicity	3 (10)

Bassetti M, et al. *J Antimicrob Chemother.* 2008;61:417-420.

Summary

MRSA
- Vancomycin effective when used appropriately
- Recognize when alternative agent needed

ESBL/KPC-producers
- Agent selection and dose optimization critical
- Recognition of KPC-producing organisms important to guide appropriate therapy selection

P. aeruginosa/A. baumannii
- Combination therapy, if desired, based on local resistance patterns
- Dose optimization to reduce risk of treatment-emergent resistance and to improve outcomes